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Mutations in genes involved in oestrous cycle associated expression of oestrus[☆]

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ABSTRACT

Detection of oestrus is a key determinant of profitability of dairy herds, but oestrus is increasingly difficult to observe in the modern dairy cow, with shorter duration and less intense oestrus. Concurrent with the unfavourable correlation between milk yield and fertility, oestrous detection rates have decreased to less than 50%. A number of mutations have been identified in genes associated with fertility and production traits, but, to date, no single nucleotide polymorphism (SNP) has been associated with oestrous expression. Therefore, the objective of this study was to investigate SNPs, linked to fertility, for the association with oestrous expression. Blood was collected from 205 Holstein Friesian dairy cows and genotyped at 41 loci of 18 genes chosen for their roles in the oestrous cycle and milk production. SNPs were then examined for correlations with increase in activity at oestrus, recorded via activity monitors, using generalised linear models. Physical activity increased at oestrus between two and four fold. Larger increases were associated with mutant alleles in oestrogen receptor-α and gonadotrophin releasing hormone receptor genes ($P < 0.05$) and in the *STAT5A* gene ($P < 0.05$). Smaller increases were associated with mutant alleles of the activin receptor type IIB and prolactin receptor genes ($P < 0.10$). In conclusion, alleles in these five genes provide the opportunity for selection of animals displaying greater oestrous activity which could aid reversal of the decrease in oestrous detection and thereby contribute to sustainability of the dairy industry worldwide.

1. Introduction

Oestrous detection is key to profitability of dairy herds (Pecsok et al., 1994), but oestrous detection is becoming increasingly difficult due to decreased expression in the modern dairy cow. Cows are reported to display shorter duration and less intense oestrus (Dransfield et al., 1998), where fewer cows stand to be mounted (Dobson et al., 2008). The decrease in fertility associated with increases in milk yield (Royal et al., 2000; Pryce et al., 2004) is thought to have a strong genetic basis (Veerkamp and Beerda, 2007) and it is apparent that a genetic approach may be employed to solve the problem. It appears that poor expression of oestrus is 50% of the problem contributing to poor dairy cow fertility, as only 50% of cows are detected in oestrus (Van Eerdenburg et al., 2002). Sequencing of the bovine genome in 2003 (http://www.hgsc.bcm.tmc.edu/projects/bovine) has provided a wealth of information at a molecular level and it is possible that genomic approaches might provide a novel solution to the problem of poor expression of oestrus.

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There are many effects of single nucleotide polymorphisms (SNPs) and so relationships can be determined between SNPs and a functional trait (Ibeagha-Awemu et al., 2008). A number of SNPs have been identified and reported for their association with reproductive and production traits (Table 1); however, as yet there is no report of effects of SNPs on oestrous expression. Based on a literature review and in-house genotyping, genes were chosen for analysis in the present study on the basis of the association with (i) hypothalamic/ovarian/uterine function, (ii) roles in central nervous pathways controlling oestrous behaviour, and (iii) associations with production traits such as milk yield, energy balance and feed intake and metabolic influences which can all impact upon fertility and oestrous expression. Therefore SNPs on genes that had been identified previously (Table 1) were investigated for the effects on physical activity at oestrus.

Selecting for increased activity at oestrus may lead to an increase in overall oestrous expression and thereby aid a more rapid reversal of decreasing oestrous detection rates. Due to the low heritability of reproductive traits ($h^2 < 0.05$; Berglund, 2008), genomic selection provides a method of rapid and cumulative genetic gain with the possibility of doubling the rate of genetic gain (Hayes et al., 2009). Furthermore the accuracy of SNP selection has been reported to be increased between 10% and 30% for traits with low heritability (Muir, 2007).

By improving oestrous expression, more cows would be detected in oestrus and thus oestrous detection rates would be improved. Identifying SNPs for strong oestrous expression would allow selection of bulls for breeding that would produce cows that display greater oestrous behaviour. Therefore, the objective of the present research was to identify DNA polymorphisms that could provide a means of identifying cows that display oestrous expression more strongly.

2. Materials and methods

2.1. Animals

Animals used in the present study were 205 Holstein Friesian dairy cows housed at the Nottingham University Dairy Centre (Sutton Bonington, Leicestershire, UK; average annual milk yield 10,000 L/cow). The lactating cows were kept indoors in groups of approximately 40. Housing consisted of a purpose built barn with four pens, which was well ventilated, with rubber matting, cubicles and sawdust for comfort whilst lying. Cows were milked by robotic automatic milking stations (Lely Astronaut A3 AMS units) voluntarily; visiting between two and six times per day. All cows were fed the same silage-based diet, with concentrates fed in the robot at milking.

2.2. Phenotypic data

Physical activity of each cow was monitored continuously by a Lely Qwes-HR Activity Tag mounted on a neck collar. The tag contains a three-dimensional accelerometer which responds to cow movement and movement intensity. Accelerometer signal is converted to an activity index by an internal algorithm, which is patented and undisclosed by the manufacturer. Activity data, therefore, are expressed as ‘activity units’, but cannot be translated into any specific activity measure such as number of steps or shakes of the head. Activity data were downloaded at milking from the tag, which was read on entry to the robotic milking station.

Activity data were recorded for each cow as 12 readings daily of mean activity units per 2 h interval. Activity data were analysed by plotting activity against date and time resulting in 12 activity readings daily with peaks denoting oestrus. An increase in activity at oestrus was defined as three consecutive 2-h periods of increased activity compared with the baseline before onset of increased physical activity. The threshold for physical activity increase to be considered a possible oestrous event was 30% above baseline.

Peaks in activity were confirmed as oestrus events by visual detection (observations in the morning; 06:00 h and evening; 20:00 h during daily routine activities). Only peaks after 25 days postpartum were classified as oestrus. Any increase in activity within 10 days postpartum was discounted from analysis as these may be due to management practices or measurement errors and hence not a true representation of oestrous cyclical activity.

Oestrus, insemination and pregnancy data were known for all animals. Oestrous data collected over 2 years were collated from 205 cows, including 930 individual oestrous events across different lactations and stages of lactation. Measurements of oestrous expression were calculated as maximum activity at oestrus.

2.3. Blood sampling, DNA extraction and genotyping

Whole blood samples were collected from the coccygeal vein of each cow into lithium heparin coated tubes, under ethically approved Home Office Licence regulations. Blood samples were then genotyped commercially by KBiosciences Ltd (Herts, UK), using primer extension. Based on a literature review and in-house genotyping in other studies, genes were selected for analysis on the basis of involvement in reproductive processes and are detailed in Table 1. DNA was genotyped at 41 loci, in 18 genes for inclusion in the analysis.

2.4. Statistical analysis

Statistical analysis was conducted using Genstat 14th edition (VSN International Ltd, Hemel Hempstead, UK). Activity data were analysed as generalised linear mixed models (GLMM) using the residual maximum likelihood (REML) procedure, with Poisson distribution and logarithmic link function. The model fitted fixed effects for SNP (wildtype homozygote, 0; heterozygote, 1; mutant homozygote, 2), parity (classified according to lactation number as 1, 2 and ≥ 3) and oestrous season (classified as January–March, 1; April–June, 2; July–September, 3; October–December, 4). Stage of lactation (days in milk) and oestrous number within a lactation were not significant fixed effects, so were omitted from the final model. For the random effects of the model, individual cows