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Associations between Gene Polymorphisms, Breeding Values, and Glucose Tolerance Test Parameters in German Holstein Sires

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ABSTRACT

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The association between several gene polymorphisms, the estimated breeding values for milk performance traits, and glucose metabolism measured by the glucose tolerance test (GTT) in German Holstein sires were evaluated. Polymorphisms in *DGAT1*, *GH1*, *GHR*, *FASN*, and *OLR1* genes were not associated with the GTT. A significant relationship was obtained for the *DGAT1 AA/GC* polymorphism and estimated breeding values for milk performance (milk yield, fat and protein yield, fat and protein percentage). The polymorphism in *GHR* was significantly associated with estimated breeding values for fat yield, and the polymorphism in *OLR1* with estimated breeding value for protein yield. It shows the importance of the polymorphisms and makes their use in the breeding possible. GTT may be helpful in metabolic analyses, but the gene polymorphisms assessed in our study were not associated with GTT traits and further studies should examine other gene polymorphisms to support the role of GTT for potential breeding purposes.

Keywords: *Bos taurus*; milk; glucose metabolism; *DGAT1*; *GH1; GHR; FASN; OLR1; ABCG2*

The primary goal of breeding is to find animals in which high performance and good health are genetically connected. Lately, in addition to the association analyses of gene polymorphisms and performance also the metabolomic approach is believed to be promising (Fontanesi 2016). Among other metabolic traits, the importance of glucose metabolism is substantial and it can be evaluated by the glucose tolerance test (GTT) (Panicke et al. 2001).

In cattle, there is a number of polymorphic genes associated with milk performance, and we selected several to determine their associations with breeding values and glucose metabolism. *DGAT1* coding for diacylglycerol *O*-acyltransferase 1 is the causative gene for milk fat. The non-conservative 694-695*AA>GC* substitution in the *DGAT1* gene has a major effect on milk fat content and other milk characteristics. It is located on bovine chromosome 14 (Coppieters et al. 1998; Grisart et al. 2002).

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The growth hormone receptor (GHR) determines the biological activity of growth hormone (GH1), the regulator of metabolism affecting growth, body composition, and milk production (Blott et al. 2003; Etherton 2004). ABCG2 belongs to the adenosine triphosphate binding cassette family of transmembrane drug transporters (Farke et al. 2008). Fatty acid synthase (FASN) is an enzyme that participates in the metabolism of lipids, and single nucleotide polymorphisms (SNPs) in the bovine gene have been shown to be associated with variations in fatty acid composition in milk (Morris et al. 2007). The oxidized low-density lipoprotein receptor (OLR1) protein binds, internalizes, and degrades oxidized low-density lipoprotein. The results of previous whole-genome association studies have prompted the investigation of *OLR1* as a candidate gene affecting milk composition (Khatib et al. 2006). Despite the currently prevailing genomic approach (Bauer et al. 2015; Pribyl et al. 2015; Suchocki et al. 2016), the polymorphisms in major genes have still been of interest.

The objective of this study was to evaluate the relationships between the variation in several genes and breeding values for milk performance. As the glucose metabolism is of interest for the possible use in breeding (Panicke et al. 2001; Pieper et al. 2016), the relationships between the variation in the genes and the GTT were analysed.

MATERIAL AND METHODS

German Holstein bulls were born in 1993 (n = 42), 1998 (n = 95), 1999 (n = 102), 2000 (n = 72), 2001 (n = 89), 2002 (n = 83), and 2003 (n = 24). Bulls were kept at two breeding stations in Germany. GTT was performed in sires according to Burkert (1998) at different age of 6.5–17 months. Since their last feeding on the previous day they received only water. The basic concentration of glucose (G_0) was determined. Bulls were injected 1 g glucose per $kg^{0.75}$ body weight into *v. jugularis* and then 9 blood samples were taken in 7-minute intervals to evaluate the glucose reaction. The glucose half life time (G_{HLT}) and the glucose area equivalent (G_A) between each course of concentration and basic level were determined as described in Burkert (1998). G_{MAX1} was the maximal glucose concentration in the 1st sample 7 min after injection. G_{MAX} was the maximal glucose concentration over the basal level in the 1st sample after subtraction of G_0. The effects of animal were estimated for each parameter of GTT using PEST software package (Groeneveld 2006). The model equation contained the effect of animal, the fixed effect of herd, the date of test day, the age of bulls on the test day (the bulls were divided according to their age into classes of 6 months), and random residuum (Fischer et al. 2003). The GTT values were logarithmically transformed before processing. The data on GTT were kindly provided by Prof. L. Panicke, and overlap with those of Pieper et al. (2016).

German Holstein sires (n = 507) were genotyped for the polymorphisms in the genes as follows. *ABCG2* (ATP binding cassette sub family G member 2, junior blood group, gene ID: 536203, BTA6, gene region: exon 14, rs43702337, NM_001037478.3:c.1742A>C or NP_001032555.2:p.Tyr581Ser); *DGAT1* (diacylglycerol *O*-acyltransferase 1, gene ID: 282609, BTA14, gene region: exon 8, rs109234250, rs109326954, NM_174693.2:c.694-695AA>GC or NP_777118.2:p.Lys232Ala); *OLR1* (oxidized low density lipoprotein lectin-like receptor 1, gene ID: 281368, BTA5, gene region: 3'-UTR, NM_174132.2:c.1070C>A); *FASN* (fatty acid syntase, gene ID: 281152, BTA19, gene region: exon 40, rs41919985, NM_001012669.1:c.6787A>G or NP_001012687.1:p.Ala2263Thr); *GHR* (growth hormone receptor, gene ID: 280805, BTA20, gene region: exon 10, rs109300983, NM_176608.1:c.1685A>G or NP_788781.1:p.Ser555Gly); *GH1* (growth hormone 1, gene ID: 280804, BTA19, gene region: exon 5, rs41923484, NM_180996.1:c.457C>G or NP_851339.1:p.Leu-153Val).

DNA was extracted from whole blood or frozen sperm. Analyses were performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods. For *DGAT1*, PCR and digestion with restriction endonuclease *Cfr*I were performed as described in Winter et al. (2002). For *GH1*, PCR and restriction with *Alu*I were as in Mitra et al. (1995), for *GHR*, PCR and restriction with *Alu*I as in Di Stasio et al. (2005). *ABCG2* was genotyped by PCR and restriction with *Pst*I as in Komisarek and Dorynek (2009), for *FASN,* PCR and restriction by *Msc*I were as in Zhang et al. (2008), and for *OLR1*, PCR and restriction with *Pst*I as in Khatib et al. (2006).

The results of the GTT were analysed among different genotypes of the polymorphic genes, and

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similarly, the estimated breeding values (EBVs) were analysed according to the genotype.

The EBVs of 2012 provided by Vereinigte Informationssysteme Tierhaltung, Verden, Germany (VIT) (http://www.vit.de/fileadmin/user_upload/vit-fuers-rind/zuchtwertschaetzung/milchrinder-zws-online/Zws_Bes_english.pdf2012) were used. The EBVs for milk production traits (milk yield in kg, fat percentage, fat yield in kg, protein percentage, and protein yield in kg) were assessed. Intra-herd test day variance was standardised according to the production level on herd test day and the number of cows in the same lactation within the particular herd test day. Breeding values of the first three lactations were estimated by VIT using the Random Regression Model, representing the desired breeding goal of high lifetime production. Unfortunately, the reliabilities of EBV used in this paper are not given by VIT. However, for the complex indicator Relative Breeding Value Milk they report the reliability for the sires involved of 94.1%.

Statistical analyses were performed using the SAS software (Statistical Analysis System, Version 9.3, 2015). The MIXED procedure, Least Squares Means method was used to compare contrasts between genotypes. We have developed the following model:

$$Y_{ij} = \mu + genotype_i + e_{ij}$$

where:

Y_{ij} = breeding value of the sire for each trait of milk yield or the breeding value of GTT parameter

μ = population mean

$genotype_i$ = fixed effect of genotype in respective gene

e_{ij} = residual random error

For post-hoc comparisons, the Scheffe's test was used. The Hardy-Weinberg equilibrium (HWE) was tested using the χ^2 test by SAS. The actual (empirical) and genotype frequencies calculated on the basis of HWE were compared.

RESULTS AND DISCUSSION

The genotype and allele frequencies of polymorphic genes are provided in Table 1. The *ABCG2* gene was monomorphic when the allele *A* was fixed and so it was not included in the tables. In this paper, the *GHR* and *OLR1* genes were not in HWE.

The differences in GTT according to the genotype of the genes analysed were small and non-significant (Table 2). The genes were evaluated separately. When evaluating the polymorphic genes together (data not shown), their impact on the GTT variance was also non-significant. The glucose metabolism is controlled by many genetic and non-genetic factors. Some studies (Panicke et

Table 1. Frequencies of genotypes and alleles of the genes in Holstein sires

Gene	Genotype	*n*	(%)	χ^2	Allele frequencies	
	GC/GC	205	44.47		*A*	*K*
DGAT1	*GC/AA*	201	43.60	0.068^{ns}	0.66	0.34
	AA/AA	55	11.93			
	AA	34	18.48		*A*	*G*
FASN	*AG*	97	52.72	0.434^{ns}	0.45	0.55
	GG	53	28.80			
	CC	434	89.48		*L*	*V*
GH1	*CG*	50	10.31	0.082^{ns}	0.95	0.05
	GG	1	0.21			
	AA	216	91.53		*A*	*G*
GHR	*AG*	16	6.78	9.091*	0.95	0.05
	GG	4	1.69			
	AA	53	36.30		*A*	*C*
OLR1	*AC*	89	60.96	14.080***	0.67	0.33
	CC	4	2.74			

significant differences between genotype frequencies calculated on the basis of Hardy-Weinberg equilibrium (HWE) and empirical frequencies *($P < 0.05$), ***($P < 0.001$); ^{ns}non-significant, the group was in HWE

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al. 2001) showed only low heritability of GTT in the range of 0.12–0.20. This suggests a high impact of non-genetic factors on glucose metabolism, high and changing number of genes involved and variability in their expression. On the other hand, Pieper et al. (2016) refer in repeated analyses higher heritability of 0.43 for glucose area equivalent, and 0.40 for glucose half-life period, correlations between GTT and breeding values for milk yield and composition were not found. Their results indicate that heritability for response to glucose is high, which warrants further investigation of this trait for genetic improvement of metabolic disorders. The authors suggest research to determine the target levels of GTT and potential associations between GTT in breeding bulls and periparturient diseases in their offspring. However, from the genomic point of view the genetic

Table 2. Glucose tolerance test (GTT) parameters of sires

Gene	Least Squares Means of lnGTT parameters				
	G_0	G_{MAX1}	G_{MAX}	G_A	G_{HLT} (min)
	(mmol/l)				
DGAT1					
GC/GC	1.482	2.582	2.173	3.568	3.851
GC/AA	1.495	2.575	2.156	3.566	3.852
AA/AA	1.489	2.599	2.194	3.584	3.835
r^2	0.0019	0.0055	0.0064	0.0007	0.0004
P-value	0.650	0.281	0.231	0.855	0.914
FASN					
AA	1.510	2.584	2.158	3.568	3.893
AG	1.481	2.596	2.196	3.584	3.857
GG	1.470	2.559	2.147	3.570	3.792
r^2	0.0070	0.0246	0.0230	0.0014	0.0220
P-value	0.531	0.105	0.122	0.883	0.133
GHR					
AA	1.494	2.608	2.205	3.587	3.834
AG	1.464	2.614	2.240	3.649	3.854
GG	1.341	2.568	2.215	3.456	3.563
r^2	0.0182	0.0023	0.0031	0.0138	0.0170
P-value	0.118	0.764	0.694	0.198	0.135
GH1					
CC	1.494	2.582	2.167	3.567	3.855
CG	1.476	2.559	2.149	3.544	3.827
GG	1.370	2.579	2.224	3.690	3.811
r^2	0.0032	0.0049	0.0016	0.0017	0.0011
P-value	0.460	0.304	0.679	0.657	0.771
OLR1					
AA	1.501	2.587	2.173	3.624	3.895
AC	1.455	2.590	2.198	3.585	3.807
CC	1.478	2.598	2.174	3.532	3.741
r^2	0.0174	0.0003	0.0065	0.0102	0.0271
P-value	0.285	0.977	0.627	0.479	0.140

G_0 = basic concentration of glucose, G_{MAX1} = maximal glucose concentration in the 1st sample 7 min after injection, G_{MAX} = maximal glucose concentration over the basal level in the 1st sample after subtraction of G_0, G_A = glucose area equivalent between each course of concentration and basic level, G_{HLT} = glucose half life time

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architecture of complex traits is even more complex than previously thought (Goddard et al. 2016). In almost every trait studied there are thousands of polymorphisms that explain genetic variation. Complex approach to the energetic metabolism is desirable. There may also be opportunities to select for general disease resistance in terms of metabolic stability (Pryce et al. 2016). The authors inform that some countries have already initiated genetic evaluations of metabolic disease traits and currently most of these use clinical observations of disease. But there are opportunities to use clinical diseases in addition to predictor traits and genomic information to strengthen genetic evaluations for metabolic health in the future.

The analysis of the relationship between polymorphic genes and EBVs for milk performance (Table 3) showed that *DGAT1* was significant consistently with the previous observations by Grisart et al. (2002) and Hanusova et al. (2014). The *GC/GC* genotype (*GC* coding for alanine) was associated with high milk yield like in the previous reports. The sires with the *AA/AA* genotype (*AA* coding for lysine) had high EBVs for fat percentage and

Table 3. Estimated breeding values of sires for milk performance traits

Gene	Least Squares Means of estimated breeding values				
	Milk (kg)	Fat (%)	Fat (kg)	Protein (%)	Protein (kg)
DGAT1					
GC/GC	466.288[a]	–0.170[a]	3.737[a]	–0.038[a]	12.356[a]
GC/AA	166.410[b]	0.058[b]	10.860[b]	0.012[b]	6.310[b]
AA/AA	–144.127[c]	0.311[c]	18.091[c]	0.050[c]	–1.255[c]
r^2	0.1062	0.2903	0.0456	0.0650	0.0571
P-value	< 0.0001****	< 0.0001****	< 0.0001****	< 0.0001****	< 0.0001****
FASN					
AA	471.441	–0.033	15.618	–0.005	15.324
AG	281.155	–0.012	8.969	0.022	10.969
GG	325.358	–0.041	8.698	–0.002	10.566
r^2	0.0131	0.0017	0.0121	0.0095	0.0099
P-value	0.302	0.860	0.333	0.421	0.405
GHR					
AA	223.310	0.021	9.509[a]	0.013	8.315
AG	144.063	0.011	4.938	0.026	6.750
GG	–122.250	–0.158	–18.750[b]	0.008	–3.750
r^2	0.0060	0.0049	0.0291	0.0009	0.0076
P-value	0.498	0.567	0.032*	0.902	0.409
GH1					
CC	265.014	–0.016	8.353	–0.004	8.353
CG	346.640	–0.004	12.540	–0.024	9.420
GG	335.000	–0.230	–6.000	–0.250	–10.000
r^2	0.0016	0.0012	0.0040	0.0107	0.0023
P-value	0.685	0.753	0.382	0.075	0.577
OLR1					
AA	453.094	–0.044	14.057	–0.005	14.642[a]
AC	205.607	0.018	8.281	0.004	6.910[b]
CC	293.250	0.008	12.500	–0.025	8.000
r^2	0.0362	0.0079	0.0124	0.003	0.0415
P-value	0.071	0.566	0.409	0.834	0.048*

significant differences between genotypes [a–c]($P < 0.05$); *($P < 0.05$), ****($P < 0.0001$)

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despite the lower milk yield their breeding values for fat yield were significantly high as well. The heterozygotes *AA/GC* showed intermediate values indicating additive heredity in the gene. It is also evident that the *DGAT1* polymorphism contributes to the negative correlation between milk production and fat content. The *AA/AA* genotype had a higher EBV for protein percentage, but the difference was considerably lower than for fat yield. Therefore, the EBV for protein yield was higher in sires with *GC/GC* genotype due to their high EBV for milk yield. *DGAT1* is considered to be one of the most important major genes influencing fat percentage, but also other genes are in focus in which significant effects have been found (Pasandideh et al. 2015; Shi et al. 2016).

In this paper, the impact of other polymorphisms on the breeding values was non-significant ($P > 0.05$) in most cases except for *GHR* polymorphism and milk fat yield, and *OLR1* polymorphism and protein yield ($P < 0.05$). It hints at the importance of the genes and their possible application in the breeding.

The insignificant differences for polymorphisms, referred by other authors as significant, are not rare. Schennink et al. (2009) found significant influence of *FASN* and *OLR1* on the fat percentage, but not of *PPARGC1A*, *PRL,* and *STAT5A* genes, so they were not able to confirm results reported in the literature that showed effects of all evaluated polymorphisms on milk fat percentage or milk fat yield. Moreover, in this paper we have analysed the association between the polymorphisms and the sires' breeding values, not the milk recording data of the offspring as usual in other analyses. The comparison to the published results can be commented with respect to the limited transferability of estimates between populations (e.g. Pribyl et al. 2015).

The complex approach involving genomics, metabolomics as well as major genes seems to be promising in analyses of the biology of complex traits (Suravajhala et al. 2016). This is especially relevant for the milk fat, where the estimated number of genes is relatively low (Suchocki et al. 2016).

CONCLUSION

The significant influence of *DGAT1* polymorphism on the milk fat percentage and yield was confirmed. The relation between some polymorphic genes and glucose metabolism was not found. Further studies should examine other gene polymorphisms to support the role of the GTT for potential breeding purposes.

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