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Genome scan detects quantitative trait loci affecting female fertility traits in Danish and Swedish Holstein cattle

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ABSTRACT

Data from the joint Nordic breeding value prediction for Danish and Swedish Holstein grandsire families were used to locate quantitative trait loci (QTL) for female fertility traits in Danish and Swedish Holstein cattle. Up to 36 Holstein grandsires with over 2,000 sons were genotyped for 416 microsatellite markers. Single trait breeding values were used for 12 traits relating to female fertility and female reproductive disorders. Data were analyzed by least squares regression analysis within and across families. Twenty-six QTL were detected on 17 different chromosomes. The best evidence was found for QTL segregating on *Bos taurus* chromosome (BTA)1, BTA7, BTA10, and BTA26. On each of these chromosomes, several QTL were detected affecting more than one of the fertility traits investigated in this study. Evidence for segregation of additional QTL on BTA2, BTA9, and BTA24 was found.
Key words: quantitative trait locus, genome-wide scan, female fertility

INTRODUCTION

Female fertility has been declining in recent decades in the Holstein cattle populations (Sørensen et al., 2007). Improving female fertility is becoming more and more important as the consequences of impaired fertility include additional inseminations, higher veterinary costs, increased culling rate, and higher replacement costs.

Traditional selection methods to improve fertility have not been able to prevent this decline in female fertility (Strudsholm et al., 2007). There are several reasons for this. First, heritabilities for fertility traits are generally low (ranging from 2 to 4% for Holstein populations in the Nordic countries; Strudsholm et al., 2007), they have sex-limited expression, and some of them are expressed late in life. This in itself causes genetic gain to be slow at best. Furthermore, the genetic correlations between fertility and production traits are generally unfavorable. Genetic correlations between milk yield traits and fertility traits are in the range of −0.2 to −0.5 (Pryce et al., 1997; Dematawewa and Berger, 1998; Roxström et al., 2001). Given the high economic weight put on production traits in most countries' breeding programs, this has lead to the continuing decline in female fertility. Even the much higher weight on female fertility in breeding goals in Nordic countries has not been sufficient to offset this trend.

Identification of QTL for fertility traits would contribute to improve the efficiency of selection for fertility traits. Expression of fertility traits is sex-limited. The AI bulls have to be progeny-tested before they are proven for fertility traits. Hence, it could be a significant advantage to obtain information of young bulls' breeding values for fertility traits at an early age. Genetic gain could then be increased. Detection of QTL for fertility traits could make information available at an early age through the use of marker-based tests. Even if the use of genomic selection should become widespread, QTL with effects on low heritability traits such as fertility will remain valuable particularly where recordings for fertility traits are not available.

Several studies have reported the detection of QTL for fertility traits (Schrooten et al., 2000; Kühn et al., 2003; Ashwell et al., 2004; Schnabel et al., 2005; Holmberg and Andersson-Eklund, 2006). Generally, overlap between the QTL detected in different studies is incomplete. In part, this may be caused by insufficient statistical power of detection studies due to the low heritability of the traits. Hence, the probability of obtaining strong evidence for the same QTL in multiple studies will be greatly reduced. Also, trait definitions and computational procedures for estimating breeding values differ among countries, which in turn may lead to detection of different QTL between countries.

International cooperation can overcome some of these problems. Cattle breeding organizations in Denmark, Sweden, and Finland have established a joint breed-

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ing value estimation system, the Nordic Cattle Genetic Evaluation. Trait definitions have been standardized across the countries. The Nordic countries record a wide range of fertility traits. In this study, we include 12 different measures of female fertility. Simultaneously, combining data across a larger base of recorded data will lead to more precise prediction of breeding values. This will in turn improve the statistical power to detect QTL. For genetic polymorphisms with effects on several traits, detection of QTL for several biologically related traits can lend each other added support. The large number of fertility-related traits available in the Nordic Cattle Genetic Evaluation can therefore be exploited to gain additional confidence in detections of QTL.

The objective of this study was to detect QTL for multiple female fertility traits in Danish and Swedish populations of Holstein cattle.

MATERIALS AND METHODS

Population

A total of 36 Danish and Swedish Holstein grandsires with more than 16 offspring-tested sons were analyzed in a granddaughter design (Weller et al., 1990). Of these 36 families, 29 were tested only in Denmark, 2 only in Sweden, and 5 across the countries. The sires with offspring in both countries had twice as many sons tested in Denmark as in Sweden. The number of sons per grandsire ranged from 16 to 160 with an average of 61 sons per grandsire family. Of the grandsire families, 5 had less than 30 sons, 14 had between 31 and 60 sons, 9 had between 61 and 100 sons, whereas 5 had more than 100 sons. In total 2,182 sons were genotyped.

Marker Data

The genome was screened using 416 microsatellite markers representing a total of 3,179 cM with an average marker spacing of 7.64 cM. All 29 autosomes were typed for an average of 14 markers (Table 1). The number of grandsire families typed varies between chromosomes because chromosomes considered interesting in past QTL mapping projects varied (Table 1). As a measure of the amount of available marker information, the average number of heterozygote markers in the grandsires included in this study is listed in Table 1. Markers and their positions were taken from the USDA Cattle Genome Mapping Project (http://www.marc.usda.gov/genome/cattle/cattle.html).

Genomic DNA was extracted from semen or blood samples (DNeasy tissue extraction kit, Qiagen, Valencia, CA) and used in multiplex PCR in which 4 to 10 microsatellite markers were amplified. Polymerase chain reactions (15 μL) were performed in a 96-well thermal cycler (GeneAmp PCR System 9700, Applied Biosystems, Foster City, CA) using 2.5 m*M* $MgCl_2$, 0.25 m*M* deoxynucleoside triphosphate, 0.3 μ*M* of each forward primer, 0.3 μ*M* of each reverse primer, 0.75 U of TEMPase DNA polymerase (VWR-Bie & Berntsen, Denmark), and 30 to 100 ng of genomic DNA in 1× TEMPase PCR buffer (VWR-Bie & Berntsen). An initial denaturing step at 94°C for 15 min was followed by 10 touchdown cycles at 95°C for 30 s, annealing at 67 to 58°C for 1.5 min, and extension at 72°C for 45 s; then 25 cycles at 95°C for 30 s, annealing at 58°C for 1.5 min, extension at 72°C for 45 s, and ending with 72°C for 20 min. The products of PCR were analyzed on an automated sequence analyzer (ABI 3730 DNA Analyzer, Applied Biosystems). Alleles were assigned using the GeneMapper software, version 3.7 (Applied Biosystems).

Phenotypic Data

Single-trait breeding values (**STBV**) were custom made by the Nordic Cattle Genetic Evaluation. The STBV was calculated for each animal using BLUP procedures and a sire model. The STBV were adjusted for the same systematic environmental effects as in the official routine evaluations. However, the correlation to other traits was set to 0 and calculated without pedigree information. This is to avoid information from phenotypes of correlated traits to affect results of a particular trait. The STBV were calculated for 12 fertility traits. For details of the phenotypes recorded and models used in breeding value prediction, see http://www.nordicebv.info/Routine+evaluation/Fertility+traits/Fertility+traits.htm and Ancker et al. (2006). The predicted breeding values for sires were predicted on data for the first to third parity in cows. The STBV were available from national evaluation separately for cows (^{C}) and heifers (^{H}) for number of inseminations per conception (or culling) (**AIS**^{C} and **AIS**^{H}), 56-d nonreturn rate (**NRR**^{C} and **NRR**^{H}), days from first to last insemination (**IFL**^{C} and **IFL**^{H}), and heat strength (**HST**^{C} and **HST**^{H}). Length in days of the interval from calving to first insemination (**ICF**) is only defined for cows. It should be noted that HST was assessed subjectively by the individual farmer on a scale from 1 to 5, and it was only recorded in Sweden.

Because of differences between the Danish and Swedish recording systems for fertility treatments in the first 3 parities (FRT1, FRT2, and FRT3), only records from Denmark were used in this study. In Denmark, fertility treatments are recorded by veterinarians and trained AI technicians. Fertility treatments include hormonal reproductive disorders, ovarian cyst treatments, and in-