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## Genome-Wide Scan for Reproductive Traits of Beef Heifers Using High Density SNP Panels

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**ABSTRACT:** Quantitative Trait Loci (QTL) detection for sexual precocity and fertility of beef heifers was performed by a Bayesian approach and based on performance recorded in French progeny test station of Blonde d'Aquitaine bulls. Heifer oestrus and fertility were observed on about 25 daughters for each of the 158 genotyped bulls. Genotyping was mainly carried out with the Bovine high density BeadChip®. A total of 78 QTL were identified with strong evidence for an effect on sexual precocity. Comparing these results with QTL previously reported in the literature, 2 unknown QTL were identified for sexual precocity among the 7 regions with major evidence for a QTL. Regarding heifer fertility, only 6 QTL were detected, 3 of them matched with previous studies on dairy cattle. Two common QTL regions were identified as playing a strong role on both reproductive traits.

Keywords:

Beef cattle

Blonde d'Aquitaine

Age at puberty

Fertility

### Introduction

Among the beef traits for which gene or marker-assisted selection will be the most useful are those that are expressed only in one sex or very costly to measure. These are precisely the reasons why detecting quantitative trait loci (QTL) or genes for age at puberty and fertility of heifers could be useful to facilitate beef cattle selection for reproductive traits. Those traits are indeed not easy to record on-farm on a large scale (Snelling et al. (2011)). In French Blonde d'Aquitaine breeding program, selection for artificial insemination bulls is therefore based on daughters testing in station. The female traits recorded in station consist of the heifer growth, its sexual precocity, its fertility, its calving performance at 2 years and, eventually, its suckling performance. The objective of this research was to present results of a genome-wide scan for fine mapping of QTL for two reproductive traits, sexual precocity and fertility, using a Bayesian approach to locate the QTL and estimate their effects.

### Materials and Methods

**Genotypes.** A total of 158 registered Blonde d'Aquitaine bulls were genotyped either with the Bovine SNP50 BeadChip® (50K) or with the Bovine HD BeadChip® (777K). Animals with genotypes inconsistent with pedigree information were discarded. To fine map QTL, analyses were performed using the 777K chip. After quality control, 706,791 single nucleotide polymorphisms (SNP) of the 777K SNP chip were retained on 147 animals and 37,634 SNP of the 50K SNP chip were retained on 11 animals. Imputation of the 50K genotype data to 777K

genotypes was performed using BEAGLE software for these 11 animals (Browning and Browning (2009); Saatchi et al. (2012)). A detailed description of genotype editing and imputation procedure is given by Hozé et al. (2013). The SNP were mapped to the UMD 3.1 bovine genome sequence assembled by the Center of Bioinformatics and computational Biology at the University of Maryland.

**Phenotype Data.** Since the mid-eighties, 6 to 8 sires had been progeny tested each year in Blonde d'Aquitaine progeny test station with about 25 daughters recorded per sire. The classical BLUP (Best Linear Unbiased Predictor) sire evaluation gave the ingredients to derive accurate 'pseudo-phenotypes' that were the deregressed estimates breeding values (DEBV) and their weights according to Garrick et al. (2009) methodology. These DEBV were considered in weighted analysis to account for heterogeneous variances of the response variable due to a various amount of progeny records among genotyped animals.

The female traits analysed in this research were the observation of oestrus before the age of 15 months for measuring its sexual precocity (SP=0/1) and the observation of calving success after a fixed insemination period for assessing its fertility (FE=0/1). Oestrus was observed by visual appraisal early in the morning and late in the afternoon every day from 10 to 16 months with the help of a vasectomized bull. Heifers were inseminated during a fixed 10-weeks period in order to get a first calving at the age of 2 years. Only two purebred mating bulls were used each year. They were used for several years in order to correct for their effects on calf performance and on heifer fertility.

### Statistical analyses.

**Method.** Bayesian Variable Selection is a powerful method in genome-wide association studies because it simultaneously estimates all SNP effects and should therefore improve localization of the true association between genotype and phenotype (Schurink et al. (2009)). A BayesC approach (Habier et al. (2011)) was therefore performed to find and localize the main QTL. In this Bayesian method, the priors of all SNP effects were assumed to share the same variance. The effects of SNP were fitted with a probability  $\pi$ , where  $\pi$  is the fraction of SNPs having a non-zero effect. The same number (38) of expected SNP with non-zero effect at a given iteration was considered for the 2 traits, corresponding to  $\pi=0.005\%$  on the 777K chip. Analyses were performed using GS3 software (Legarra et al. (2013)). For each analysis, 100,000 iterations were run with a burn-in of 10,000 and a thin of 10.

**Bayes Factor.** The degree of the association between SNP and QTL was assessed through the Bayes Factor (BF) which involved the  $\pi$  and  $P_i$ , the probability of each SNP to have a non-zero effect:

$$BF = \frac{P_i/(1 - P_i)}{\pi/(1 - \pi)}$$

The value of logBF was computed as twice the natural logarithm of the Bayes Factor. This log scale was introduced to be on the same scale as deviance and likelihood (Kass & Raftery (1995)). It gave a better visual representation of QTL on a genome-wide scale. Different thresholds were defined to identify QTL regions along the genome.

**QTL Region definition.** A QTL was considered with a strong evidence when the logBF for the SNP reached a peak value greater or equal to a threshold of 8. To reduce the false positive rates, very strong evidence for a QTL was considered when the peak value of logBF was above the threshold of 10. QTL region around the peak location was built considering a lower threshold for the logBF. Due to the small number of records and the low heritabilities of reproductive traits, the lower-threshold was fixed at a logBF value equal to 2.2 in order to be confident enough in the fact that the gene would be truly positioned within the identified region. According to Kass and Raftery (1995), this threshold of 2.2 can be considered as positive evidence for a SNP with a non-zero effect. Therefore, markers with logBF higher than this lower-threshold were included in the QTL region if its distance to the previous marker was less than 500 kilobases (kb). This approach to extend the QTL region around the logBF peak was repeated while a marker with a logBF above the lower-threshold exists within a distance of 500 kilobases with the previous incorporated marker.

## Results and Discussion

**Whole genome.** LogBF for the genome-wide scan was plotted on the graphics 1 and 2 for sexual precocity and fertility, respectively. Lower-threshold and upper-threshold used for identification of QTL region and the major level of 12 were represented by dotted lines. 78 QTL regions affecting sexual precocity were identified, including 6 QTL also having strong evidence for an effect on fertility. The number of regions identified was summarized in table 1, considering 3 levels of evidence for the QTL according to the peak value of the logBF within the identified QTL regions. It seems that the low heritability of fertility ( $h^2=0.08$ ) makes impossible to conclude with a very strong evidence for any QTL. On the contrary, heritability of sexual precocity ( $h^2=0.17$ ) (Phocas and Sapa (2004)) allows to get strong evidence for some QTL.

A literature review was carried out to compare the identified regions with those described for reproductive traits of cattle in previous studies, based on the use of the Iowa QTL database (Hu et al. (2012)). For sexual precocity, only the main regions where logBF peak was over 12, where no false positive should be highlighted, were detailed in the next paragraph. For fertility, the 6 identified regions were presented, then focusing on the 2 chromosomal regions (on chromosomes 6 and 29) that were identified as QTL for the 2 traits.

**QTL identified for sexual precocity.** A region of 10 Mb at the end of the chromosome 4 was identified as having an effect on sexual precocity. The peak of this region was located at a distance slightly upper than 1 megabase (Mb) of a QTL reported by Pimentel et al. (2011). This QTL included the *PARP 12* gene which is involved in early endometrial response to pregnancy in cattle (Forde et al. (2012)). On the last quarter of chromosome 6, a very large region of 23 Mb was identified as QTL for sexual precocity. In a distance lower than 1 Mb near the peak at the beginning of this QTL region, Daetwyler et al. (2008) identified a QTL affecting the age at first service on Holstein. On the second part of the QTL found in this study, a region of about 10 Mb was also identified by Shrooten et al. (2000) influencing the interval from calving to first insemination. In Charolais breed, length of post-partum anoestrus was shown to be genetically linked (0.64) to the age at puberty (Mialon et al. (2000)). Therefore, it is likely that some common QTL regions may be detected for sexual precocity and cyclicity of the cow.

A region of 10 Mb was highlighted at the beginning of chromosome 7. The peak of this region was included in a QTL region for ovulation rate (Kirkpatrick et al. (2000)). Two regions with very significant peak logBF (13.5 and 15.3) were found on the second part of the chromosome 21 and at the end of the chromosome 24 respectively. No QTL matching these regions were found in the literature. The biggest peak logBF (17.5) of this study was located on the middle of the chromosome 22. It was located in a relatively small region (3.5 Mb) which shared a common part with a QTL region affecting the non-return rate in Holstein (Hoglund et al. (2009)).

**QTL identified for fertility.** On chromosome 1, a small peak, just over the upper-threshold, was identified in the middle of the chromosome in a common region with a QTL discovered by Boichard et al. (2003) on conception rate on dairy French breeds. A large region of 9.4 Mb was found in the beginning of chromosome 3. This region was also identified by Guillaume et al. (2007) on non-return rate with the same dataset as Boichard et al. (2003). The peak they found was very close to the peak of the QTL region from this study (less than 500 kb).

The major peak logBF (9.6) for fertility was located in a region of 1.6 Mb in the first third of chromosome 12. This region matched a QTL for non return rate for Holstein cows (Hoglund (2009)). Another region of 1.7 Mb was found on chromosome 11, but did not match any QTL recorded in the Iowa database.

**QTL detected for both traits.** Detection of common QTL between sexual precocity and heifer fertility was consistent with the high genetic correlation (0.76) estimated between these 2 traits in Blonde d'Aquitaine heifers (Phocas and Sapa (2004)). Among the 2 common QTL regions, the region located in chromosome 29 had already been identified as having an effect on the age at puberty on beef bulls *Bos indicus* (Brahman) x *Bos taurus* (Hereford) (Casas et al. (2004)). The end of the large region identified for sexual precocity on chromosome 6 was also detected for fertility in this study. This region had been highlighted for its impact on the interval from calving to first insemination (Schrooten et al. (2000)).

## Conclusion

Most of the QTL identified in this study had been previously reported in dairy cows or in Brahman-Hereford crossbred animals. However, 3 new QTL were identified for sexual precocity and heifer fertility. Sexual precocity and fertility are visibly under the strong control of 7 and 6 QTL, respectively. Two of these QTL have an influence on both traits. Further investigation is needed to find the causative mutations in these chromosomal regions.

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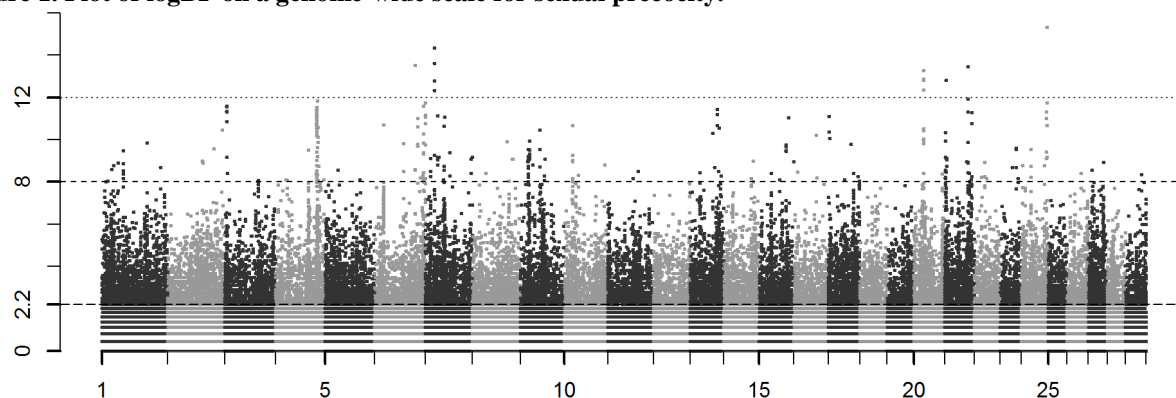
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**Table 1. Number of QTL regions for sexual precocity and fertility, according to the peak value of logBF.**

Evidence level for a QTL	Peak LogBF	Sexual precocity	Fertility
Strong	8 – 10	57	6
Very strong	10 – 12	14	0
Major	> 12	7	0

**Figure 1. Plot of logBF on a genome-wide scale for sexual precocity.**



**Figure 2. Plot of logBF on a genome-wide scale for fertility.**

