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Novel BMP15 mutations responsible for an atypical hyperprolificacy phenotype in sheep

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Major genes increasing litter size (LS) and ovulation rate (OR) were suspected in the French Grivette and the Polish Olkuska sheep populations, respectively. To identify the genetic variants responsible for the highly prolific phenotype in these two breeds, genome-wide association studies (GWAS) followed by complementary genetic and functional analyses were performed. Highly prolific ewes (cases) and normal prolific ewes (controls) from each breed were genotyped using the Illumina OvineSNP50 Genotyping Beadchip. In both populations, an X chromosome region, close to the BMP15 gene, harbored clusters of markers with suggestive evidence of association at significance levels between $1E^{-05}$ and $1E^{-07}$. The BMP15 candidate gene was then sequenced and 2 novel non-conservative mutations called FecX^{Gr} and FecX^O were identified in the Grivette and Olkuska breeds, respectively. The two mutations were associated with the highly prolific phenotype ($p_{\text{FecX}^{\text{Gr}}}=5.98E^{-06}$ and $p_{\text{FecX}^{\text{O}}}=2.55E^{-08}$). Homozygous ewes for the mutated allele showed a significantly increased prolificacy (FecX^{Gr}/FecX^{Gr}, LS=2.50±0.65 vs. FecX⁺/FecX^{Gr}, LS=1.93±0.42, $P<1E^{-03}$ and FecX^O/FecX^O, OR=3.28±0.85 vs. FecX⁺/FecX^O, OR=2.02±0.47, $P<1E^{-03}$). Both mutations are located in very well conserved protein coding motifs and would alter the *in vitro* BMP15 signaling activity. Thus, we have identified 2 novel mutations in the BMP15 gene associated with increased LS and OR. Noteworthy, homozygous FecX^{Gr}/FecX^{Gr} Grivette and homozygous FecX^O/FecX^O Olkuska ewes are hyperprolific in striking contrast with the sterility exhibited by all other known homozygous BMP15 mutations. These results were obtained through the EC funded FP7 project 3SR-245140.

Genome re-sequencing in sheep used to detect signatures of selection

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Patterns of genetic variation are highly informative for understanding the diversity and evolutionary history of domestic animal species. Within this context, the International Sheep Genomics Consortium sequenced 73 sheep to a depth of 10-fold coverage. Following variant calling to identify approximately 20 million high confidence SNP, three methods were applied to search for regions that have undergone accelerated change in response to domestication and/or the establishment of sheep breeds with divergent phenotypic characteristics. These were: (1) detection of runs of homozygosity within individual genomes; (2) searching for regions of heterozygote deficiency within a set of 68 domestic sheep genomes; and (3) a polymorphism-divergence test that compares within, to between, species variability rates (HKA test) using 5 out-group wild sheep genomes. Known pigmentation genes MC1R, MITF, and ASIP were identified as outliers using one or more of the tests, confirming that the experimental strategy successfully detected selection events. The spectrum of variability within each gene will be presented, along with predictions concerning their functional consequence. Evidence was obtained to suggest developmental genes were selected during the domestication process, particularly those involved in controlling aspects of skeletal morphology. These results advance our understanding of the genetic history of this important livestock species.

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