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In this study, we exploit the bovine population structure with large paternal progeny groups to detect loci with transmission disequilibrium, corresponding to multiple determinism defects frequently overlooked by other approaches. Transmission disequilibrium test (TDT) in large genotyped families is an efficient tool to detect these conditions. In a healthy progeny group, both haplotypes are expected to be inherited equally from the parent. In contrast, if the parent carries a deleterious abnormality, a deficit is expected in the surviving progeny carrying the haplotype associated with the mutation. For a recessive defect, this disequilibrium increases with the frequency of the deleterious allele in the population. For a defect with incomplete penetrance or mosaicism, the disequilibrium depends on these parameters. To conduct this study, we selected 401 Holstein bulls with at least 500 genotyped calves, resulting in a total of 532,864 calves. In each progeny, we observed the transmission of 20-SNP haplotypes and selected the haplotypes in significant transmission disequilibrium. The minimum number of calves required for a disequilibrium to be considered significant was determined from a binomial distribution adjusted for multiple testing. Of the 401 bulls tested, 321 bulls had at least one haplotype in disequilibrium. We then grouped all significant identical haplotypes and, for each 10 MB window, selected the most unbalanced haplotypes shared by at least five bulls. This resulted in a subset of 33 significant haplotypes. To detect candidate variants, we used whole genome sequences of 301 bulls. We selected 56 candidate variants (SNPs or structural variants in a 20 MB window around the peak) on the basis of their correlation with the haplotype status of each animal and their Sift score. We propose candidate variants for the previously known QTL in BTA 18 associated to viability and suggest candidate variants in BOLA region that could partly explain early mortality. The functional impacts of these variants are currently under investigation. FB is a recipient of a CIFRE grant with the financial support of ANRT and APIS-GENE.

Genomic selection strategies and their potential to maintain rare alleles and de-novo mutations

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Sustainable breeding programs need to balance short-term genetic improvement with the conservation of genetic diversity. While genomic selection has considerably increased the genetic gain for many breeding programs, consequences on diversity can be less desirable. This is particularly the case for rare alleles and de-novo mutations, as markers used in genomic selection are generally not strongly associated to rare alleles. Moreover, genomic selection allows for the selection of young individuals without records, thereby ignoring the effects of de-novo mutations. To study possible solutions, we simulated populations of 1000 individuals subject to 50 generations of selection. We evaluated four selection strategies to identify the ones which best conserve favourable rare variants and de-novo mutations in the presence of additive and non-additive gene action. The genomic selection strategies represent a variety of approaches to balance between genetic improvement and diversity management and were: truncation selection, which only focuses on short-term gain; optimal contribution selection, which balances that gain with a constraint in the relatedness of the selected individuals; allele-reweighted selection, which upscales the effect of rare alleles in the breeding values; and constrained allele loss selection, a novel strategy which balances short-term gain with a constraint on the reduction in frequency of rare alleles estimated to be favourable. Systematic differences between the strategies were not observed for traits with non-additive gene action. For the trait under additive gene action, allele-reweighted selection obtained a higher genetic gain than truncation selection while preserving a similar level of genetic variance. Meanwhile, constrained-allele-loss selection obtained a similar genetic gain than truncation selection while accumulating a higher number of favourable de-novo mutations. These and similar strategies may contribute to the sustainable long-term use of genomic selection. This project has received funding from the European Union's Horizon 2020 Programme for Research & Innovation under grant agreement n°101000226.