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The F279Y polymorphism of the *GHR* gene and its relation to milk production and somatic cell score in German Holstein dairy cattle

**Siham A. Rahmatalla · Uwe Müller ·
Eva M. Strucken · Monika Reissmann ·
Gudrun A. Brockmann**

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Abstract The bovine *growth hormone receptor* (*GHR*) gene has been identified as a strong positional and functional candidate gene influencing milk production. A non-synonymous single nucleotide polymorphism (SNP) in exon 8 leads to a phenylalanine to tyrosine amino acid substitution (F279Y) in the receptor. The aim of the study was to estimate the effects of the F279Y mutation on milk yield, fat, protein, casein, and lactose yield and content, as well as somatic cell score (SCS), in a German Holstein dairy cattle population. The analysis of 1,370 dairy cows confirmed a strong association of the F279Y polymorphism with milk yield, as well as with fat, protein, and casein contents. Furthermore, increasing effects on lactose yield and content for the 279Y allele were found. Even though the tyrosine variant occurred as the minor allele (16.5%), its substitution effects were 320 kg (305 d), 0.02 kg per day, and 0.07 kg per day for milk, casein, and lactose yields, respectively. The same allele had negative effects on fat, protein, and casein contents. Finally, the high-milk-yield tyrosine allele was also associated with lower SCS ($p < 0.05$). The data support the high potential of the F279Y polymorphism as a marker for the improvement of milk traits in selection programs.

Keywords Cattle · Dairy breed · *GHR* gene · Milk traits · Single nucleotide polymorphism · Somatic cell score

S. A. Rahmatalla · U. Müller · E. M. Strucken · M. Reissmann ·
G. A. Brockmann (✉)
Department for Crop and Animal Sciences,
Humboldt-Universität zu Berlin,
Invalidenstraße 42,
10115 Berlin, Germany
e-mail: gudrun.brockmann@agrar.hu-berlin.de

Introduction

Since the first systematic genome-wide scan for quantitative trait loci (QTL) with an effect on milk production traits in cattle (Georges et al. 1995), many partial and full genome scans have been performed in different populations. Several studies in cattle have described and confirmed QTL with impacts on milk production, reproductive, and udder traits on bovine chromosome 20 (Georges et al. 1995; Arranz et al. 1998; Ashwell et al. 2001; Viitala et al. 2003; Ashwell et al. 2004). Blott et al. (2003) reported for the first time that the lod score peak in the *growth hormone receptor* (*GHR*) region was completely erased when the F279Y single nucleotide polymorphism (SNP) was included as a fixed effect in an association model. This provided strong evidence that a chromosome segment including the gene encoding the growth hormone receptor accounted at least partially for the effect of the QTL on chromosome 20. Moreover, Blott et al. (2003) identified that the phenylalanine to tyrosine substitution at the amino acid position 279 of the *GHR* gene was associated with a strong effect on milk yield and composition.

The *GHR* gene encodes the transmembrane receptor for the growth hormone that belongs to a large superfamily of cytokine and hematopoietic growth factor receptors (Frank et al. 1994; Ji et al. 2002). The growth hormone receptor is a transducer for growth hormone action, which plays a pivotal role in the lipid and carbohydrate metabolism (Lucy et al. 2001). Furthermore, it has a major role in the growth hormone axis through the initiation and maintenance of lactation (Parmentier et al. 1999).

Mutation analyses in Holstein Friesian cattle revealed ten polymorphic sites within the bovine *GHR* gene (Blott et al. 2003). Four of the mutations were SNPs in introns, one was in the 3′ untranslated region, three were synonymous mutations in the third codon position, and two SNPs modify the amino acid sequence. The single nucleotide substitution in exon 8 from T to A, which causes the replacement of the amino acid sequence from a neutral phenylalanine (279F) to an uncharged but polar tyrosine (279Y) at position 279 (F279Y), is located in a transmembrane domain of the *GHR* gene. This mutation showed strong effects on milk protein and fat content, and, to a lesser extent, on milk yield in Dutch, New Zealand, and Irish Holstein Friesian, as well as in New Zealand Jersey populations and Finnish Ayrshire (Blott et al. 2003; Viitala et al. 2006; Waters et al. 2011). However, until now, no information has been available for allele frequencies and allele effects in German Holstein populations.

The objectives of the current study were the determination of genotype and allele frequencies of the F279Y mutation of the *GHR* gene in a German Holstein dairy cattle population and the estimation of genetic effects on milk yield and composition, as well as somatic cell score (SCS).

Materials and methods

Animals

The study was performed with a total of 1,370 German Holstein dairy cows kept under similar feeding and management conditions in three herds in North-East Germany. Cows calved between 1999 and 2006. The first three lactations were used. These cows were daughters of 265 sires, with 1 to 79 daughters per sire.

Genotyping

DNA was extracted from blood samples using the E.Z.N.A. Tissue DNA Kit II (Peqlab Biotechnology GmbH, Erlangen, Germany). Genotyping for the *GHR* F279Y mutation was performed with a gene test on the pyrosequencer PSQ™ 96MA (Biotage AB, Uppsala, Sweden). Primers for polymerase chain reaction (PCR) were designed from the *GHR* gene sequence available at GenBank accession no. AM161140.1 using the Biotage Assay Design Software. Primer sequences were as follows: forward primer 5′-TTTGGAATACTTGGGCTAGCA-3′, reverse primer 5′-AATAACTGGCAAAACATATCAGAGT-3′, sequencing primer 5′-GGCTAGCAGTGACATTAT-3′. PCR reactions were performed in a total volume of 50 µl using 100 ng of genomic DNA as templates, 1× PCR buffer, 2.5 mM $MgCl_2$, 0.1 mM of each dNTP, 1 U polymerase enzyme (FirePol, Solis BioDyne, Tartu, Estonia), and 5 pmol of forward and reverse primer. The PCR conditions consisted of an initial denaturation step at 95°C for 5 min, primer annealing at 57°C for 30 s, and elongation at 72°C for 20 s, followed by 50 cycles of 95°C for 15 s, 57°C for 30 s, 72°C for 20 s, and a final step at 72°C for 5 min. PCR products were prepared for subsequent pyrosequencing using the sequencing primer according to a standard protocol at the PyroMark Vacuum Prep Workstation (Biotage AB, Uppsala, Sweden).

Phenotypic data

The data set of 305-day-traits comprised own performance data for milk, fat, and protein yield and content. In the analysis, only cows with complete 305th day records for milk production from the first to third lactation were considered. Milk, fat, and protein yields and animal-specific performance data for the different lactations were provided by the “Vereinigte Informationssysteme für Tierzucht (VIT)” in Verden, Germany (Table 1). The data used for the association analysis was based on yield deviation (YD), defined as the deviation of the performances from the mean of the population for each lactation and averaged over all three lactations. During the estimation of YDs, correction for herd (three herds), the effect of season of calving (four seasons), and the effect of the year of calving (8 years) was applied. Genetic effects were analyzed for yield deviation of milk yield, fat yield and content, and protein yield and content.

A set of test-day-traits contained 10,775 records for casein and lactose yields and contents as well as for SCS for the years 2001 to 2006 over the first three lactations (Table 1).

Data analysis

Allele and genotype frequencies were estimated based on the detected genotypes. The Chi-squared test for Hardy–Weinberg equilibrium (HWE) was applied to assess the deviations of the number of observed versus expected genotypes.

For the estimation of the effects of *GHR* F279Y genotypes on 305-day-traits (milk, fat, and protein yields, fat and protein contents), the following model was used:

$$Y_{ijk} = \mu + F279Y_i + S_j + e_{ijk} \qquad \text{(Model1)}$$

where Y_{ijk} is the yield deviation of 305-day-traits, μ is the overall mean of observations, $F279Y_i$ is the fixed effect of the *GHR* F279Y genotypes i (FF, FY, YY), S_j is the random effect of sire (j=265), and e_{ijk} is the residual error. A similar

Table 1 Characterization of milk production traits in the first three lactations in German Holstein Friesian cattle

Data	Traits	Lactation	No.	Mean	SD
305-day-traits	Milk yield (kg)	1	1,370	7,535.44	1,358.08
		2	1,325	8,495.57	1,570.90
		3	1,046	8,806.73	1,580.66
	Fat yield (kg)	1	1,370	298.24	46.61
		2	1,325	339.19	57.23
		3	1,046	355.84	57.97
	Protein yield (kg)	1	1,370	259.48	42.35
		2	1,325	290.56	48.52
		3	1,046	298.84	48.95
	Fat content (%)	1	1,370	4.01	0.50
		2	1,325	4.04	0.50
		3	1,046	4.08	0.49
	Protein content (%)	1	1,370	3.46	0.20
		2	1,325	3.44	0.21
		3	1,046	3.41	0.21
Test-day-traits	Casein yield (kg)	1	1,954	0.64	0.17
		2	4,388	0.73	0.23
		3	4,433	0.74	0.24
	Lactose yield (kg)	1	1,954	1.09	0.33
		2	4,388	1.26	0.47
		3	4,433	1.27	0.49
	Casein content (%)	1	1,954	2.87	0.28
		2	4,388	2.82	0.28
		3	4,433	2.80	0.31
	Lactose content (%)	1	1,954	4.78	0.19
		2	4,388	4.70	0.24
		3	4,433	4.64	0.26
	SCS (units)	1	1,954	3.09	1.64
		2	4,388	3.21	1.67
		3	4,433	3.50	1.83

allelic model was used to estimate the allele effects on the yield deviation.

To calculate the effect of *GHR* F279Y genotypes on the test-day-traits for casein and lactose yields and contents as well as SCS, a random animal model was used. The model included the fixed effect of the genotype of the cows, number of lactations, and the date of the test day, as well as a combination of herd, season, and year of calving as one variable. Four covariates of days in milk (DIM) were used to account for the shape of the lactation curve according to Ali and Schaeffer (1987). The test-day-model included the random effect of the sire and the animal. The age at first calving was included as a covariate. Sire and the cow itself were fitted as random effects to account for paternal half-sib relationships and the permanent environmental effects. The analysis was performed with Model 2:

$$
\begin{aligned}
\mathrm{Y}_{\mathrm{ijklmnop}} = \mu &+ \mathrm{F279Y}_{\mathrm{i}} + \mathrm{HSYC}_{\mathrm{j}} + \mathrm{L}_{\mathrm{k}} \\
&+ \mathrm{Date}_{\mathrm{l}} + \mathrm{b}_{\mathrm{m1}}(\mathrm{DIM}/\mathrm{c}) \\
&+ \mathrm{b}_{\mathrm{m2}}(\mathrm{DIM}/\mathrm{c})^2 + \mathrm{b}_{\mathrm{m3}}\log(\mathrm{c}/\mathrm{DIM}) \\
&+ \mathrm{b}_{\mathrm{m4}}[\log(\mathrm{c}/\mathrm{DIM})]^2 + \mathrm{g}_{\mathrm{n}}\mathrm{AFC} \\
&+ \mathrm{S}_{\mathrm{o}} + \mathrm{A}_{\mathrm{p}} + \mathrm{e}_{\mathrm{ijklmnop}} \qquad \text{(Model2)}
\end{aligned}
$$

where $\mathrm{Y}_{\mathrm{ijklmnop}}$ is the test-day-record of the trait, μ is the overall mean of observations, $\mathrm{F279Y}_{\mathrm{i}}$ is the fixed effect of the *GHR* F279Y genotypes (FF, FY, YY), $\mathrm{HSYC}_{\mathrm{j}}$ is the fixed combined effect of herd, season, and year of calving (j=1–59), L_{k} is the fixed effect of lactation (k=1–3), $\mathrm{Date}_{\mathrm{l}}$ is the fixed effect of the date of the test-day, b_{m1} to b_{m4} are regression coefficients associated with the fixed lactation function, DIM are the days in milk as a covariable, c is a constant set to 305, g_n is a regression coefficient associated with the age at first calving (AFC), S_o is the random effect of the sire, A_p is the random effect of the animal, and $e_{ijklmnop}$ is the residual error. A similar model was used to estimate the allele effects on the test-day-traits.

All models were analyzed using SAS PROC MIXED (SAS Institute Inc., 2008, version 9.1) with a spatial exponential covariance structure for repeated measurements ($\sigma^2 \exp\{-d_{ij}/\theta\}$, where d_{ij} is the Euclidean distance between the ith and jth observation). To account for multiple comparisons, Tukey–Kramer correction was applied (Kramer 1956).

Results

Genotype and allele frequencies

The minor allele was the tyrosine 279Y allele of the *GHR* gene with a frequency of 16.5%. The observed genotype frequencies of 69.1%, 28.8%, and 21% for FF (homozygous for the phenylalanine *GHR* variant), FY (heterozygous), and YY (homozygous for the tyrosine *GHR* variant) genotype classes, respectively, are consistent with the expectations of the HWE.

Genotype effects

The *GHR* F279Y genotypes showed highly significant effects ($p<0.0001$) on milk and lactose yield, as well as all content traits apart from lactose (Table 2). Homozygous FF compared to FY carriers had 414±88 kg less milk, which is consistent with 0.08±0.02 kg less lactose as osmotic active milk compound. Fat (0.13±0.03%), protein (0.10±0.01%), and casein contents (0.07±0.01%) were higher in cows of FF than FY genotypes. Protein and fat yields were also highest in heterozygous animals, but did not reach statistical significance at $p<0.05$. For fat as well as protein and casein contents, significant differences were not only found between FF and FY genotypes, but also between FY and YY genotype classes, which suggest additive genetic effects of the two *GHR* alleles (Fig. 1). However, because animals of YY genotype were rare (29 for 305-day-traits, 19 for test-day-traits), most test statistics were not strong enough to provide significance for differences between YY and other genotype classes (Table 2).

Allele substitution effects

Corresponding with genotype effects, the tyrosine (279Y) variant had highly significant ($p<0.0001$) positive effects on milk and lactose yields, and negative effects on fat, protein, and casein contents (Table 3). Replacement of the phenylalanine (279F) by the tyrosine (279Y) variant led to increased milk yield by 320±78 kg and lactose yield by 0.07±0.02 kg. The presence of the 279Y allele led to, on average, a reduction of the fat and protein contents by 0.12 and 0.09%, respectively. Albeit the protein and casein contents were reduced by the 279Y allele, the protein (3.68±2.40, $p=0.1310$) and casein yields (0.02±0.01 kg, $p=0.0169$) were increased.

Interestingly, the high-milk-yield 279Y allele was associated with a reduction of the SCS by 0.14±0.07 units ($p=0.0469$) (Table 3).

Discussion

The allele frequencies in the German Holstein cow population were very similar to other Holstein populations

Table 2 Differences among genotypes at the F279Y locus on milk production traits and somatic cell score (SCS) (least square mean [LSM], standard error [SE], and *p*-values)

Data	Traits	Genotype differences		
		FF-YY	FY-FF	FY-YY
305-day-traits	Milk yield (kg)	−126.25±276.75 (0.8917)	414.21±88.49 (<0.0001)	287.96±281.84 (0.5633)
	Fat yield (kg)	11.72±10.17 (0.4820)	6.51±3.27 (0.1144)	18.23±10.32 (0.1812)
	Protein yield (kg)	4.97±8.55 (0.8298)	5.87±2.73 (0.0801)	10.85±8.72 (0.4271)
	Fat content (%)	0.21±0.09 (0.0332)	−0.13±0.03 (<0.0001)	0.09±0.09 (0.5815)
	Protein content (%)	0.11±0.04 (0.0045)	−0.10±0.01 (<0.0001)	0.016±0.04 (0.8938)
Test-day-traits	Casein yield (kg)	−0.001±0.03 (0.9997)	0.03±0.01 (0.0133)	0.03±0.03 (0.6909)
	Lactose yield (kg)	−0.05±0.06 (0.7487)	0.08±0.02 (<0.0001)	0.04±0.06 (0.8179)
	Casein content (%)	0.11±0.04 (0.0063)	−0.07±0.01 (<0.0001)	0.04±0.04 (0.5575)
	Lactose content (%)	−0.04±0.04 (0.4735)	0.03±0.01 (0.0078)	−0.01±0.04 (0.9651)
	SCS (units)	0.12±0.26 (0.8861)	−0.16±0.08 (0.1010)	−0.04±0.26 (0.9877)

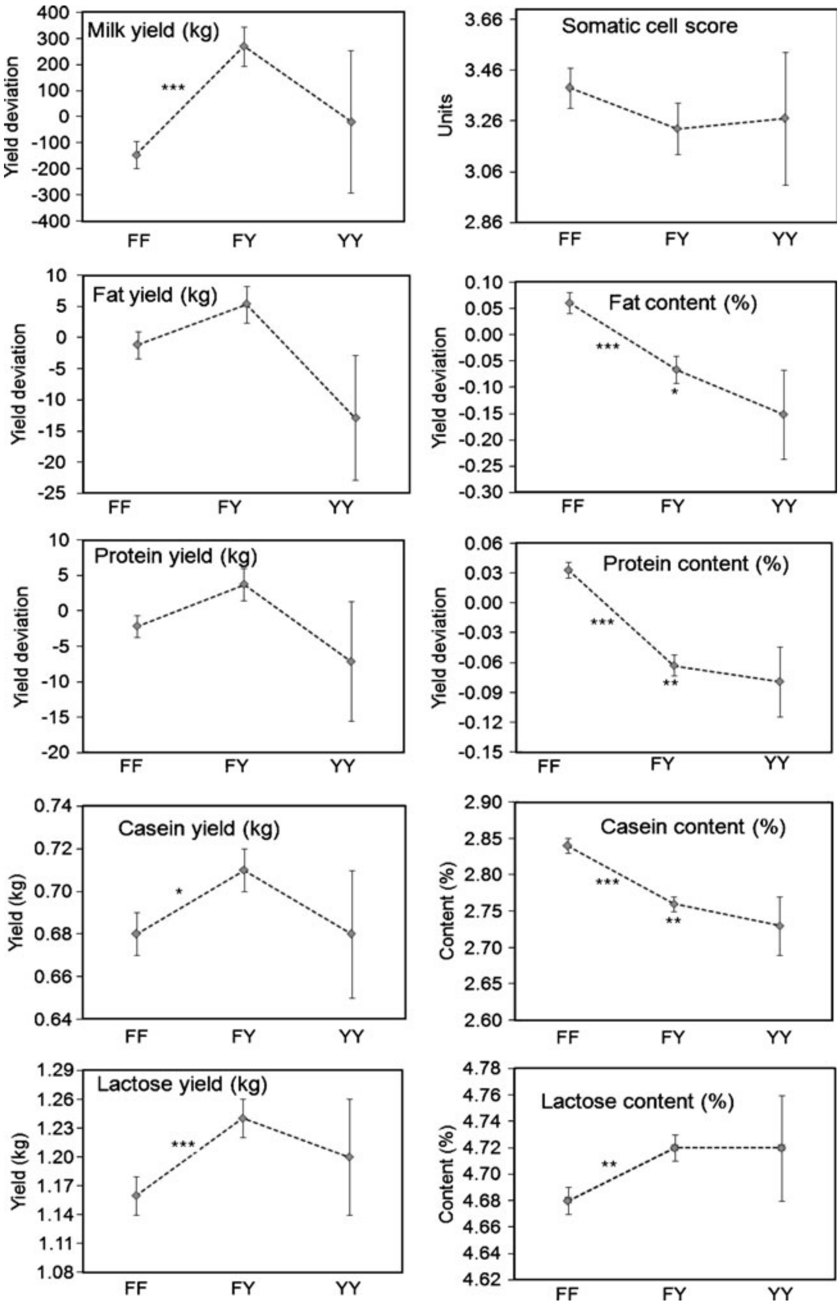

Fig. 1 Effect plots visualizing the impact of *GHR* F279Y variants on production traits based on the least square means (LSMs) and standard errors (SEs). The genotype effects are given for the 305-day-traits (milk yield, fat yield and content, protein yield and content) and the test-day-traits (lactose yield and content, casein yield and content, and somatic cell score [SCS]). For the 305-day-traits, the number of animals was: FF=946, FY=395, and YY=29. For the test-day-traits, the number of animals was: FF=716, FY=286, and YY=19. $^{\dagger}p<0.10$, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ for differences between genotypes

from the Netherlands, New Zealand (Blott et al. 2003), Greece (Oikonomou et al. 2009), and Ireland (Waters et al. 2011). So far, higher frequencies of homozygous carriers of the *GHR* phenylalanine variant (FF genotypes) were found in New Zealand Jersey cattle (81–89%) (Blott et al. 2003), while a lower FF genotype frequency was observed in Italian Holstein sires (51%) (Fontanesi et al. 2007).

As reported previously in other populations (Blott et al. 2003; Viitala et al. 2006), our study confirms the significant effects of *GHR* F279Y genotypes on milk yield as well as protein and fat content in a German Holstein cow population, with homozygous FF cows having the highest fat and protein contents when compared with other genotype groups.

In addition to previous findings, we found also significant effects of *GHR* F279Y genotypes on casein yields and contents, as well as lactose yield and content. The directions of allelic effects on casein correspond well with the effects on total milk protein content and yield, suggesting a direct effect of the analyzed genomic region on the major protein fraction in bovine milk.

Several studies have reported a highly positively correlation of lactose yield and content with milk yield traits (Welper and Freeman 1992; Stoop et al. 2007).

Table 3 Effects of the 279Y variant at the *GHR* locus on milk production traits and SCS

Data	Traits	279Y allele		
		α	SE	*p*-value
305-day-traits	Milk yield (kg)	320.00	77.98	<0.0001
	Fat yield (kg)	3.20	2.89	0.2683
	Protein yield (kg)	3.67	2.40	0.1310
	Fat content (%)	−0.12	0.02	<0.0001
	Protein content (%)	−0.09	0.01	<0.0001
Test-day-traits	Casein yield (kg)	0.02	0.01	0.0169
	Lactose yield (kg)	0.07	0.02	<0.0001
	Casein content (%)	−0.07	0.01	<0.0001
	Lactose content (%)	0.03	0.01	0.0020
	SCS (units)	−0.14	0.07	0.0469

Accordingly, the positive effect on milk yield was accompanied by a positive effect of the tyrosine variant on lactose yield and content.

Furthermore, our study provided significant evidence for positive effects of the high-milk-yield tyrosine variant (279Y) of the *GHR* gene on the reduction of the SCS by 0.14 units in the German Holstein population. These results confirm the tendencies reported by Gengler et al. (2008) and Waters et al. (2011). Therefore, the tyrosine allele could be useful in selection to improve resistance to mastitis. The results in the current study are also in line with the repeated mapping of QTL for SCS on chromosome 20 close to the *GHR* gene (Rodriguez-Zas et al. 2002; Ashwell et al. 2004; Ron et al. 2004; Casas and Snowder 2008).

It is interesting to note that, in the examined German Holstein cow population, the homozygous genotype FF with the lowest milk yield and highest fat and protein content occurred with the highest frequency, even though Holstein Friesians have been selected for high-milk-yield over the past several decades. This contradiction between genotype frequency, effect, and selection for high milk performance has also been recently pointed out by Waters et al. (2011). A possible explanation for this contradiction is that the Y allele might also be associated with a longer calving interval (Waters et al. 2011), which might have been selected against to a greater degree than for high milk yield.

The magnitude of allele effects on milk traits is higher in our cow population compared with other studies. While the tyrosine variant (279Y) had a strong positive allele substitution effect of 320 kg milk (305 d) in our German Holstein population, the same allele only led to 67 kg more milk in Dutch Holstein sires, 87 kg in New Zealand Holstein cows (Blott et al. 2003), and 74 kg in Irish Holstein Friesian cattle (Waters et al. 2011). This could be explained by different background gene effects that also contribute to milk production, but differ among the different populations.

As the direction of the allele effects are consistent across different breeds and populations, it is very likely that the F279Y mutation is the causative mutation for the observed allele effects, although the exact mechanism by which the F279Y amino acid change influences milk parameters is not yet clear. Therefore, it cannot be excluded that SNPs which are in close linkage disequilibrium to the F279Y locus or additional loci could be causal for the observed genetic effects on milk traits or modify the effect size. For example, among candidates in close neighborhood is the *prolactin receptor* gene (*PRLR*). *PRLR* gene variants have shown associations with fat and protein yields in Finnish Ayrshire dairy cattle (Viitala et al. 2006). Moreover, the interactions of the *GHR* gene with other genes on the same or other chromosomes can also contribute to the observed effects.

Conclusions

Our results confirm the significant association of the *growth hormone receptor* (*GHR*) F279Y polymorphism with milk yield as well as fat and protein contents in German Holstein cows. Furthermore, we provided new evidence for a significant association of this polymorphism with casein and lactose contents. We suggest differences in lactose production among genotypes as the driver for differences in milk yield and milk content traits. We also found that the high-milk-yield allele positively contributed to lowered somatic cell scores (SCSs). Therefore, the F279Y polymorphism of the cattle *GHR* gene seems to be a useful marker for milk production traits and, possibly, together with other traits, for selection to improve resistance against mastitis.

In the examined German Holstein population, the minor allele (279Y) was the allele with the strongest effects on high milk yield, despite selection for high lactation performance. This contradiction might be explained by the circumstance that the *GHR* gene is also affecting other traits, such as calving interval. Further studies will be necessary in order to analyze the effect of this polymorphism on reproductive and fitness traits in dairy cattle. To understand the genetic effects of the F279Y *GHR* polymorphism and the linked chromosomal region and to clarify the molecular origin of the trait variation, additional analyses are necessary, including re-sequencing of the linked genomic region.

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