

A nonsense mutation causes hydrocephalus in Friesian horses

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Hydrocephalus in Friesian horses is a developmental disorder that often results in stillbirth of affected foals and dystocia in dams. The occurrence is probably related to a founder effect and inbreeding in the population. The aim of our study was to identify the causal mutation for hydrocephalus in Friesian horses, as it will help in understanding its aetiology and allow selection against the disease allele using a DNA test. Genotypes were obtained using the Illumina® EquineSNP50 Genotyping BeadChip, where 29,270 SNPs remained after quality control. Significance level of genotype differences between cases (n = 13) and controls (n = 69) per SNP was determined with a χ^2 -test using the *ccfast* function in the GenABEL package in R. One strongly associated region was found and examined to identify overlapping regions of homozygosity between cases. Next generation DNA sequence analysis was performed of gene exons in the identified region on 4 cases and 6 controls. A genome-wide association study of hydrocephalus indicated the involvement of a region on ECA1 ($P < 1.68 \times 10^{-6}$). All cases, and none of the controls, carried 2 copies of a 0.58 Mb haplotype. Next generation DNA sequence analysis revealed a nonsense mutation that was identical to a mutation identified in a human case of muscular dystrophy-dystroglycanopathy with hydrocephalus. All available cases and none of the controls were homozygous for the mutation. 32 controls were heterozygotes of which 17 were dams of cases and 36 controls were homozygous for the normal allele. Hydrocephalus in Friesian horses has an autosomal recessive mode of inheritance. A nonsense mutation is responsible for hydrocephalus in Friesian horses and classifies the phenotype as a muscular dystrophy-dystroglycanopathy. Currently, Friesian horses are tested for the presence of the disease allele, which allows selection against this allele and thereby reduction in losses and suffering caused by hydrocephalus in the Friesian horse population.

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