



## A genome-wide association study of calf birth weight in Holstein cattle using single nucleotide polymorphisms and phenotypes predicted from auxiliary traits

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### ABSTRACT

Previous research has found that a quantitative trait locus exists affecting calving and conformation traits on *Bos taurus* autosome 18 that may be related to increased calf birth weights, which are not routinely recorded in the United States. Birth weight data from large, intensively managed dairies in eastern Germany with management systems similar to those commonly found in the United States were used to develop a selection index predictor for predicted transmitting ability (PTA) of birth weight. The predictor included body depth, rump width, sire calving ease, sire gestation length, sire stillbirth, stature, and strength. Genetic and phenotypic correlations and heritabilities from the United States were substituted for the German values, and birth weight PTA predicted for 31,984 bulls with US genetic evaluations. A genome-wide association study was conducted on the predicted birth weight PTA with the 2-step genomic BLUP procedure used for routine evaluations in the United States. Allele substitution effects were predicted for 43,188 single nucleotide polymorphisms (SNP). Genotypes were available for 53,644 predictor animals. Gene set enrichment analysis was performed on the 100 SNP that had the largest effects expressed in additive genetic standard deviations. Several SNP related to growth and development were found among the 25 SNP with the largest effects, including markers located within or near ( $\leq 100$  kbp) *ABCA12*, *FLRT2*, *LHX4*, *MAP3K5*, *NRAC*, *NTNG1*, *PIGN*, and *ZNF75A*. The gene set enrichment analysis identified the Kyoto Encyclopedia of Genes and Genomes “Regulation of actin cytoskeleton” pathway (bta04810) as being enriched. That pathway includes the *ROCK* gene, which is involved in placental function in the human, as well as other developmental genes (e.g., *FAK* and *PAK*). Prediction equations

derived from one population are useful for identifying genes and gene networks associated with phenotypes that are not directly measured in a second population. This approach will identify only genes associated with the traits used to construct the birth weight predictor, and not loci that affect only birth weight.

**Key words:** birth weight, quantitative trait loci, selection index, single nucleotide polymorphism

### INTRODUCTION

Many studies have reported on QTL affecting calving traits in several populations of Holstein cattle (Kühn et al., 2003; Schnabel et al., 2005; Holmberg and Andersson-Eklund, 2006; Kolbehdari et al., 2008; Thomassen et al., 2008; Seidenspinner et al., 2011; Purfield et al., 2014), and there appears to be a major gene on BTA18 affecting dystocia, stillbirth, conformation, and lifetime economic merit (Cole et al., 2009b; Brand et al., 2010; Sahana et al., 2011; Purfield et al., 2014). Qanbari et al. (2011) also identified a signature of selection in the same region of the cattle genome. Cole et al. (2009b) suggested that sequestration of leptin by a sialic acid-binding immunoglobulin-type lectin may result in increased gestation lengths and, in turn, increased calf birth weights.

Numerous studies have examined relationships among calving traits, including calving ease (**CE**), stillbirth (**SB**), gestation length (**GL**), and calf birth weight. The relationship of these traits has been known for some time, and Philipsson et al. (1979) discussed the importance of these interrelationships in the context of breeding strategies. Meijering (1984) surveyed the literature and reported correlations of CE and SB with birth weight ranging from 0.08 to 0.41. Meyer et al. (2001) found that CE was negatively correlated with perinatal survival, meaning that increased dystocia was associated with decreased calf survival, and correlations were similar using data from first (−0.16) and all (−0.13) lactations. Correlations of direct CE and SB with direct GL of 0.18 and 0.38, respectively, were reported for Danish Holsteins by Hansen et al.

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(2004). López de Maturana et al. (2009) used structural equation models to explore genetic relationships among dystocia, GL, and SB in US Holsteins, and reported significant but heterogeneous correlations among all 3 traits. More recently, Johanson et al. (2011) reported significant, positive genetic correlations of direct birth weight with direct dystocia (0.73), GL (0.52), and direct SB (0.57). Cole et al. (2009b) reported that genetic correlations among direct and maternal CE and SB differ when comparing whole-genome and chromosome 18-specific genetic marker effects.

Several recent studies have reported on QTL associated with birth weight. Eberlein et al. (2009) reported that the non-SMC condensin I complex, subunit G (*NCAPG*) gene on BTA6 is associated with fetal growth rates in Charolais cattle. Microsatellites on chromosomes 2, 6, and 14 had significant associations with birth weight in a Holstein × Jersey crossbred population (Maltecca et al., 2008). Markers associated with body size, CE, daily gain, and SB have been identified on BTA14 and BTA21 in German Fleckvieh (Pausch et al., 2011). These results lend support to the proposal of Cole et al. (2009b) that the QTL on BTA18 affecting calving and conformation traits may be associated with increased birth weight.

Calf birth weights are not routinely collected by US dairymen, although they are recorded in some experimental herds (Johanson and Berger, 2003; Olson et al., 2009; Heins et al., 2010). Birth weights are recorded in German contract test herds associated with the breeding organization Rinderzuchtverband Mecklenburg-Vorpommern GmbH (Karow, Germany), which also use US sires and manage their herds similarly to American producers, suggesting that those data could be used to develop a predictor of sire PTA to be applied to both populations. The resulting birth weight data previously have been used for an unpublished genetic evaluation for calving traits as well as for analyses on the relationship of calving traits with conformation traits (Waurich et al., 2010) and for an assessment of the reliability of estimated birth weight in contrast to real weighing records (Waurich et al., 2011).

Selection index methodology (e.g., Cameron, 1997) can be used to identify the set of traits that best predict birth weight, and those predictors combined with population-specific genetic and phenotypic (co)variance matrices to produce correct weightings. The objectives of this study were to (1) develop a predictor for calf birth weight in the United States using correlated traits and data from similar herds in Germany, (2) use SNP markers to identify regions of the genome associated with birth weight, and (3) identify candidate genes located in genomic regions of interest that could have an effect on birth weight.

## MATERIALS AND METHODS

### *Prediction of Birth Weight Using EBV and Selection Indices*

**Estimation of (Co)variances.** Data for the estimation of variances and (co)variances needed for the selection index came from 20 contract herds of the breeding organization Rinderzuchtverband Mecklenburg-Vorpommern in northeastern Germany. The contract herd system initially was set up for the purpose of progeny testing and is now mainly used to collect additional data as a complement for the milk-recording data. All contract herds are relatively large by German standards, the average herd size is 780 cows, and recording of birth weights is mandatory. Considering the calving complex and first calvings only, data were recorded in the period of October 2005 to June 2010 and comprised 25,462 records on birth weight (kg), CE (4 classes: 1 = without assistance, 2 = little assistance, 3 = heavy assistance, and 4 = operation), GL (d) and SB status (0 or 1). Calving ease records were recoded into a binary form such that class 1 was coded as 0 and all other classes as 1. Calving data were merged with data on conformation scores stemming from the official classifications that use a linear 1 to 9 scale. In total, 14,022 records for dams of calves and 2,989 records on calves with a recorded calving and their later classification in first lactation could be used.

The fixed effects for calving traits, with the number of classes given in parentheses, were herd (20), year-season (15), sex (2), and age at first calving (9). For conformation traits from the official classification, the fixed effects were herd (20), year-season (15), age at first calving (9), stage of lactation (5), and classifier (3).

Due to the different nature of the 2 trait complexes and the structure of the data used for the estimation of (co)variances, the variance components needed for the set-up of the selection index equations could not be estimated with 1 unique model. Rather, a series of models was used. A general overview of the models is given in Table 1. Essentially, bivariate sire-maternal grandsire models were used for the estimation of (co)variances among traits of the calving complex. Sire-maternal grandsire models including direct additive and maternal genetic effects can be used as an alternative to animal models, as shown by Eaglen et al. (2012). Whereas birth weight and GL were treated as continuous traits using linear models, for the categorical traits CE and SB, threshold models applying logit link and probit link functions were used. Both types of link functions were used, depending on the convergence of estimates. All bivariate runs for calving traits were

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