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Mapping genes for resilient dairy cows by means of across-breed genome-wide association analysis

Franziska Keßler[1*†], Maximilian Zölch[1†], Robin Wellman[1] and Jörn Bennewitz[1]

Abstract

Background Indicator traits based on variance and autocorrelation of longitudinal data are increasingly used to measure resilience in animal breeding. While these traits show promising heritability and can be routinely collected, their genetic architecture remains poorly understood. We conducted GWAS for three resilience indicators across German Holstein ($n = 2{,}300$), Fleckvieh ($n = 2{,}330$), and Brown Swiss ($n = 1{,}073$) dairy cattle (*Bos Taurus*) populations. The indicators included variance (v_d) and autocorrelation (r_{Auto}) of deviations of observed from predicted daily milk yield and variance of relative daily milk yield (v_r). Additionally, we analysed a selection index combining these traits. Prior to GWAS, we examined population structure through multi-dimensional scaling (MDS) and LD patterns, revealing distinct genetic clusters for each breed and similar LD decay patterns.

Results The GWAS results confirmed the polygenic nature of resilience, with multiple genomic regions showing significant associations. Notable signals were detected on *BTA5* (v_r), *BTA14* (v_d), *BTA2* and *BTA8* (r_{Auto}) for single indicator traits. For selection index resilience, strong suggestive SNPs are located on *BTA4*, *BTA16*, *BTA21*, and *BTA27*. Detected regions overlapped with previously reported QTLs for performance, reproduction, longevity and health, providing new insights into the biological pathways underlying dairy cattle resilience.

Conclusions Our findings demonstrate that resilience indicators have a complex genetic architecture with both breed-specific and shared components, supporting their potential use in selective breeding programs while highlighting the importance of careful trait definition.

Keywords Resilience, Variance, Autocorrelation, Linkage Disequilibrium, GWAS, MDS, Dairy cattle

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Background

In a challenging environment with an increased incidence of external disturbances such as heat waves intensified by climate change [1], there is a growing need for performance-stable and healthy livestock. One option is to breed for resilience, i.e., for the ability of an individual to react to short-term disturbances and maintain or quickly restore its own homeostasis and performance level [2, 3].

Since directly measuring responses to each disturbance is impractical in commercial settings, indirect approaches using routinely collected longitudinal data have been developed. The most promising is the use of indicator traits to determine performance variability and recovery speed. Performance variability can be expressed by the fluctuation of daily milk yield. Therefore, the variance of deviations between observed and predicted daily milk yield (v_d) is calculated. The variance is small for cows with smooth lactation curves, but also for cows with low milk yield [2, 4, 5]. To addresses the influence of the milk production level, a second parameter is the variance of relative daily milk yield (v_r)[6]. This parameter is small for cows with smooth lactation curves that show a low decrease in milk yield during the lactation. The heritability for both variance-based indicator traits are moderate, in the range of 0.13 to 0.24 [4–6]. Furthermore, the genetic correlations with performance traits are desirable when the standardized v_r is used or v_d is corrected for the original performance level [5, 6]. Several studies have shown that resilient individuals have better values for health traits [5, 7, 8] or the productive lifetime [4, 9] than non-resilient cows. Recovery speed is captured by the autocorrelation (r_{Auto}) calculated from the deviations between observed and predicted daily milk yield of a cow over the time of one lactation. A resilient cow with fast recovery has a value for r_{Auto} near to 0 [2]. The heritability is low with an average of 0.05 across several studies and breeds, and genetic correlations with other traits were mostly desirable but rarely significant [5, 8, 10]. A selection index can combine different resilience indicators in an optimal way. Since the economic value of resilience is difficult to measure, it was not used to determine the weighting factors of the single indicator traits and alternative approaches were considered. Previous studies offer two options: On the one hand, the genetic correlation between resilience indicators and health and functional traits could be considered [11], on the other hand, the weighting factors could be optimized by maximizing the selection response in health traits when breeding for resilience [8]. The latter is used in the following.

While previous studies estimated heritabilities and genetic correlations [4–6], and discussed the power and accuracy of single resilience indicator traits [2, 12], deeper analysis of the genetic architecture are lacking. To our knowledge, there has been one GWAS of resilience indicators in dairy cows [13], pigs [14] and laying hens [15]. Their results indicate a polygenic nature of resilience, with many gene loci having a small effect. Chen et al. [13] detected a strong peak on *BTA14* for performance variability.

This study builds on this state of research and uses in-depth genomic analysis to analyze the genetic architecture and relationships to other traits. Therefore, the aim of this study was to assess the genetic architecture of several resilience indicator traits by GWAS in the three large German dairy cattle (*Bos Taurus*) breeds German Holstein (HF), German Fleckvieh (FV) and German Brown Swiss (BS) using imputed HD SNP genotypes. Since we performed an across-breed and a within-breed GWAS, we also studied the across- and within-breed LD pattern and the population structure. This provided us information on the genetic relationship between the three breeds and supports the interpretation of the GWAS results.

Methods

Data processing and evaluation as well as statistical analyses were performed in software R 4.2.1 [16]. Genotype preparation, phasing, imputation and population analysis were done by using PLINK 1.9 and PLINK 2.0 [17] and Beagle 5.4 [18, 19]. ASReml-R 4.1.0 [20] was used for univariate estimation of breeding values and GCTA 1.94.1 [21] for GWAS with de-regressed GEBVs as phenotypes.

Materials

The dataset consists of 5,703 dairy cows of the breeds German Holstein (HF, $n = 2{,}300$), German Fleckvieh (FV, $n = 2{,}330$) and German Brown Swiss (BS, $n = 1{,}073$), originating from 48 farms. The farms are members of the breeding organization Rinderunion Baden-Württemberg e.V. (Herbertingen, Germany) and work with automatic milking systems. The milking data, consisting of yield per milking and start time of milking, from the automatic milking systems were longitudinally recorded between October 2017 and April 2024 and were provided by the Landeskontrollverband Baden-Württemberg e.V. (Stuttgart, Germany).

Animals in our study were genotyped with 50 K SNP chips. For HF, the Eurogenomics-MD-Chip was used in several versions. The merging of the chips and the imputation of undetermined SNPs were done by Vereinigte Informationssysteme Tierhaltung w.V. (Verden, Germany). Genotyping of FV and BS was done by Landeskontrollverband Bayern (Munich, Germany) and Bayerische Landesanstalt für Landwirtschaft (Grub, Germany) using Illumina BovineSNP50v2 BeadChip or DAC-BS50 Illumina. For both breeds, we obtained a standardized data set over the different chips, whereby missing SNPs were called with the population mean. We

excluded SNPs on sex chromosomes, on undefined position, with minor allele frequency (MAF) < 0.03 or missing call rate > 0.01. The MAF threshold was stricter than in comparable studies [13, 22] in order to cause fewer false-positive results in the GWAS and was based on a study with a similar data set to our BS sample [23]. SNPs that are not included in the high-density reference panels were excluded, as they would be automatically removed during imputation. All genotypes were updated to the reference genome assembly ARS-UCD1.2 by manually replacing the existing coordinates with the updated ones [24]. SNPs, which are not listed in the ARS-UCD1.2, were excluded. This left 31,416 SNPs for HF, 34,238 SNPs for FV and 31,527 SNPs for BS.

A detailed overview of the size of the raw genotype and phenotype data and remaining data sets after filtering per breed can be found in the Supplementary (see Additional File 1).

Methods

Calculation of resilience indicator traits

Milk yields per milking were added up to daily milk yields, whereby the first milking was divided proportionally between the current and the previous day. Daily milk yields were filtered as follows. Days where the number of animals milked on the farm deviated by three standard deviations from the mean number of animals normally milked on the farm as well as the day before and after were removed for all animals on this farm. Furthermore, the day before and after an individual gap of an animal, meaning one or more days without available data, was removed. Lactations were considered from day 10 to day 305, and those with less than 50% coverage respectively 148 data points were excluded. For each lactation of each cow, a lactation curve was predicted using spline interpolation with *pspline* in R [25] with degrees of freedom set to 5 and data points weighted by the strength of assumed disturbances. Details are described in Keßler et al. [6].

We considered three resilience indicator traits. The variance of the deviations between observed and predicted absolute daily milk yield (v_d) was calculated as:

$$v_d\left(\mathbf{y}_{il}\right) = \frac{1}{n-1} * \sum_{t=10}^{n} \left(\left(\boldsymbol{y_{ilt}} - \widehat{\boldsymbol{y}}_{\boldsymbol{ilt}}\right) - \overline{\left(\boldsymbol{y_{il}} - \widehat{\boldsymbol{y}}_{\boldsymbol{il}}\right)} \right)^2$$

with $\boldsymbol{y}$ a n-vector with daily milk yields of a cow i in a certain lactation l, $\widehat{\mathbf{y}}$ the vector with interpolated daily milk yields and t the lactation day. The variance of relative daily milk yields (v_r) in considered lactation period was calculated as:

$$v_r\left(\mathbf{y}_{il}\right) = \frac{1}{n-1} * \sum_{t=10}^{n} \left(\left(\alpha_{ilt}\mathbf{y}_{ilt}\right) - \overline{\left(\alpha_{il}\mathbf{y}_{il}\right)} \right)^2$$

with $\boldsymbol{y}$ a n-vector with daily milk yields of a cow i in a certain lactation l and the scaling factor $\alpha_{il} = \frac{100}{\sum_{t=10}^{n} y_{ilt}}$ with t the lactation day. The two parameters were logarithmized to conform to the assumption of normal distribution according to previous analyses in Keßler et al. [6].

The autocorrelation of the deviations between observed and predicted absolute daily milk yield (r_{Auto}) was calculated as:

$$r_{Auto}\left(\mathbf{y}_{il}\right) = \frac{cov\left(\mathbf{y}_{il} - \widehat{\mathbf{y}}_{il}\right)}{var\left(\mathbf{y}_{il} - \widehat{\mathbf{y}}_{il}\right)}$$

and in detail:

$$r_{Auto}\left(\mathbf{y}_{il}\right) = \frac{\frac{1}{n-2} * \sum_{t=2}^{n} \left(\left(\left(\boldsymbol{y_{ilt}} - \widehat{\boldsymbol{y}}_{\boldsymbol{ilt}}\right) - \left(\boldsymbol{y_{il}} - \widehat{\boldsymbol{y}}_{\boldsymbol{il}}\right) \right) * \left(\left(\boldsymbol{y_{il,t-1}} - \widehat{\boldsymbol{y}}_{\boldsymbol{ilt}}\right) - \left(\boldsymbol{y_{il}} - \widehat{\boldsymbol{y}}_{\boldsymbol{il}}\right) \right) \right)}{\frac{1}{n-1} * \sum_{t=1}^{n} \left(\left(\boldsymbol{y_{ilt}} - \widehat{\boldsymbol{y}}_{\boldsymbol{ilt}}\right) - \left(\boldsymbol{y_{il}} - \widehat{\boldsymbol{y}}_{\boldsymbol{il}}\right) \right)^2}$$

Genetic analysis

The resilience indicators described above were genetically analyzed separately for each breed and two different lactation groups. The first one, labelled P for primiparous, included phenotypes from the first lactation. For the second one, named M for multiple lactations, we added information also from higher lactations of the cows in P as repeated measurements. Thus, a univariate analysis was performed for each of six groups: first lactation HF, all lactation HF, first lactation FV, all lactation FV, first lactation BS, all lactation BS. The animal model for the data sets with information about cows in the first lactation was:

$$y = Xb + Zu + e$$

with y vector of observations, u vector of additive genetic effects, e vector of residuals, and incidence matrices X and Z. The animal model for all lactations of the considered cows was:

$$y = Xb + Zu + Wpe + e$$

where pe is the vector of permanent environmental effects and W is the incidence matrix. The additive genetic effects u, the permanent environmental effects pe and the residual effects e were normally distributed with $u \sim N(0, G\sigma_u^2)$, $pe \sim N\left(0, I_{pe}\sigma_{pe}^2\right)$ and $e \sim N\left(0, I_e\sigma_e^2\right)$, whereby I are identity matrices. The genomic relationship matrix G was built according to VanRaden et al. [26]. The vector of fixed effects b comprises in each model age at first calving in month, herd-year-season effect and completeness of lactation data. In the second model the effect of the lactation separated in first and higher lactation was added. Season in herd-year-season was divided into spring from March to May, summer from June to August, autumn from September to November, and winter from December to February and completeness of lactation data was graded in ≥ 90%, 80%—< 90%, 70%—< 80%, 60%—< 70%, 50%—< 60%. In all analyses, effect levels with fewer than six animals are excluded. This left 1,370 HF cows for P and 1,538 HF cows for M, for FV 1,135 cows in P and 1,551 in M and for BS P includes data from 310 and M from 488 cows. For further analysis, we de-regressed the cow's additive genetic effects, i.e. their GEBV, by dividing the effects by their reliabilities and standardized them to a mean of 0 and a standard deviation of 1 within each group. We also calculated the heritability as the proportion of additive genetic variance of the total variance.

Additionally, a selection index (SI) was computed that combines the resilience indicators into a single trait. The selection index is a linear combination of the GEBVs of individual resilience indicators, with weights chosen to optimally describe overall resilience. Weighting factors were determined in Keßler et al. [8], by maximizing the selection response in health traits when selecting on resilience indicators based on the performance trait daily milk yield. The weighting factors were adopted from this study, which were estimated in the same data set [8]. The selection index was calculated as

$$SI\left(\mathbf{y}_i\right) = 0.65 * \widetilde{v}_d\left(\mathbf{y}_i\right) + 0.35 * \widetilde{v}_r\left(\mathbf{y}_i\right),$$

where $\widetilde{v}_d\left(\mathbf{y}_i\right)$ and $\widetilde{v}_r\left(\mathbf{y}_i\right)$ were GEBVs of the logarithmized, negated $v_d\left(\mathbf{y}_i\right)$ and $v_r\left(\mathbf{y}_i\right)$, for cow i. The selection index was calculated in both lactation groups, P and M, and all three breeds.

Imputation

For further analyses we imputed the 50 K genotypes to high-density genotypes. The following reference panels were used. For HF, we used data from 1,278 Australian Holsteins with 585,517 SNPs that were genotyped with the BovineHD Genotyping BeadChip [27]. High-density data from 3,439 FV cows and bulls including 629,028 SNPs genotyped with Illumina BovineHD Bead chip [28] and 192 BS individuals with 613,140 SNPs genotyped with Illumina Bovine-HD [23] were available. Similar to the 50 K genotype data, SNPs whose MAF was < 0.03, whose missing call rate was > 0.01 or which were found on sex chromosomes were removed. The positions of considered SNPs were updated to the reference genome ARS-UCD1.2 [24]. 522,726 SNPs in HF, 580,873 SNPs in FV and 503,971 SNPs in BS remained.

Reference panel data were phased using beagle 5.4 within each dataset. 50 K and high-density data of each breed were concorded with *conform-gt* and then imputed with beagle 5.4. According to [29], the effective population size Ne was set to 100. Apart from that, the default settings were used. SNPs with a dosage R-Squared < 0.75 are removed to maintain a sufficiently high imputation quality [19]. The final imputed data set contains 2,300 HF cows with 503,263 SNPs, 2,330 FV cows with 569,056 SNPs and 1,073 BS cows with 493,637 SNPs. For the across-breed population analysis, the imputed genotypes were merged with PLINK 1.9 [30], leaving 401,491 SNPs shared across all breeds.

Population analysis

Population analyses were done in PLINK 1.9 for MDS and PLINK 2.0 for LD analysis [17]. Genomic relationship between the breeds was studied with a MDS based on imputed genotypes, considering only SNPs that remained in all three breeds after all filtering steps described above. The LD was analysed across breeds and breed-specific, using the maximum number of available SNPs in the imputed genotype datasets of each breed, respectively the merged imputed dataset after all filtering steps. The LD was calculated as the r^2 [31]:

$$r^2 = \frac{\left(p_{A_1B_1} - p_{A_1}p_{B_1}\right)^2}{p_{A_1}p_{A_2}p_{B_1}p_{B_2}}$$

with p the allele frequency, A_1 and A_2 alleles on gene locus A and B_1 and B_2 alleles on gene locus B. The LD between pairs of SNPs that were a maximum of 1,000 SNPs or 3,000 kilobases apart was calculated.

Genome-wide association study

For each of the six groups defined above, a GWAS was performed for the resilience indicator traits and the selection index. We optimized the GWAS model by

minimizing the difference of the genomic inflation factor lambda λ_{GC} to 1 in each breed. λ_{GC} is calculated as the ratio between the median of the observed chi-squared test statistics and the expected median of 0.455 [32]. The value should be close to 1 or slightly above [22, 33]. We therefore decided for a mixed linear model based association analysis ($MLMA$) for HF, a $MLMA$ excluding the GRM of the chromosome where the SNP is located ($MLM-LOCO$) for BS and a $MLM-LOCO$ corrected for a fixed effect of the principal components calculated based on the whole genome ($\mathrm{MLM-LOCO}_{PCGenome}$) to account for population stratification for FV [21] (λ_{GC} of the selected GWAS are provided in the results, all λ_{GC} are provided in Additional File 2).

GWAS were performed using the following model:

$$y = \mu + Xb + Zu + e,$$

with y vector of de-regressed, standardized additive genetic effects of each animal derived from univariate analysis for each resilience indicator trait and the selection index, the population mean μ, fixed effects b with the incidence matrix X, including the reference allele coded with 0, 1 or 2, the vector of additive genetic effects u with $u \sim N(0, G\sigma_u^2)$ and G the genomic relationship matrix created according to Yang et al. [34], and the residual term e with $e \sim N(0, I_e\sigma_e^2)$. In $MLM-LOCO$ and $\mathrm{MLM-LOCO}_{PCGenome}$, G is calculated for each chromosome separately and leaves out the chromosome, where the SNP to be tested for association is located. The vector b includes the additive effect of the candidate SNP to be tested for association and for $\mathrm{MLM-LOCO}_{PCGenome}$ in FV a covariate of 20 principal components, which were calculated based on the whole genome with software GCTA [35]. For the calculation of GWAS in GCTA, the reference allele was specified in accordance with ARS-UCD1.2.

For across-breed evaluation, we pooled the p-values in data set P and data set M per resilience indicator using the package *poolr* in R [36]. We used the Fisher method, which is based on the chi^2-statistic:

$$X^2 = -2\sum_{i=1}^{k} \ln(p_i)$$

with K number of tests (three) and pi the *p*-values of the GWAS.

The results of the single GWAS and pooled GWAS are shown as Manhattan plots, whereby two significance thresholds were defined. Genome-wide significance was determined using Bonferroni correction with, with N number of SNPs, and a less stringent, suggestive level of significance was set to $p \leq \frac{0.05}{N}$. For SNPs showing significant association at the stringent significance level, the Cattle QTL Database release 53 [27] was used to search for QTL in the range from 25 kB up- and downstream.

Results

Heritabilities

Heritabilities were in the range of 0.1 to 0.15 for v_d. BS showed the highest h^2 with 0.23 (SE = 0.15) in P and 0.15 (SE = 0.07) in M. HF and FV were similar with 0.13 (SE = 0.05) and 0.12 (SE = 0.06) in P and 0.1 (SE = 0.03) and 0.13 (SE = 0.03) in M. Repeatability was 0.26 (SE = 0.02) in HF, 0.25 (SE = 0.03) in FV and 0.19 (SE = 0.05) in BS. For v_r FV showed the lowest h^2 with 0.04 (SE = 0.04) in P and 0.08 (SE = 0.03) in M, and BS the highest h^2 with 0.18 (SE = 0.15) in P and 0.2 (SE = 0.08) in M. HF ranged between them with 0.13 (SE = 0.04) in P and 0.15 (SE = 0.03) in M. Repeatabilities were higher than for v_d, with 0.32 (SE = 0.02) in HF, 0.35 (SE = 0.03) in FV and 0.4 (SE = 0.05) in BS. Estimates of h^2 for r_{Auto} were rarely significant and low with values between 0.03 in FV and 0.12 in BS. Repeatability's were 0.17 (SE = 0.02) for HF, 0.2 (SE = 0.03) for FV and 0.27 (SE = 0.06) for BS. Reliabilities for GEBVs were smaller in P data sets than in M data sets with an average difference of 0.1. The highest values in M were estimated in HF (0.37) and BS (0.33) for v_r and the lowest in HF (0.15) and FV (0.14). Reliabilities of v_d in M ranged around 0.29. Genetic correlation between the resilience indicator traits were analysed in a previous study and can be seen in Keßler et al. [6].

Population analyses

The MDS (Fig. 1) shows three distinct clusters, each corresponding to one breed. The distances between the clusters are similar.

The r^2 of the LD decreases with increasing marker distance (Fig. 2). This can be observed across all breeds as well as within breeds. The strongest decline in LD can be observed in FV, the lowest in BS. The LD within the breeds is similar, which means that the across-breed analysis showed comparable results.

Genome-wide association study

Table 1 shows the values of λ_{GC} for $MLMA$ in HF, $MLM-LOCO$ in BS and $MLM-LOCO_{PCGenome}$ in FV. Based on these values, we decided on the respective method for the GWAS. Our aim was to detect significant SNPs as accurately as possible without the inflation of false-positive results, therefore λ_{GC} should be close to 1 or slightly above. Since the other methods considered led to a strong inflation of false-positive results (λ_{GC} >1.5) in HF [see Additional File 2], we decided to use the conservative MLMA approach.

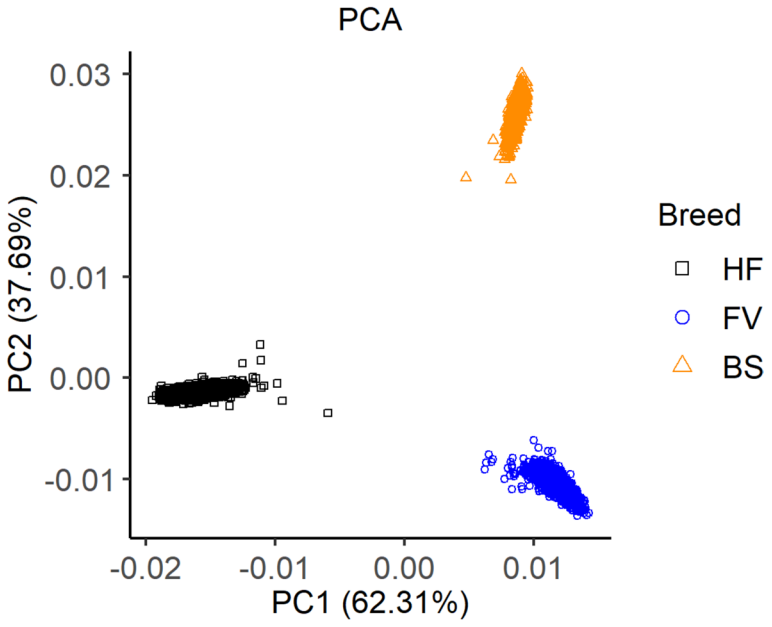

Fig. 1 Genomic relationship between the breeds HF, FV and BS represented in a MDS-plot

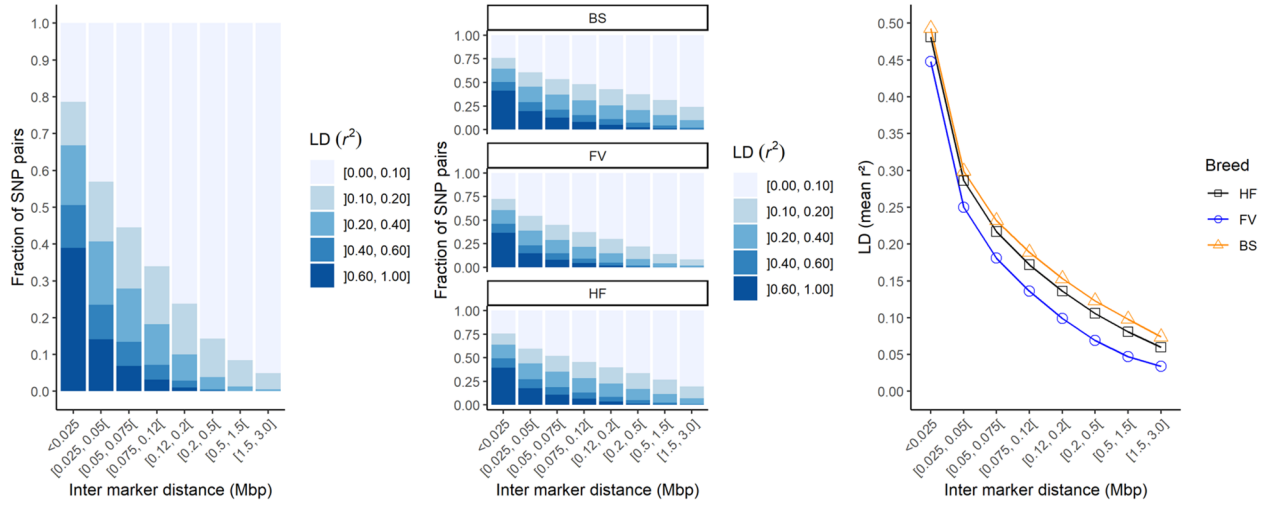

Fig. 2 The decay of mean r.^{2} as a function of physical distance for breeds HF, FV and BS analyzed jointly (left), separated by breed (middle) and compared between the breeds (right)

Table 1 Genomic inflation factors λ_{GC} for GWAS in German Holstein, German Fleckvieh, German Brown Swiss and pooled data sets of first lactation (P) and first and higher lactations (M) for resilience indicator traits

German Holstein		German Fleckvieh		German Brown Swiss		Across-Breed	
P	M	P	M	P	M	P	M
0.811	0.805	1.197	1.374	1.140	1.242	1.081	1.253
0.811	0.810	1.155	1.373	1.153	1.191	1.084	1.251
0.842	0.823	1.117	1.353	1.103	1.164	1.048	1.233
0.822	0.807	1.185	1.374	1.142	1.198	1.099	1.235

v_d– variance of deviations between observed and predicted absolute daily milk yield

v_r– variance of relative daily milk yield

r_{Auto}– autocorrelation of deviations between observed and predicted absolute daily milk yield

SI– selection index resilience composed of single resilience indicators

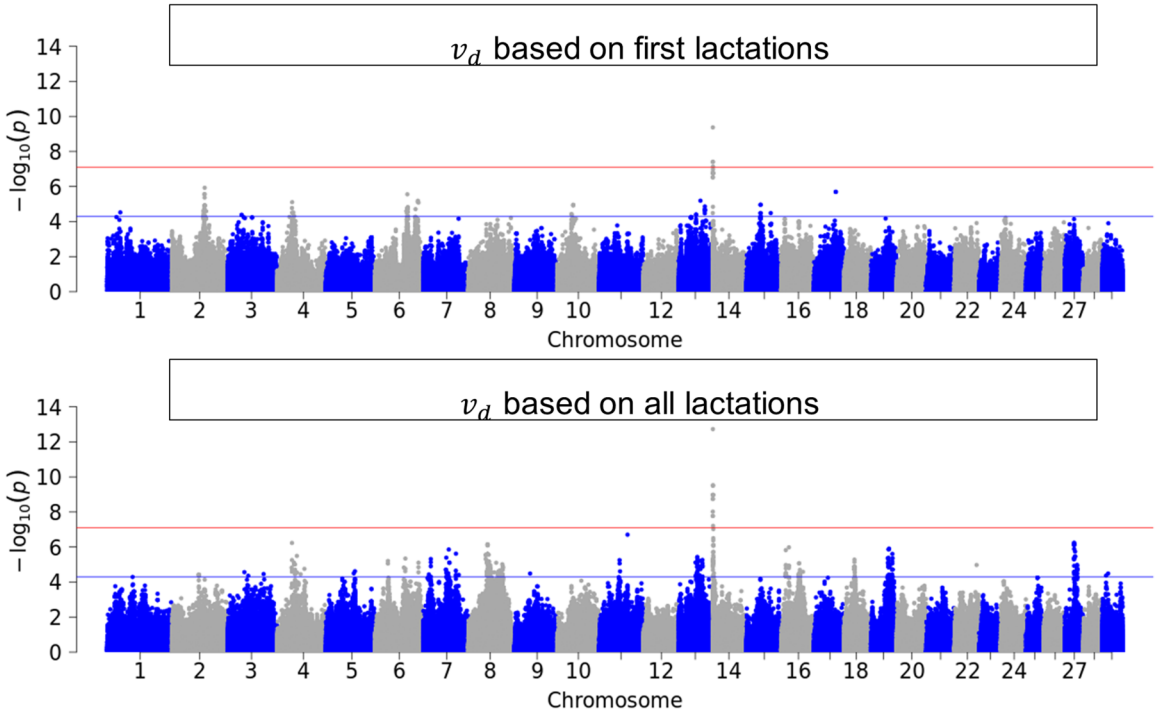

Fig. 3 Manhattan-Plot of pooled p-values from single GWAS in the three breeds

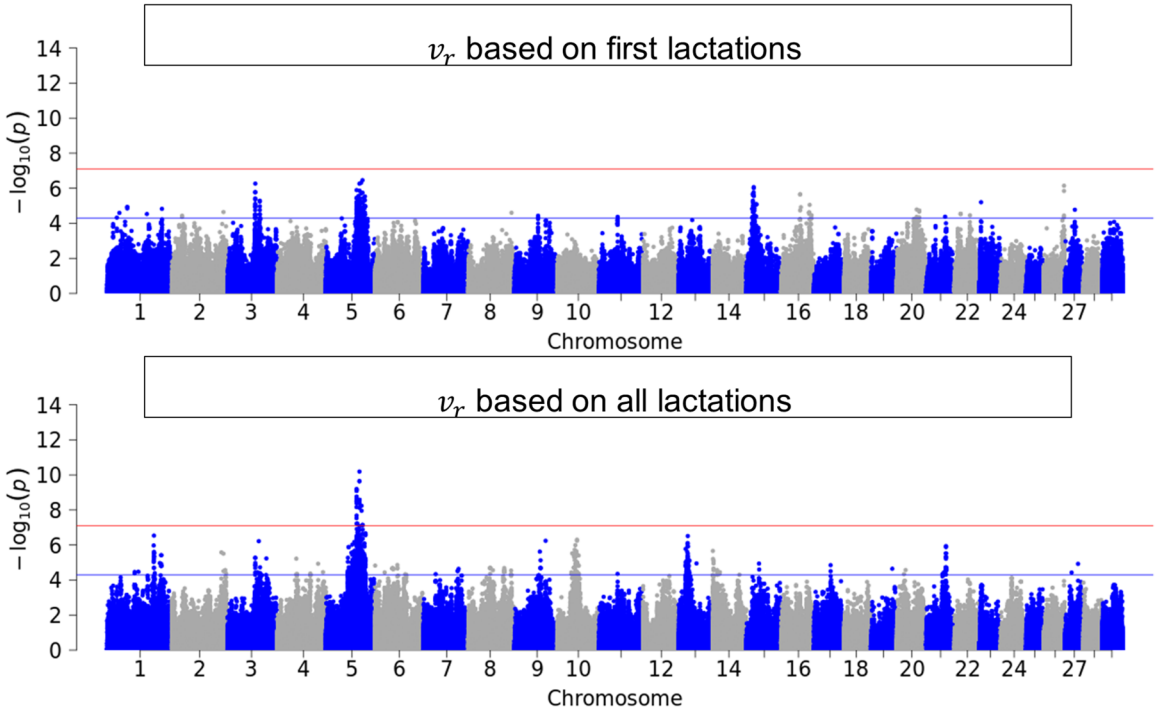

Fig. 4 Manhattan-Plot of pooled p-values from single GWAS in the three breeds German Holstein, German Fleckvieh and German Brown Swiss for the resilience indicator trait v_r, which is the variance of relative daily milk yield in first lactation (top) and first and higher lactations (bottom)

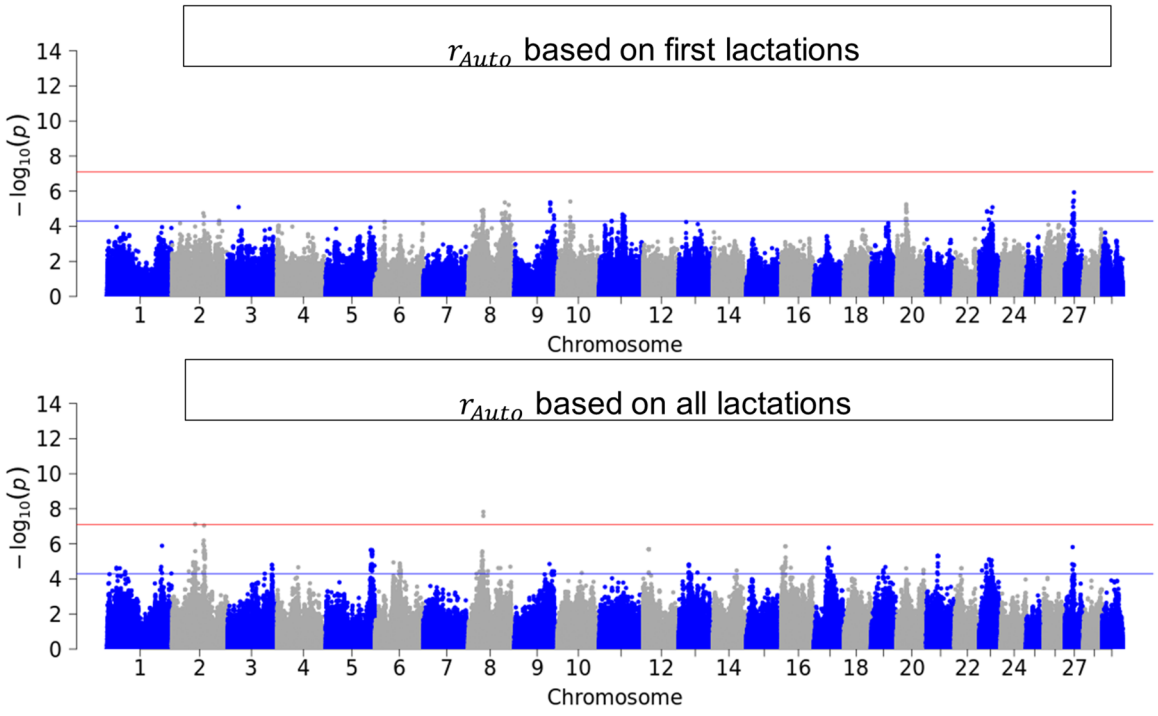

Fig. 5 Manhattan-Plot of pooled p-values from single GWAS in the three breeds German Holstein, German Fleckvieh and German Brown Swiss for resilience indicator trait r_{Auto}, which is the autocorrelation in first lactation (top) and first and higher lactations (bottom)

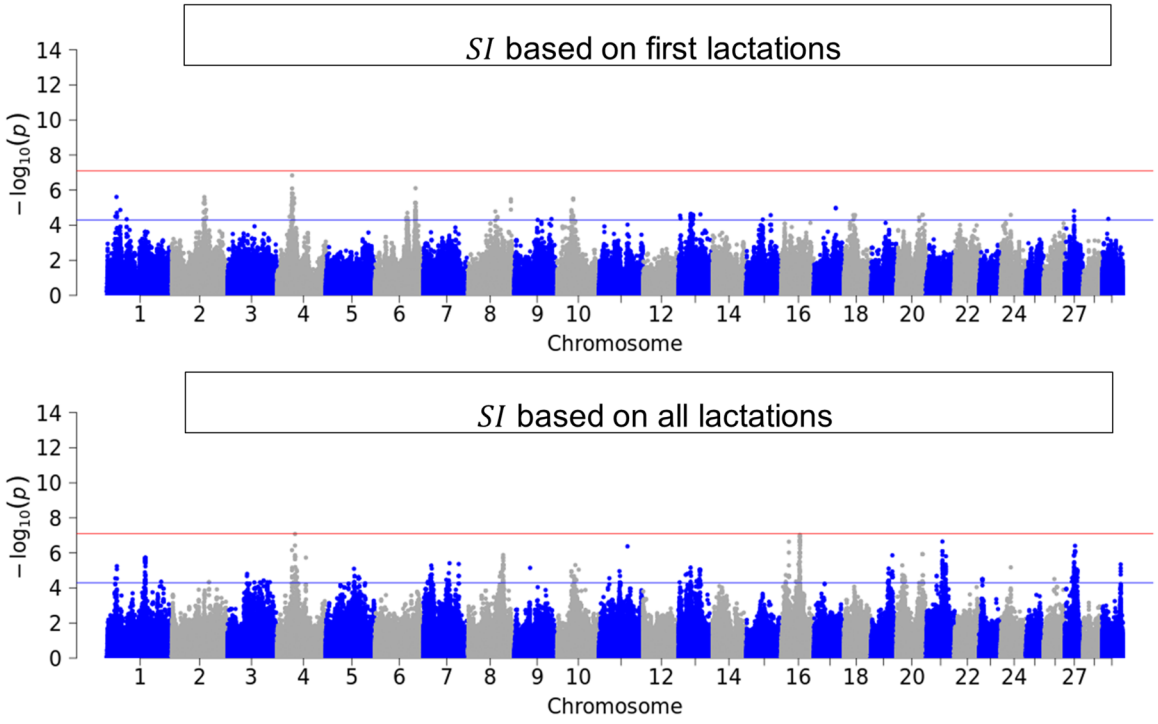

Fig. 6 Manhattan-Plot of pooled p-values from single GWAS in the three breeds German Holstein, German Fleckvieh and German Brown Swiss for the resilience selection index SI computed from resilience indicator traits calculated from daily milk yield in first lactation (top) and first and higher lactations (bottom)

Table 2 Number of significant SNPs for resilience indicator traits based on suggestive ($p < 5 * 10^{-5}$) and genomewide ($p \leq \frac{0.05}{Numberof SNPs}$) significance threshold for first lactation of (P) and for first and higher lactations of cows (M)

Significance of the SNP	v_d		v_r		r_{Auto}		SI	
	P	M	P	M	P	M	P	M
Genome-wide	4	13	0	38	0	3	0	0
Suggestive	93	379	214	716	84	234	196	441

v_d – variance of deviations between observed and predicted absolute daily milk yield

v_r – variance of relative daily milk yield

r_{Auto} – autocorrelation of deviations between observed and predicted absolute daily milk yield

SI – selection index resilience composed of single resilience indicators

Figures 3, 4, 5 and 6 illustrate the results of GWAS for each resilience indicator trait after pooling p-values across breeds for first and for all available lactations. Genome-wide significant SNPs were found for v_d in the first lactation and for all single resilience indicator traits in the data set with all available lactations. SNPs that reached the suggestive significance threshold were found for all traits and groups, also for SI. These SNPs were distributed throughout the genome, with the variance-based indicators showing more significant SNPs. For the sake of completeness, the Manhattan plots can be viewed separately by breed in the Supplementary (see Additional File 4).

Number of suggestive and genome-wide significant SNPs can be seen in Table 2, while the name of the genome-wide significant SNPs and their base pair positions can be viewed in the Supplementary [see Additional File 3]. According to previous studies [e.g. [37, 38], most correlated QTL potentially influence milk yield, reproductive performance, body condition or longevity. Furthermore, QTL associated with udder, metabolic and claw health as well as immunological parameters were found (see Additional File 3 for an overview).

Discussion

General discussion

In Germany, there are hardly any studies that compare and, above all, combine the genomic data from HF, FV and BS, likely also due to the division of breeding value estimation between different organisations. We matched the three data sets, which enabled us to increase our data basis and thus our power. In addition, we can draw conclusions about all three breeds, whereas analysing the BS alone would have been critical due to the small number of individuals. Multibreed analyses lead to a higher accuracy of estimates for breeds with small reference populations [39], like BS, and also allow estimates for crossbred animals, for example when estimating genomic breeding values [40]. For purebred, large reference populations a single breed analysis would be more advantageous [41], which is why we did a two-step analysis: run the mixed-linear model and the genome-wide association study for each breed in the first step, and combine the results in a second step.

Heritabilities in our data set were in the range with previous studies with Holstein Friesian [4, 5, 10]. Higher heritabilities with higher standard errors in BS could be due to the limited number of individuals and farms, which is why fewer estimations of variance components per trait were significant. The inclusion of all lactations of the individuals compared to only the first lactation tended to explain a higher proportion of the total variance, captured by the permanent environment effect.

Population analysis

The breeds studied are genetically different, which was as expected and previously reported for the same breeds in Switzerland [42]. The number of SNPs considered was > 300,000 and the decrease in LD with increasing distance between SNPs was similar in all breeds. Thus, all three breeds could be analysed and discussed jointly in the GWAS [43]. For the subsequent search for QTL associated with the genome-wide significant SNPs for resilience indicators, a window had to be defined. This is limited by the useful LD between SNP and QTL, which was described by de Roos et al. [40] and Sargolzaei et al. [44] with r^2 >0.3. In our study, we observed a mean r^2 >0.4 in a distance of up to 25 kb. In addition, as this was an across-breed study, we were more stringent with the window size.

Genome-wide association study

The inflation factor λ_{GC} was close to 1 or slightly above for most of the data sets (Table 1) and only for FV first and higher lactations above 1.3. This suggests that the p-values of the GWAS might be slightly inflated for the latter, but not for the remaining data sets. A conservative approach with λ_{GC} <1 was chosen for HF, as the other methods tested resulted in highly inflated results. The pooled, across-breed analysis showed that resilience indicators are polygenic traits influenced by many gene loci. This was shown by the high number of suggestive significant SNPs distributed across the entire genome and the small number of genome-wide significant SNPs. Similar results were reported by previous studies about resilience indicators in laying hens [15], pigs [14] and dairy cows [13]. Chen et al. [13] reported a strong peak

on *BTA14*, whereby the milk yield level had a significant causal effect on the performance variability over several lactations. QTL that are closely adjacent to our genome-wide significant SNPs simultaneously influence several traits of performance, fertility and health [45]. The inclusion of repeated measurements per individual led to a higher power of the GWAS. In contrast to the data set of the first lactation, genome-wide significant SNPs were found for r_{Auto} and v_r in the data set including all lactations. For v_d, there was an increase in the number of genome-wide significant SNPs when all lactations were considered rather than just the first. However, they did not share their genetic backgrounds, i.e. different genome regions influence different resilience indicators. This was previously described in Chen et al. [13] for traits similar to our v_d and r_{Auto} and were expected from us, because previous analysis of genetic correlation between single resilience indicator traits showed only less to moderate correlation, which can be interpreted as different traits[6].

Common genetic background of resilience and other traits

Genomic regions that have a strong effect on our resilience indicators influence milk yield, milk ingredients, health and fertility traits. A significant genetic effect on the resilience indicator v_r occurs from *BTA5*, in the region of the genes *CACNG2*, *EIF3D*, *IFT27* and *PVALB*, which influence milk yield, and next to *5s_RNA*, which influences the amount of milk fat [37]. With *7SK*, r_{Auto} on *BTA8* also has a milk yield-regulating gene in the analysed window. A significant effect of v_d were detected on *BTA14* in a region in which pleiotropic genes have an effect on milk quantity and ingredients, especially milk fat acids [46]. Known genes are for example *DGAT1*, *ARHGAP39*, *bta-mir-2308*, *LRRC24*, *CPSF1*, *RECQL4*, *PLEC*, *PPP1R16A*, *MFSD3*, *GPT*, *KIFC2*, *CYHR1*, *TONSL* or *FOXH1* [37, 38, 45]. A strong antagonism between the SNP effects on the amount of milk fat and the amount of milk and milk protein yield is known for *PLEC* and *PPP1R16A* [38]. An unbalanced fat-to-protein ratio can be a sign of a negative energy balance and metabolic diseases [47, 48], which is why animals with a strong genetic antagonism may be less resilient. In addition, this shared genetic background of performance and resilience influences the stability of milk and milk fat yield under heat stress [49] and the overall profitability of a dairy cow [50], which was also described in Poppe et al. [51].

Jiang et al. [38] reported a QTL next to *MRPS35* on *BTA5*, which is in a high LD with genome-wide significant SNPs for v_r, influencing pregnancy and conception rate, and Cochran et al. [45] a QTL on *CPSF1*, influencing conception rate and v_d. Galliou et al. [52] detected on *BTA2* in a genomic region with an effect on r_{Auto}, QTL for heifer reproduction traits that may also affect reproduction in cows. Health indicator traits like the somatic cell score for mastitis [45] or the concentration of beta-hydroxybutyrat (BHB) in milk for ketosis [53] are affected by genomic regions on *BTA14*, also influencing v_d. This is confirmed by a study with the EBV of mastitis, showing a significant influence in the same genomic area [54].

The selection index SI was not influenced by genome-wide significant SNPs, but strong suggestive peaks emerged on *BTA4*, *BTA16*, *BTA21* and *BTA27*. QTL on these chromosomes influence milk yield and especially milk fat, longevity and reproduction ability. This underlines the polygenic characteristics of resilience.

Breeding for resilience

Breeding for resilience to increase recovery speed and reduce performance variability reduces sensitivity to external disturbances. The current approach of using indicator traits calculated on the basis of longitudinal data seems promising: moderate heritabilities and desirable correlations with other traits have been shown in previous studies [4–7, 10, 55]. The combination of different indicator traits is suitable for integration into practical breeding [11]. For example, the weighting factors can be determined by maximizing selection response in functional and health traits. In this way, performance and functionality are combined and mediated. Because of favorable genetic correlations, breeders could use this EBV in addition to the total merit index to more easily identify sires that combine yield, longevity and health [8].

There are two main points in favor of breeding for resilience: First, no extra data collection is necessary for breeding value estimation [2]. Second, in some breeds, little or no health traits are recorded; breeding for resilience could improve animal health [6, 8]. A homogeneous, healthy herd with stable performance is easier to manage and more profitable [2, 51]. In the future, the suitability of other statistical parameters as resilience indicator traits [12] and new longitudinal measured phenotypes (e.g. activity data, omics data) will be studied [7, 56].

Conclusion

Our study demonstrated clear genetic differentiation between German populations of HF, FV, and BS breeds, while showing similar patterns of LD decay across breeds. Significant heritabilities for resilience indicators were estimated across all three breeds. GWAS results revealed the polygenic nature of resilience, with significant SNPs distributed across multiple BTA. Genome-wide significant SNPs for v_d were found on *BTA14*, for v_r on *BTA5* and for r_{Auto} on *BTA2* and BTA8, which indicate a different genetic background. A selection index combined of v_d and v_r was mainly influenced by SNPs on *BTA4*, BTA*16*, BTA*21* and BTA*27*. We found strong links

with QTL affecting production, health and fertility, which confirms the complex genetic architecture of resilience. Notably, analyzing resilience across multiple lactations increased statistical power and revealed additional significant associations compared to first-lactation analysis.

Abbreviations

BS	German Brown Swiss
FV	German Fleckvieh
HF	German Holstein
P	First lactation
M	First and higher lactation
r_{Auto}	Resilience indicator trait (autocorrelation of deviations between observed and predicted absolute daily milk yield)
SI	Selection index resilience composed of single resilience indicators
v_d	Resilience indicator trait (variance of deviations between observed and predicted absolute daily milk yield)
v_r	Resilience indicator trait (variance of relative daily milk yield)

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Authors' contributions

FK, MZ, RW and JB conceptualised and planned the methodology. FK, MZ and RW analysed and validated the data. FK and MZ contextualised and discussed the results and wrote the manuscript. RW and JB reviewed the manuscript. JB supervised and administered the project and its funding. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available upon request and after signing a material transfer agreement with the cattle breeding organization Rinderunion Baden-Württemberg e.V. (Herbertingen, Germany). GWAS summary statistics can be shared without any restrictions. For data requests, please contact JB.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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