Phenotypic, genetic, and single nucleotide polymorphism marker associations between calf diseases and subsequent performance and disease occurrences of first-lactation German Holstein cows

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ABSTRACT

A total of 31,396 females born from 2010 to 2013 in 43 large-scale Holstein-Friesian herds were phenotyped for calf and cow disease traits using a veterinarian diagnosis key. Calf diseases were general disease status (cGDS), calf diarrhea (cDIA), and calf respiratory disease (cRD) recorded from birth to 2 mo of age. Incidences were 0.48 for cGDS, 0.28 for cRD, and 0.21 for cDIA. Cow disease trait recording focused on the early period directly after calving in first parity, including the interval from 10 d before calving to 200 d in lactation. For cows, at least one entry for the respective disease implied a score = 1 (sick); otherwise, score = 0 (healthy). Corresponding cow diseases were first-lactation general disease status (fIGDS), first-lactation diarrhea (fIDIA), and first-lactation respiratory disease (fIRD). Additional cow disease categories included mastitis (fIMAST), claw disorders (fICLAW), female fertility disorders (fIFF), and metabolic disorders (fIMET). A further cow trait category considered first-lactation test-day production traits from official test-days 1 and 2 after calving. The genotype data set included 41,256 single nucleotide polymorphisms (SNP) from 9,388 females with phenotypes. Linear and generalized linear mixed models with a logit link-function were applied to Gaussian and categorical cow traits, respectively, considering the calf disease as a fixed effect. Most of the calf diseases were not significantly associated with the occurrence of any cow disease. By trend, increasing risks for the occurrence of cow diseases were observed for healthy calves, indicating mechanisms of disease resistance with aging. Also by trend, occurrence of calf diseases was associated with decreasing milk, protein, and fat yields. Univariate linear and threshold animal models were used to estimate heritabilities and breeding values (EBV) for all calf and cow traits. Heritabilities for cGDS and cRD were 0.06 and 0.07 for cDIA. Ge-

netic correlations among all traits were estimated using linear-linear animal models in a series of bivariate runs. The genetic correlation between cDIA and cRD was 0.29. Apart from the genetic correlation between fIRD with cGDS (−0.38), EBV correlations and genetic correlations between calf diseases with all cow traits were close to zero. Genome-wide association studies were applied to estimate SNP effects for cRD and cDIA, and for the corresponding traits observed in cows (fIRD and fIDIA). Different significant SNP markers contributed to cDIA and fIDIA, or to cRD and fIRD. The average correlation coefficient between cRD and fIRD considering SNP effects from all chromosomes was 0.01, and between cDIA and fIDIA was −0.04. In conclusion, calf diseases are not appropriate early predictors for cow traits during the early lactation stage in parity 1.

Key words: calf and cow disease, genetic parameter, genetic and genomic associations

INTRODUCTION

As reviewed by Egger-Danner et al. (2015), a variety of recent quantitative genetic studies have focused on the estimation of genetic (co)variance components for cow health traits, with a focus on mastitis, claw disorders, metabolism, and female fertility. Especially in the phase of a natural negative energy balance during the first third of lactation, disease incidences were quite large (Gernand et al., 2012). For most of the disease traits recorded during the early lactation period, low heritabilities and antagonistic genetic relationships with productivity were identified. Nevertheless, in deterministic predictions (König et al., 2005), a sustainable selection response for cow health after calving was only generated through direct selection strategies instead of using health indicators; for example, functional conformation traits.

In the era of genomic selection, large cow training sets combining phenotypes with high-throughput genomic SNP marker data allow implementation of selection strategies for novel functional traits (Buch et al., 2012). A second major advantage of genomic selection is the

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substantial reduction of generation intervals (Schaeffer, 2006). In such a perspective, traits measured early in life (e.g., calf traits) may be valuable early predictors for subsequent health or cow productivity.

The most important disease problems observed in calves in the past decades in North America (Curtis et al., 1988) and central Europe (Perez et al., 1990) include respiratory infections and different kinds of diarrhea. Despite optimization of farm management, including calf feeding strategies and improvements of calf husbandry systems, both disease categories still have high incidence rates. The importance of both diseases was shown based on a random herd sampling in the Norwegian Red population (Gulliksen et al., 2009a,b), based on a farmer survey in Austria (Klein-Jöbstl et al., 2015), and when referring to official calf mortality statistics in the United States and Asia (Cho and Yoon, 2014). Especially in the Holstein breed (e.g., Becher et al., 2004), moderate to high incidences were identified for respiratory infections and diarrhea.

Presence of diarrhea or respiratory diseases in calves affects the performance and productivity of the animal later in life. In most cases, occurrence of a calf disease increases the probability of heifer health disorders (e.g., Sivula et al., 1996). Warnick et al. (1994) indicated that calf respiratory disease was phenotypically associated with an increased occurrence of dystocia at first calving. Rossini (2004) studied phenotypic associations between calf respiratory and digestive diseases with age at first calving and first-lactation production traits. Nonsignificant effects were identified for 305-d milk and fat yields, but protein yield moderately decreased by 0.05 kg/d. Also, age at first calving was higher for calves with multiple occurrences of respiratory disease. In contrast, Mousa et al. (2015) identified negative correlations between calf scours and age at first calving. Bünger et al. (1979) reported reduced DM feed intake in lactating dairy cows due to infections during the calfhoo d stage. Reduced feed intake causes negative energy balance with associated health problems (e.g., Collard et al., 2000). In a similar context, Beam et al. (2015) focused on calf growth rates and starter feed intake, and identified positive associations with performance traits and BW in mature cows.

Phenotypic relationships revealed that calf diseases mostly appeared in clusters. This means that, for example, a calf being susceptible to digestive infections also showed symptoms for a respiratory disease. Rossini (2004) reported that occurrence of calfhoo d digestive disease was associated with a 2-fold increase in the probability of occurrence of calf respiratory disease. Lundborg et al. (2003) confirmed the positive relationships between calf diarrhea and calf respiratory disease. In a study conducted in New York State (Henderson et

al., 2011), the residual correlation between calf respiratory and bloat disease was positive and that between respiratory and umbilical disease slightly negative.

So far, only a few studies have estimated quantitative genetic parameters for diseases in calves of dairy or dual-purpose breeds. In the study by Henderson et al. (2011), heritabilities for bloat, respiratory, and umbilical diseases were 0.040, 0.095, and 0.139, respectively. Fuerst-Waltl et al. (2010) estimated genetic parameters for diseases in Austrian dual-purpose Fleckvieh heifer calves: heritability was 0.027 for liability to diarrhea and 0.039 for liability to respiratory diseases. Based on the Norwegian health data recording system and using records from 250,212 Norwegian Red calves, the heritability for respiratory disease on the underlying liability scale was 0.05 (Heringstad et al., 2008). Given the low heritability combined with a low incidence rate (only 0.7% of the calves had a veterinary treatment for respiratory disease within the first 180 d of age), Heringstad et al. (2008) saw limited possibilities for genetic improvement. Nevertheless, the same authors pointed to the accurate genetic predictions of sires for respiratory disease resistance. With regard to genetic associations among calf traits, genetic correlations differed substantially from phenotypic correlations. For example, in the study by Henderson et al. (2011), the phenotypic correlation between calf bloat disease with respiratory disease was close to zero, but the genetic correlation between the same traits was quite high (0.62).

Given a data set of genotyped females, application of genome-wide association studies (GWAS) allows detection of important SNP markers contributing to the phenotypic health trait expression. Pimentel et al. (2011) suggested utilization of specific SNP to improve simultaneously selection response for antagonistically related production and fertility traits. Until now, GWAS have focused on cow health; that is, addressing classical health disorders (e.g., van der Spek et al., 2015), specific diseases with low incidences (displaced abomasum, Biffani et al., 2014), infectious diseases (e.g., Bermingham et al., 2014), or immune responses (Thompson-Crispi et al., 2014). To our knowledge and with regard to GWAS in calves, the size of SNP marker effects was only estimated for calf birth weight (Cole et al., 2014).

The objective of the present study was to infer relationships between calf diseases and cow production and health traits from the early lactation period in first parity on the phenotypic, quantitative genetic, and genomic scales. The objective implies for (1) the application of linear and generalized linear mixed model analyses for cow traits considering the calf disease as a fixed effect, (2) the estimation of genetic correlations

between calf and cow traits using the pedigree relationship matrix and animal models, and (3) the determination of SNP marker effects for calf and cow diseases based on GWAS.

MATERIALS AND METHODS

Data

Phenotypes. Health data recording was implemented in the framework of the dairy cattle test-herd system of northeast Germany, including the federal states of Mecklenburg-Westpommern and Berlin-Brandenburg. Dairy cattle farmers and veterinarians used electronically recording systems, which were based on the diagnosis key as developed by Feucker and Staufienbiel (2003). This diagnosis key was also considered when developing the International Committee for Animal Recording (ICAR) guidelines for recording, evaluation, and genetic improvement of health traits (Stock et al., 2013). An explanation for this hierarchical disease entry system is given by Gernand et al. (2012) for the major cow disease categories claw disorders, mastitis, female fertility, and metabolism. We considered in total 31,396 female calves from 43 herds born in the years 2010, 2011, 2012, and 2013. All calves had a calving date and at least their first official test-day record from 2012 to 2015. The female calves born in the 43 herds represented a female pool of possible replacements, and were raised in the same farms until first lactation. Ages at first calving of the cows ranged from 20 to 39 mo.

The 3 trait categories included (a) calf disease traits, (b) first-lactation disease traits, and (c) first-lactation test-day production traits. Diseases were defined as binary traits without considering repeated measurements. For the recording of calf diseases, we defined a time window from birth to the age of 2 mo, and for cow diseases, the interval from 10 d before calving up to lactation d 200 (a 210-d period). At least one entry for the respective disease implied a score = 1 (sick); otherwise, score = 0 (healthy). The DIM at test-day 1 ranged from 5 to 50 d, with an average value of 20.78 d. Hence, the minimal period for a cow considered in the present study included 15 d (10 d before up to 5 d after calving). Only a small percentage of cows (1.11%) with a calving date, but no first test-day, was excluded. The calf disease traits were (1) general calf disease status (**cGDS**), (2) calf diarrhea (**cDIA**), and (3) calf respiratory disease (**cRD**). For cGDS, the calf received the score = 0 when no disease entry was assigned in the disease database. All forms of calf scours and the recorded phenotype “diarrhea” from digestive imbalances were considered when defining cDIA. In detail, and according to the diagnosis key, the following

diseases contributed to cDIA: diseases of the intestine, rotavirus infection, *Escherichia coli* infection, salmonellosis, coccidiosis, and cryptosporidiosis. With regard to cRD, the following respiratory diseases were considered: diseases of nasal cavity and paranasal sinuses, diseases of the bronchial tubes and lungs, and bovine respiratory syncytial virus.

The cow disease traits within the 210-d time window were (1) first-lactation general disease status (**fGDS**), (2) first-lactation diarrhea (**fDIA**), and (3) first-lactation respiratory disease (**fRD**). In addition to the traits included in cDIA, fDIA considered diarrhea symptoms due to diseases of the reticulum and the abomasum. Following the disease categorization by Gernand et al. (2012), further cow diseases in the present study were (4) first-lactation mastitis (**fMAST**), including clinical and subclinical mastitis, (5) first-lactation claw disorders (**fCLAW**), including purulent and nonpurulent claw disorders, (6) first-lactation female fertility disorders (**fFF**), including the sub-categories “uterus” (puerperal disorders, retained placenta, endometritis) and “ovary” (silent estrus, ovarian cysts, corpus luteum persistent), and (7) first-lactation metabolic disorders (**fMET**), including ketosis, fatty liver syndrome, adiposity, and excessive loss of weight. The incidence rates for diseases of female calves (diseased female calves in relation to 31,396 female calves) and of cows (diseased cows in relation to 31,396 cows) for the defined periods are given in Table 1.

With regard to the first-lactation test-day production traits, we focused on the measurements from the official test-days 1 and 2 after calving, including (1) milk yield (**MY_1**, **MY_2**), (2) fat percentage (**FP_1**, **FP_2**), (3) protein percentage (**PP_1**, **PP_2**), (4) fat yield (**FY_1**, **FY_2**), (5) protein yield (**PY_1**, **PY_2**), and (6) the fat-to-protein ratio (**FPR_1**, **FPR_2**) as an indicator for energy balance. For the calf disease-cow disease trait, and for the calf disease-cow test-day 1 trait association studies, all data sets included 31,396 animals. Because of dairy cow disposals after test-day 1, the data set for test-day 2 observations included 30,360 cows. The DIM at test-day 2 ranged from 27 to 105 d, with an average value of 52.92 d.

Genotypes. Of the 31,396 animals with phenotypes, 9,401 individuals were genotyped. Genotyping was performed using the Illumina Bovine 50K SNP BeadChip V2 (applied to 3,192 animals; Illumina Inc., San Diego, CA), and with the Illumina Bovine Eurogenomics 10K low-density chip (applied to 6,209 animals). The low-density genotypes were imputed by the project partner Vereinigte Informationssysteme Tierhaltung (Verden, Germany) to the 50K panel applying the algorithm by Segelke et al. (2012), resulting in 45,613 SNP for all animals. Post-imputation SNP quality checks identified

13 animals with almost identical SNP genotypes (>95% congruency). These animals were eliminated from the ongoing analyses. In total, 362 SNP with minor allele frequency <0.01 and 3,995 SNP showing a significant ($P < 10^{-5}$) deviation from Hardy-Weinberg equilibrium were discarded. All SNP had a genotype call rate larger than 95%. The final SNP data set included 41,256 SNP from 9,388 animals. For the genotyped animals, the disease incidence was 29.0% for cRD and 25.5% for cDIA, and 1.13 and 3.77% for fIRD and fDIA, respectively.

Statistical Models

Phenotypic Effect of Calf Diseases on First-Lactation Cow Traits. Generalized linear mixed models (GLMM) with a logit link function were applied to test the effect of binary calf diseases on first-lactation binary cow diseases, and to estimate least squares means for the probability of disease occurrence in cows. For this purpose, the Glimmix procedure in SAS (version 9.4, SAS Institute Inc., Cary, NC) was used. Detailed theoretical background for the calculation of least squares means in GLMM is provided by Wolfinger and O'Connell (1993). The statistical model [1] was defined as follows:

$$\text{logit}(\pi_{rstuv}) = \log[\pi_{rstuv}/(1 - \pi_{rstuv})] = \varphi + \text{Herd}_r + \text{CYear}_s + \text{CSeason}_t + \text{AFC}_u + \text{CD}_v, \quad [1]$$

where π_{rstuv} = probability of occurrence for the first-lactation cow disease; φ = overall mean effect; Herd_r = fixed herd effect (43 herds); CYear_s = fixed effect of calving year (4 years, 2012–2015); CSeason_t = fixed effect of calving season (3 mo per season); AFC_u = fixed effect of age at first calving (3 classes); and CD_v = fixed

effect of the calf disease (healthy or sick). Significance of fixed effects was determined based on Wald type III tests.

Test-day production traits followed a Gaussian distribution. Hence, linear mixed models (lm-function in R; R Core Team, 2013) were applied to investigate the effect of calf diseases on first-lactation production traits, and to calculate least squares means. The statistical model [2] was

$$y_{rstuv} = \varphi + \text{Herd}_r + \text{CYear}_s + \text{CSeason}_t + \text{AFC}_u + \text{CD}_v + e_{rstuv}, \quad [2]$$

where y_{rstuv} represents the observations for the test-day traits, and e_{rstuv} is the random error term. Other effects were as specified for model [1].

Genetic Associations Among Calf Diseases and Their Relationships with First-Lactation Cow Traits. According to the 3 overall trait categories—calf diseases, first-lactation diseases, and first-lactation production traits—genetic analyses considered 3 different univariate statistical models. For binary calf diseases, the GLMM (model [3]) was

$$\text{logit}(\pi_{rstu}) = \log[\pi_{rstu}/(1 - \pi_{rstu})] = \varphi + \text{Herd}_r + \text{BYear}_s + \text{BMonth}_t + \text{AG}_u, \quad [3]$$

where π_{rstu} = probability of occurrence for the calf disease; φ = overall mean effect; Herd_r = fixed herd effect (43 herds); BYear_s = fixed effect of birth year (4 years, 2010–2013); BMonth_t = fixed effect of birth month (12 mo); and AG_u = random additive-genetic effect.

For binary first-lactation cow diseases, the GLMM (model [4]) was

Table 1. Incidences of disease traits recorded in calves and first-lactation German Holstein cows

Trait category	Healthy (no.)	Diseased (no.)	Incidence (%)
Calf health traits ¹			
cGDS	16,429	14,967	47.67
cDIA	24,670	6,726	21.42
cRD	22,491	8,905	28.36
First-lactation health traits ²			
fIGDS	9,499	21,897	69.74
fDIA	30,035	1,361	4.33
fIRD	31,123	273	0.87
fIMAST	24,880	6,516	20.75
fICLAW	24,520	6,876	21.90
fIFF	19,106	12,290	39.15
fIMET	30,890	506	1.61

¹cGDS = general calf disease status, cDIA = calf diarrhea, cRD = calf respiratory disease.

²fIGDS = first-lactation general disease status, fIRD = first lactation respiratory disease, fDIA = first-lactation diarrhea, fIFF = first-lactation female fertility disorders, fICLAW = first-lactation claw disorders, fIMAST = first-lactation mastitis, fIMET = first-lactation metabolic disorders.

$$\text{logit}(\pi_{rstuv}) = \log[\pi_{rstuv}/(1 - \pi_{rstuv})] = \varphi + \text{Herd}_r + \text{CYear}_s + \text{CSeason}_t + \text{AFC}_u + \text{AG}_v, \quad [4]$$

with effects as specified in models [1] and [3].

For Gaussian-distributed first-lactation test-day traits, the linear model [5] was

$$y_{rstuv} = \varphi + \text{Herd}_r + \text{CYear}_s + \text{CSeason}_t + \text{AFC}_u + \text{AG}_v + e_{rstuv}, \quad [5]$$

with effects as specified in models [2] and [3].

Heritabilities and genetic variances were obtained from univariate animal models. Regarding the logit models [3] and [4], calculation of heritabilities followed the procedure described by Southey et al. (2003):

$$h^2 = \frac{\sigma_a^2}{\sigma_a^2 + \left(\frac{\pi^2}{3}\right)},$$

and the genetic (co)variance structure for models [3], [4] and [5] was

$$\text{var} \begin{bmatrix} \mathbf{u} \\ \mathbf{e} \end{bmatrix} = \begin{bmatrix} \sigma_a^2 \mathbf{A}_u & 0 \\ 0 & \sigma_e^2 \mathbf{I}_n \end{bmatrix},$$

where $\mathbf{u}$ = vector of additive genetic effects; $\mathbf{e}$ = vector of random residual effects; σ_a^2 and σ_e^2 are the variances for additive genetic and residual effects, respectively; $\mathbf{A}_u$ is an additive genetic (co)variance matrix for cows and sires (animal model); and $\mathbf{I}_n$ is an identity matrix for n observations.

For the estimation of variance components, heritabilities, and genetic values, the 3 univariate models [3], [4] and [5] were applied, using the average information (AI)-REML algorithm as implemented in the DMU software package (Madsen and Jensen, 2013). Genetic associations among calf diseases and between calf diseases and first-lactation cow traits were inferred using correlations between EBV. For this strategy, we considered the most influential 242 sires with more than 30 daughters. For the 1,115 sires, the average number of daughters with phenotypes per sire was 28.16, and 284 females had an unknown sire. Additionally, we calculated genetic correlations among all calf traits and for all calf-cow trait combinations, using a series of bivariate linear-linear models. Such a strategy implies utilization of models [3] and [4] as linear models instead of GLMM definitions with a logit link function. According to Vinson and Kliever (1976), genetic correlations

from linear-linear and from linear-threshold models are expected to be the same, but in some cases (especially for disease traits with low incidences), linear-threshold models failed to converge.

GWAS. Estimation of SNP effects for the 2 calf traits (cRD and cDIA) and for the corresponding traits observed in first-lactation cows (fIRD and fDIA) was carried out using a GWAS approach, and applying the software package GCTA (Yang et al., 2011). In matrix notation, the following single SNP threshold model was defined [6]:

$$\mathbf{l} = \mathbf{Xb} + \mathbf{Wa} + \mathbf{Zu} + \mathbf{e}, \quad [6]$$

where $\mathbf{l}$ was a vector of unobserved liabilities; $\mathbf{b}$ was the vector of the fixed effects (herd, birth year, and birth month for cRD and cDIA; herd, calving year, calving season, and age at first calving for fIRD and fDIA), $\mathbf{X}$ was an incidence matrix for the fixed effects; $\mathbf{a}$ was the vector for the additive allele substitution effects of the candidate SNP to be tested for the association; $\mathbf{W}$ was the design matrix for SNP genotypes coded as 0, 1, or 2; $\mathbf{u}$ was the vector for additive polygenic effects (random effect captured by the genomic relationship matrix) with the corresponding incidence matrix $\mathbf{Z}$; and $\mathbf{e}$ was the vector of random residual effects. The genomic relationship matrix considered all SNP except the chromosome with the candidate SNP (software package LOCO, Yang et al., 2014). As suggested by Yang et al. (2014), exclusion of the respective chromosomes was done to avoid double counting. P -values $\leq 5 \times 10^{-5}$ were used to identify significant associations between single SNP with calf and cow diseases. Such a threshold was used in previous GWAS for production and functional traits in dairy cows based on 50K SNP chip genotype data (e.g., Minozzi et al., 2013; Dadousis et al., 2016). Decision for the chosen threshold additionally based on the false discovery rate (**FDR**), being the product of the number of SNP markers (41,256) multiplied by the significance level (0.00005), in relation to the number of detected significant markers. For example, for fIRD, 12 significant SNP were detected, implying $\text{FDR} = 0.17$. According to van der Spek et al. (2015), $\text{FDR} < 0.20$ is an acceptable value for the chosen significance threshold.

RESULTS AND DISCUSSION

Calf-Cow Trait Associations on the Phenotypic Scale

Incidences of the calf diseases by birth month (number of diseased calves in relation to all calves born in

the same month and considering the following period of 2 mo) are shown in Figure 1. Incidences were larger for calves born in the late autumn, early spring, and winter seasons compared with the summer season. Calf disease incidence peaks were observed for calves born in January and February 2010, 2011, and 2013, and in April 2012. An insight into historical meteorological data (Brügemann et al., 2013) indicated extremely high ambient temperature-humidity indices (>60) for those winter months. High air moisture in winter calf indoor housing systems is identified as a major determinant for the occurrence of cRD (e.g., Gulliksen et al., 2009b). A further increase of pathogen virulence in indoor production systems in autumn and winter seasons can be caused by the combination of high humidity with high concentrations of dust (e.g., Cobb et al., 2014). Interestingly, during the peak incidence periods for cRD, a simultaneous increase of cDIA was observed in the current study (Figure 1). Such associations between these most important calf diseases have been shown in physiological experiments (Howard et al., 1989).

Effect of Calf Diseases on Cow Diseases. Most of the calf diseases were not significantly associated with the occurrence of any cow disease ($P > 0.05$) in the 210-d period around calving (Table 2, results from model [1]). For some calf-cow disease trait associations, we identified an increasing risk for the occurrence of cow diseases for healthy calves. This effect was highly significant ($P \leq 0.001$) for the effect of cGDS and cDIA

on flGDS, and was significant ($P \leq 0.01$) for the effect of both calf traits on flMAST. A comprehensive literature review by Van der Fels-Klerx et al. (2002) addressed the associations between respiratory diseases early in life with mortality and reproduction up to first calving. In this regard, most researchers identified detrimental cRD effects; for example, a 2.4-fold increase in death risk between 90 and 900 d of age for heifers with pneumonia treatments during the first 3 mo of their life (Waltner-Toews et al., 1986). Svensson et al. (2006) reported increased risks for getting ill during the rearing period for calves with diarrhea or respiratory problems. Few studies have focused on the effects of calf diseases on the occurrence of diseases in milking cows. Hultgren and Svensson (2009) identified a higher risk of clinical mastitis for females with severe diarrhea between 3 and 7 mo compared with healthy calves. However, they could not explain the reduced clinical mastitis incidence rates for mild cases of calf diarrhea. Assumptions address acquired immunity or the development of disease resistances with age (Hara et al., 2012). Colditz et al. (1996) reported fewest parasite infections in adult ruminants and referred to an improved immunity status. Adams and Templeton (1998) extended this concept of disease resistance, involving immune and nonimmune mechanisms. Those explanations might support the nonsignificant associations between the same diseases in calves and cows; that is, the nonsignificant effects of cDIA on flDIA and of cRD on flRD (Table 2). König

Figure 1. Calf disease incidences (solid black line = general calf disease status, dashed black line = calf respiratory disease, dotted gray line = calf diarrhea) by date of birth.

Table 2. Differences of least squares means (Diff. LSM) for the probability of the occurrence of different first-lactation cow diseases compared with solutions for healthy calves minus diseased calves

Cow disease ¹	Calf disease ²								
	cGDS			cDIA			cRD		
	Diff. LSM	P-value	Odds ratio	Diff. LSM	P-value	Odds ratio	Diff. LSM	P-value	Odds ratio
fIGDS	0.045	***	1.21	0.044	***	1.20	0.014	NS	1.06
fIDIA	0.001	NS	1.13	0.001	NS	1.07	0.001	*	1.25
fIRD	0.000	NS	1.39	0.000	NS	1.33	0.000	NS	1.12
fIMAST	0.007	**	1.11	0.012	***	1.18	0.001	NS	1.01
fICLAW	0.000	NS	1.01	0.001	NS	1.03	0.002	NS	1.02
fIFF	0.001	NS	1.06	0.001	*	1.10	0.001	NS	1.02
fIMET	0.000	NS	1.12	0.000	NS	1.01	0.000	NS	1.05

¹fIGDS = first-lactation general disease status, fIRD = first-lactation respiratory disease, fIDIA = first-lactation diarrhea, fIFF = first-lactation female fertility disorders, fICLAW = first-lactation claw disorders, fIMAST = first-lactation mastitis, fIMET = first-lactation metabolic disorders.

²cGDS = general calf disease status, cDIA = calf diarrhea, cRD = calf respiratory disease.

*** $P \leq 0.001$; ** $P \leq 0.01$; * $P \leq 0.05$.

et al. (2005) identified decreasing incidence of the claw disorder digital dermatitis with increasing parity. In addition to the development of disease resistance, they assumed effects of selection. In contrast, Santin et al. (2008) and Faber et al. (2002) found a lower prevalence for *Cryptosporidium* and *Eimeria* infections in young females compared with adult cows.

Effect of Calf Diseases on Cow Production Traits. Occurrence of calf diseases was associated with decreased milk, protein, and fat yields at the first 2 official test-days after calving in parity 1. Corresponding least squares means from model [2] are listed in Table 3 for the effect of cGDS, in Table 4 for the effect of cRD, and in Table 5 for the effect of cDIA. However, most of the least squares means differences for the comparison

“healthy versus diseased calves” were not significantly different ($P > 0.05$). Most obvious effects were observed for milk yield; for example, highly significant ($P < 0.001$) lower MY_2 for calves with cRD (Table 4).

Because of the naturally antagonistic relationships between milk volume and the content traits fat percentage and protein percentage, only marginal differences were identified for both calf groups (sick and healthy) with regard to FY_1, FY_2, PY_1, and PY_2. Past studies on the associations between calf disease and cow productivity (e.g., Hatch et al., 1974; Britney et al., 1984) identified nonsignificant differences for milk yield between groups (disease/no disease). In contrast, in more recent studies, milk production was higher for healthy versus cDIA calves (Svensson and Hultgren,

Table 3. Least squares means (LSM) for test-day production traits of first-lactation cows in dependency of their general calf disease status (healthy or diseased calf)

Production trait ¹	Healthy calf		Diseased calf		Difference of LSM	P-value
	LSM	SE	LSM	SE		
MY_1	29.126	0.304	29.034	0.306	0.091	NS
MY_2	32.938	0.259	32.698	0.261	0.241	**
FP_1	4.404	0.035	4.418	0.036	-0.014	NS
FP_2	3.774	0.025	3.783	0.026	-0.009	NS
PP_1	3.231	0.015	3.232	0.015	-0.001	NS
PP_2	3.073	0.011	3.078	0.011	-0.005	NS
FY_1	1.264	0.013	1.258	0.013	0.006	NS
FY_2	1.237	0.011	1.226	0.011	0.011	**
PY_1	0.928	0.009	0.926	0.009	0.003	NS
PY_2	1.008	0.008	0.999	0.008	0.009	**
FPR_1	1.371	0.011	1.367	0.011	0.004	NS
FPR_2	1.234	0.008	1.233	0.009	0.000	NS

¹MY = milk yield, FP = fat percentage, PP = protein percentage, FY = fat yield, PY = protein yield, FPR = fat-to-protein ratio; _1 and _2 indicate observations from the first and second test-days after calving, respectively.

** $P \leq 0.01$.

Table 4. Least squares means (LSM) for test-day production traits of first-lactation cows in dependency of their calf respiratory disease status (healthy or diseased calf)

Production trait ¹	Healthy calf		Diseased calf		Difference of LSM	P-value
	LSM	SE	LSM	SE		
MY_1	29.159	0.302	28.913	0.309	0.246	*
MY_2	32.924	0.258	32.630	0.263	0.295	***
FP_1	4.405	0.035	4.415	0.036	-0.010	NS
FP_2	3.766	0.025	3.784	0.026	-0.018	*
PP_1	3.231	0.015	3.233	0.015	-0.002	NS
PP_2	3.073	0.011	3.077	0.011	-0.004	NS
FY_1	1.265	0.013	1.254	0.013	0.011	**
FY_2	1.237	0.011	1.222	0.011	0.015	***
PY_1	0.929	0.009	0.922	0.009	0.007	**
PY_2	1.007	0.008	0.997	0.008	0.010	***
FPR_1	1.371	0.010	1.367	0.011	0.003	NS
FPR_2	1.235	0.008	1.231	0.009	0.004	NS

¹MY = milk yield, FP = fat percentage, PP = protein percentage, FY = fat yield, PY = protein yield, FPR = fat-to-protein ratio; _1 and _2 indicate observations from the first and second test-days after calving, respectively.

*** $P \leq 0.001$; ** $P \leq 0.01$; * $P \leq 0.05$.

2008). Modern dairy cows have been selected for increasing productivity for decades. Al-Kanaan (2016) hypothesized an effect of intensive selection on estimates for covariances and genetic correlations between functional and production traits over a 30-yr time frame.

For FPR (health/energy efficiency indicator), nonsignificant ($P > 0.05$) differences of least squares means were observed, with different trends for different calf disease traits (Table 3). A large FPR indicates metabolic disorders such as ketosis, but as found for FPR, occurrence of FPR-related fMET was independent of calf disease status (Table 2). Bergk and Swalve (2011) identified an intermediate optimum for FPR, whereas

extremely high or low FPR increased the risk for involuntary cow culling early in lactation.

Calf–Cow Trait Associations on the Quantitative Genetic Scale

Genetic Parameters for Calf Diseases. We applied univariate threshold animal models and bivariate linear-linear models, and all models converged. Due to the large data set combined with a high average number of offspring per sire, standard errors for heritabilities and genetic correlations were small to moderate. Theoretically, results from sire threshold models are more reliable compared with results from animal threshold

Table 5. Least squares means (LSM) for test-day production traits of first-lactation cows in dependency of their calf diarrhea disease status (healthy or diseased calf)

Production trait ¹	Healthy calf		Diseased calf		Difference of LSM	P-value
	LSM	SE	LSM	SE		
MY_1	29.105	0.302	29.010	0.313	0.095	NS
MY_2	32.873	0.257	32.679	0.267	0.195	*
FP_1	4.410	0.035	4.423	0.036	-0.013	NS
FP_2	3.775	0.025	3.798	0.026	-0.023	**
PP_1	3.231	0.015	3.234	0.016	-0.002	NS
PP_2	3.075	0.011	3.080	0.011	-0.005	NS
FY_1	1.261	0.013	1.263	0.014	-0.002	NS
FY_2	1.233	0.011	1.233	0.011	0.000	NS
PY_1	0.928	0.009	0.926	0.009	0.002	NS
PY_2	1.005	0.008	1.001	0.008	0.004	NS
FPR_1	1.369	0.010	1.372	0.011	-0.003	NS
FPR_2	1.232	0.008	1.239	0.009	-0.006	*

¹MY = milk yield, FP = fat percentage, PP = protein percentage, FY = fat yield, PY = protein yield, FPR = fat-to-protein ratio; _1 and _2 indicate observations from the first and second test-days after calving, respectively.

** $P \leq 0.01$; * $P \leq 0.05$.

Table 6. Heritabilities with corresponding SE (diagonal), genetic correlations with corresponding SE (above diagonal), and correlations among EBV considering 242 sires with ≥ 30 daughters (below diagonal) for the calf disease traits general disease status (cGDS), diarrhea (cDIA), and respiratory disease (cRD)

	cGDS	cDIA	cRD
cGDS	0.06 ± 0.01	0.63 ± 0.07	0.78 ± 0.05
cDIA	0.48	0.06 ± 0.01	0.29 ± 0.09
cRD	0.71	0.13	0.07 ± 0.01

models because of the “extreme data category problem.” This problem might occur when all observations within a level of an effect represent a “1” or a “0,” resulting in possible convergence problems (e.g., Hoeschele and Tier, 1995).

Heritabilities for calf diseases were 0.06 for cGDS, 0.07 for cRD, and 0.06 for cDIA (Table 6). Almost identical heritabilities for cGDS and cRD, and for cGDS and cDIA, were expected because cRD and cDIA represent subsets of cGDS. Additionally, the high EBV and genetic correlations (r_g) between the overall disease trait cGDS and subset diseases ($r_g = 0.63$ between cGDS and cDIA, $r_g = 0.78$ between cGDS and cRD; Table 6) reflect such overlaps in trait definitions. Those high correlations between unspecified disease (cGDS) and single diseases (cRD or cDIA) justify the adoption of simple recording systems (“producer data”) instead of sophisticated diagnosis keys. In most cases, correlations among EBV were less extreme than genetic correlations. For EBV accuracies of 1, EBV between different traits and corresponding genetic correlations are assumed equivalent. In the present study, EBV correlations were always biased downward because prediction accuracies (r_{TI}) were < 1 . Following selection index theory, in sires with 40 daughters, the accuracy of EBV

for the low-heritability traits cDIA and cRD was calculated as $r_{TI} = (2nh^2) / [4 + (n-1)h^2] = 0.76$, with n denoting 40 daughter records per sire. The correlation between EBV for cDIA and EBV for cRD was low (0.13) and the genetic correlation moderate ($r_g = 0.29$). Different genes seem to contribute to the different calf disease phenotypes, implying limited selection response for cRD when selection is based on cDIA, and vice versa. The phenotypic correlation between cRD and cDIA was of similar magnitude (0.18). Previous studies (e.g., Henderson et al., 2011) reported substantial differences when comparing genetic, phenotypic and residual correlations among calf diseases.

Genetic Relationships Between Calf and Cow Diseases. Heritabilities for cow diseases in the early lactation period in first parity were in a narrow range between 0.001 (fIRD and fIMET) and 0.11 (fDIA) (Table 7). Low heritability estimates and low additive genetic variances for cow diseases in the period directly after calving based on “producer data” were identified by König et al. (2005) for claw disorders when applying robust single-trait animal models, and by Gernand et al. (2012) for clinical mastitis, claw disorders, and metabolic disorders. Such small heritabilities for disease traits during the sensitive period around calving suggest modifications of feeding, husbandry, or management strategies to improve the cow health status, or continuation of in-depth phenotyping strategies on, for example, a physiological level.

Correlations between EBV for calf diseases with EBV for first-lactation cow diseases were close to zero (Table 7). The highest positive EBV correlation (0.07) was between cGDS and fICLAW, and the most pronounced negative value was -0.09 between cDIA and fIFF. Most of the genetic correlations between calf and cow

Table 7. Heritabilities (h^2) with corresponding SE for first-lactation cow disease traits, correlations between EBV for cow disease traits with calf disease traits considering 242 sires with ≥ 30 daughters ($r_{EBV-sire}$), and genetic correlations (r_g) between cow and calf disease traits with corresponding SE

Cow disease ¹	h^2	Calf disease ²					
		cGDS		cDIA		cRD	
		r_g	$r_{EBV-sire}$	r_g	$r_{EBV-sire}$	r_g	$r_{EBV-sire}$
fIGDS	0.07 ± 0.01	-0.10 ± 0.10	-0.09	-0.18 ± 0.10	-0.01	-0.03 ± 0.10	-0.07
fDIA	0.11 ± 0.02	-0.08 ± 0.10	-0.08	0.00 ± 0.10	-0.08	-0.18 ± 0.10	-0.03
fIRD	0.00 ± 0.02	-0.38 ± 0.14	-0.05	-0.02 ± 0.17	0.05	-0.05 ± 0.12	-0.02
fIMAST	0.07 ± 0.01	-0.09 ± 0.10	-0.02	-0.10 ± 0.10	-0.05	0.22 ± 0.10	0.03
fICLAW	0.06 ± 0.01	0.03 ± 0.10	0.07	0.11 ± 0.10	0.04	-0.01 ± 0.10	0.02
fIFF	0.05 ± 0.01	0.00 ± 0.10	-0.07	-0.05 ± 0.11	-0.09	-0.08 ± 0.10	-0.02
fIMET	0.00 ± 0.00	-0.03 ± 0.17	0.00	-0.21 ± 0.17	0.00	-0.02 ± 0.16	0.00

¹fIGDS = first-lactation general disease status, fDIA = first-lactation diarrhea, fIRD = first-lactation respiratory disease, fIMAST = first-lactation mastitis, fICLAW = first-lactation claw disorders, fIFF = first-lactation female fertility disorders, fIMET = first-lactation metabolic disorders.

²cGDS = general calf disease status, cDIA = calf diarrhea, cRD = calf respiratory disease.

diseases were close to zero and confirmed EBV correlations. Only the genetic correlations between fIRD with cGDS (-0.38) and between fIMET with cDIA (-0.21) substantially differed from the corresponding EBV correlations (-0.05 , and 0.00 , respectively). A negative genetic calf-cow disease trait correlation (as found for most of the trait combinations) indicates that genetic resistance against a calf disease increases genetic susceptibility to a cow disease. Such findings on the genetic scale are in agreement with phenotypic results (Table 2): probabilities for the occurrence of a cow disease decreased when the same female was infected during calthood. However, most of the phenotypic calf-cow disease associations were not significant ($P > 0.05$), and correlations among EBV were not significantly different from zero. These results imply that calf diseases are not good early predictors for genetic improvements of early lactation milking cows' health in the first parity.

Genetic Relationships Between Calf Diseases and Cow Production Traits. Heritabilities for test-day production traits (Table 8) reflected the known pattern (e.g., Brügemann et al., 2011): they were higher for all traits at official test-day 2 than at test-day 1. Across traits, again the highest heritabilities were estimated for the content traits FP and PP (0.27 and 0.36 , respectively). Smaller heritabilities at test-day 1 were due to larger residual variances.

For the health trait indicator FPR, heritabilities (0.14 for FPR_1 and 0.19 for FPR_2) were substantially larger compared with the corresponding disease trait fIMET (0.001 , Table 7), or compared with corresponding single diseases such as ketosis based on pro-

ducer data (e.g., Zwald et al., 2004). The FPR recorded early in lactation might be a valuable indicator of cow disease or cow culling (Bergk and Swalve, 2011), but in analogy with remaining test-day traits, only weak EBV relationships and weak genetic correlations with calf disease traits were identified (Table 8). However, negative EBV correlations and negative genetic correlations were found between FPR_1 and FPR_2 with all calf disease traits. Such results confirm the negative correlations between calf diseases cDIA and cRD with the cow diseases fIFF and fIMET, because extremely high FPR indicate metabolic disorders (code = 1) early in lactation.

Genetic correlations between MY_1, MY_2, FY_1, FY_2, PY_1, and PY_2 with calf disease traits were slightly positive. Positive genetic correlations between productivity and functional traits suggest that breeding on, for example, increasing milk yield simultaneously increases the risk for the occurrence of a disease. Nevertheless, due to the very-close-to-zero EBV and genetic correlations between calf diseases with all first-lactation test-day production traits, breeders cannot use those calf traits as early predictors to select, for example, high-yielding milking cows for the first lactation period in parity 1. From a dairy cattle breeding perspective, it is imperative to improve selection response on the cow-dam pathway, because of the increasing replacement rates combined with long generation intervals. Weigel et al. (2012) defined the potential for improved selection intensities when genotyping female calves, but it remains questionable whether commercial farms will invest in genotyping. As an alternative, it might be in-

Table 8. Heritabilities (h^2) with corresponding SE for first-lactation test-day production traits, correlations between EBV for test-day production traits with calf disease traits considering 242 sires with ≥ 30 offspring ($r_{EBV-sire}$), and genetic correlations (r_g) between test-day production traits and calf disease traits with corresponding SE

Production trait ¹	h^2	Calf disease ²					
		cGDS		cDIA		cRD	
		r_g	$r_{EBV-sire}$	r_g	$r_{EBV-sire}$	r_g	$r_{EBV-sire}$
MY_1	0.16 ± 0.01	0.04 ± 0.08	0.05	0.06 ± 0.08	0.03	0.04 ± 0.08	0.02
MY_2	0.25 ± 0.02	0.02 ± 0.07	0.01	0.08 ± 0.08	0.03	0.02 ± 0.07	-0.03
FP_1	0.13 ± 0.01	0.04 ± 0.07	-0.03	-0.15 ± 0.09	-0.06	0.03 ± 0.08	-0.06
FP_2	0.27 ± 0.02	-0.02 ± 0.07	-0.04	-0.14 ± 0.07	-0.02	-0.04 ± 0.07	-0.06
PP_1	0.15 ± 0.01	0.03 ± 0.07	0.03	-0.03 ± 0.08	-0.12	0.05 ± 0.08	0.03
PP_2	0.36 ± 0.02	-0.02 ± 0.07	0.09	0.01 ± 0.07	-0.03	0.02 ± 0.08	0.08
FY_1	0.14 ± 0.01	0.08 ± 0.08	0.02	0.06 ± 0.09	-0.01	0.07 ± 0.08	-0.01
FY_2	0.19 ± 0.02	0.02 ± 0.08	-0.02	0.06 ± 0.08	0.03	0.05 ± 0.08	-0.08
PY_1	0.14 ± 0.01	0.08 ± 0.08	0.08	0.08 ± 0.09	-0.03	0.08 ± 0.08	0.05
PY_2	0.19 ± 0.01	0.04 ± 0.08	0.07	0.08 ± 0.08	0.02	0.04 ± 0.08	0.01
FPR_1	0.14 ± 0.01	-0.02 ± 0.08	-0.05	-0.17 ± 0.08	-0.03	-0.01 ± 0.08	-0.08
FPR_2	0.19 ± 0.02	-0.04 ± 0.07	-0.10	-0.14 ± 0.08	0.00	-0.01 ± 0.07	-0.12

¹MY = milk yield, FP = fat percentage, PP = protein percentage, FY = fat yield, PY = protein yield, FPR = fat-to-protein ratio; _1 and _2 indicate observations from the first and second test-days after calving, respectively.

²cGDS = general calf disease status, cDIA = calf diarrhea, cRD = calf respiratory disease.

teresting to identify phenotypic indicators in potential selection candidates early in life, as done by Biermann et al. (2015) for meat quality traits in pigs.

SNP Marker Associations Between Calf and Cow Traits

Different SNP markers from different chromosomes contributed to the occurrence of calf or cow diseases. Manhattan plots of $-\log(P\text{-values})$ showed significant SNP effects on chromosomes 8 and 19 for cRD (Figure 2A), and on chromosomes 7, 8, and 23 for fIRD (Figure 2B). On chromosome 8, we identified SNP within a segment of 8 cM that were significantly associated with traits cRD and fIRD, but their exact location and the direction of marker effects differed between calves and cows. The marker for fIRD on chromosome 23 is close to a QTL for “bovine respiratory disease” (Keele et al., 2015). The correlation based on SNP effects between cRD and fIRD was only 0.05 considering SNP on chromosome 7, and was marginally larger for SNP on chromosome 8 (0.14; Figure 3). The average correlation coefficient between cRD and fIRD considering SNP ef-

fects from all chromosomes was 0.01, supporting the “zero-EBV-correlations” between both traits from the quantitative genetic analysis (Table 7).

With regard to cDIA and fDIA, only a limited number of SNP affected both traits significantly. For cDIA, we identified 9 significant SNP located on chromosomes 1, 2, 5, 10, 11, 14, and 24 (Figure 4a), but only 2 SNP on chromosomes 4 and 10 significantly contributed to fDIA (Figure 4b). The most significantly associated marker on chromosome 10 at 34.38 cM was close to a QTL detected for bovine viral diarrhea virus susceptibility in cattle (Casas et al., 2015). The highest correlation between cDIA and fDIA based on SNP effects was identified on chromosome 23 (0.17), and a pronounced antagonistic relationship was found when considering estimates on chromosome 29 (-0.29 ; Figure 5). The average correlation coefficient between cDIA and fDIA considering SNP effects from all chromosomes was -0.04 . However, in spite of very low correlations, a few SNP variants favorably contributed to cow and calf diseases. In this context, Pimentel et al. (2011) combined 50K SNP data with results from gene expression profiles. Despite the naturally antagonistic relationship

Figure 2. Manhattan plots for SNP allele substitution effects for (A) calf respiratory disease, and (B) first-lactation respiratory disease. The horizontal line indicates the genome-wide significance threshold value for the 50K ($\sim 50,000$) genotypes ($P\text{-value} = 5 \times 10^{-5}$).

Figure 3. Correlation coefficients for marker effects on different chromosomes between calf respiratory disease and first-lactation respiratory disease.

Figure 4. Manhattan plots for SNP allele substitution effects for (A) calf diarrhea, and (B) first-lactation diarrhea. The horizontal line indicates the genome-wide significance threshold value for the 50K (~50,000) genotypes (P -value = 5×10^{-5}).

Figure 5. Correlation coefficients for marker effects on different chromosomes between calf diarrhea and first-lactation diarrhea.

between productivity and fertility, they identified some significant SNP simultaneously improving both trait categories. Swalve (2014) suggested selecting only those bull dams and bull sires carrying the favorable alleles, to achieve “a gradual change of genetic antagonisms.”

CONCLUSIONS

For the calf diseases cGDS, cDIA, and cRD, incidences were quite high (0.48, 0.28, and 0.21, respectively), but rather small additive genetic variances and heritabilities were estimated. Heritabilities were 0.06 for cGDS and cDIA, and 0.07 for cRD. The EBV correlation between cDIA and cRD was 0.13, and the genetic correlation was 0.29. Apart from the genetic correlation between fIRD with cGDS (-0.38), EBV correlations, as well as genetic correlations between calf diseases and cow traits from early lactation in parity 1, were close to zero. These results imply that calf diseases cDIA and cRD, as well as calf and cow disease, are genetically different traits. Calf traits are not good indicators or early predictors for the genetic improvement of cow health and productivity after calving in first parity. Correlations based on SNP marker effects from all chromosomes were close to zero between calf and cow diseases. The GWAS identified different significant SNP-markers contributing to cDIA and fDIA, or to cRD and fIRD. Weak relationships between calf diseases and cow traits were identified on the phenotypic scale. By trend, infected calves had lower probabilities for the occurrence of a cow disease, pointing to mechanisms of genetic resistance after infections.

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