Genes and variants involved in resistance to paratuberculosis in Holstein and Normande cattle

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Optimizing dairy cattle breeding goals to improve production and udder health of crossbred cows

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Crossbreeding is known to increase economic profitability by benefiting from heterosis and breed complementarity. Breeding goals (BG) used to select dairy cattle breeds have so far been aimed at improving purebred performance which may be sub-optimal when the goal is crossbred performance. The aim of this study is to compare various purebred BGs in a two-way terminal crossbreeding system for dairy cattle over several generations of crossbreeding. We postulated that differentiating BGs in purebred parental lines could be more efficient to increase crossbred performance. Breeding schemes of Danish Jersey (DJ) and Nordic Holstein (NH) cattle were simulated using real haplotypes of 200 founders sampled from each breed. We simulated a founder population where NH had a higher breeding value for milk production and a lower breeding value for udder health compared to DJ. First, genomic reference populations were constituted for 20 years to predict genomic breeding values with appropriate reliabilities. In year 21-30, a genomic selection scheme for NH and DJ aimed at crossbred performance was simulated. Each year, 2,000 young bulls and 2,000 heifers were genotyped. Out of the young bulls, 50 were selected as sires. Three scenarios were set up to test the hypothesis: (1) a reference scenario resembling the economic values in the present Nordic total merit index for DJ and NH; (2) the same BG in NH as in 1, but a higher value on health in the BG of DJ; and (3) BGs only weighing production in NH and only health in DJ. In year 25-30, a population of crossbred cows was simulated alongside the two pure breeding schemes by mating Jersey cows with Holstein bulls. Purebreds in both nuclei were evaluated both for purebred and crossbred performance. For evaluation of crossbred performance, SNP-BLUP breeding values were estimated by using allele frequencies of the purebred population that an animal was bred to, whereas GBLUP was used for purebred evaluation. Outcomes of this study will be useful to assess the importance of updating BGs in purebred breeding schemes to optimize crossbred performance.

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Bovine paratuberculosis, or Johne's disease, is a contagious and incurable disease, caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP), with adverse effects on animal welfare and serious economic consequences. The recent implementation of genomic evaluation for paratuberculosis resistance in France, effective in Holstein and ongoing in Normande, provides access to a large database of cows with disease status estimated from blood serological data, i.e. likely to be infected (with or without clinical signs), or not to be infected. Using a subset of 4,677 Holstein and 4,845 Normande cows with chip genotyping data, we performed sequence-based genome-wide association studies (GWAS) to identify genes and variants influencing resistance to paratuberculosis. Genotypes from the whole genome sequence were imputed using a multibreed reference population from the 9th run of the 1kBG consortium and in-house data comprising 1,414 Holstein and 160 Normande animals. The GWAS was carried out with a mixed linear model, testing the individual effect of ~14M variants after filtering for low imputation accuracy (R^2<0.2) or frequency (MAF<0.005), and accounting for the population structure through polygenic effects estimated from a 50k-based genomic relationship matrix. A total of 3,026 and 5,063 variants had significant effects (7.3≤-log(P)≤22) on resistance to MAP infection in Holstein and Normande, respectively. They were located on chromosomes 12, 13, 18, and 23 in Holstein and on chromosomes 3, 6, 12, and 23 in Normande. The genomic region with the most significant effect was located on chromosome 13 in Holstein (~ 63 Mb) and on chromosome 23 in Normande (~ 23 Mb). Based on their position, we identified *PEAR1*, *ELOVL5*, *HS6ST3*, *SNTA1*, and *BOLA-DRA* as the most plausible candidate genes. This study confirms the genomic regions initially identified in Holstein for resistance to MAP infection and reveals novel regions, candidate genes and variants in both Holstein and Normande breeds.