New insights into resistance to paratuberculosis from sequence-based GWAS in Holstein cattle

Marie-Pierre Sanchez, Raphaël R. Guatteo, Arnaud Delafosse, Aurore Davergne, Cécile Grohs, Philippe Blanquefort, Alain Joly, Laurent Schibler, Christine Fourichon, Didier Boichard

Impact of Holstein haplotypes

J.B.C.H.M. Van Kaam[1], M. Marusi[1] and M. Cassandro[1,2]
[1]National Association of Holstein and Jersey Breeders (ANAFIJ), Via Bergamo 292, 26100 Cremona (CR), Italy, [2]University of Padova, Department of Agronomy, Food, Natural Resources, Animals and Environment, Viale dell'Università 16, 35020 Legnaro (PD), Italy; jtkaam@anafi.it

Since genomic selection became the new standard in dairy breeding, Holstein haplotypes have been discovered by various researchers. Such haplotypes result from a mutation in an ancestor which has spread in the population. Discovery of carrier animals is now part of weekly routine genomic evaluation. Seventeen haplotypes are analysed on over 450.000 animals. These haplotypes are 13 lethal disorders, 3 hair colours and polled. Animals are assigned as homozygous affected, heterozygous carrier or homozygous non-carrier. Many of the lethal haplotypes result in abortion during the gestation or in stillbirth. While functional mutations have been discovered for all of these haplotypes, these are not always present on DNA chips, so verification of haplotype segments remains needed. Trends are computed for each semester of birth for % of carriers, and for lethal haplotypes the expected number of lethal cases and expected percentage of lethal cases. From the Italian animals 72% was non-carrier for all of the 13 lethal haplotypes, whereas 24% carried one, and 3% more than one. HH3 and HCD have been greatly reduced, however HH5 has become quite frequent with around 7% carriers leading to nearly 3,000 abortions/year. Furthermore, recessive red has a carrier frequency of 7%. Cumulative frequencies of lethal haplotypes have reduced by 44%, and lethal cases by 50% since 2012. This corresponds with a reduction from around 8,000 to around 4,000 lethal cases per year in a population of a million females.

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M.-P. Sanchez[1], R. Guatteo[2], A. Delafosse[3], A. Davergne[4], C. Grohs[1], P. Blanquefort[5], A. Joly[6], L. Schibler[7], C. Fourichon[2] and D. Boichard[1]
[1]Université Paris Saclay, INRAE, AgroParisTech, GABI, 78350 Jouy-en-Josas, France, [2]INRAE, Oniris, BIOEPAR, 44300 Nantes, France, [3]GDS, Orne, 61000 Alençon, France, [4]GDS, Haute Normandie, 76000 Rouen, France, [5]GDS, Pays de Loire, 49800 Trélazé, France, [6]GDS, Bretagne, 56000 Vannes, France, [7]Allice, 75595 Paris, France; marie-pierre.sanchez@inrae.fr

Bovine paratuberculosis is a contagious and incurable disease, caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP), with adverse effects on animal welfare and serious economic consequences. In a previous GWAS conducted on 1,644 Holstein cows with an accurately defined status for MAP (controls, non-clinical shedders and clinical cases) and whole genome sequences (WGS) imputed using the 6th Run of the 1000 bull genomes (1kBG) project (multibreed population, UMD3.1 reference genome), we identified three genomic regions with effects on resistance to MAP infection on chromosomes 12, 13, and 23. The objective of the present study was to conduct further investigations using the 7th Run of the 1kBG, which includes a larger Holstein population with WGS based on the recent ARS-UCD1.2 reference genome. Thus, 50K genotypes of the 1,644 Holstein cows were imputed to the high-density (HD) level with FImpute and then up to WGS with Minimac using reference sets of 776 and 700 Holstein bulls, respectively. GWAS was carried out with GCTA, testing the individual effect of ~25M variant and accounting for the population structure through a HD-based genomic relationship matrix. After filtering variants for low imputation accuracy (R^2<0.3) or frequency (MAF<0.001), 4,815 variants had significant effects (6≤-log(P)≤34.5) on resistance to MAP infection. They were located in eight different genomic regions on chromosomes 6, 9, 12, 13 (2 regions), 14, 18, and 23. Two-thirds of these variants (3,194) were located in genes, mainly in introns (2,170), upstream or downstream regions (907), and exons (101 including 65 non-synonymous). In each region, the variants with the most significant effects were located in the *TMPRSS11F*, *HS6T3*, *ABCC4*, *SNTA1*, *SNTB1*, *NOTCH4*, *NFKBTL1*, *ATP6V1G2*, *DDX39B*, and *ELOVL5* genes. This study confirms the three genomic regions initially detected and reveals five novel regions for resistance to MAP infection.