

Genetics Of Cervical Spine Malformations In The Horse

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This study will identify genetic causes for abnormal formation of the cervical spine in horses.



Abnormal formation, or malformations, of the cervical spine are anatomical variations that can be associated with neurological disease, lameness and neck pain in the horse. In this study, we propose to gain a better understanding of these malformations in the horse and to determine the genetic causes. Within the seven cervical vertebrae in horses, the middle vertebrae (C3 to C5) are rather uniform. However, the vertebrae at each end (closest to head, C1 and C2) and (closest to chest, C6 and C7) are specialized and demonstrate different shapes. Interestingly, both of these regions have been associated with malformations. For this proposal, we will focus on two distinct malformations. These malformations include one that affects the first few vertebrae in the neck (occipitoatlantoaxial malformation or OAAM) and malformations that affect the lower vertebrae in the neck (called TC67) malformations. Whereas OAAM is reported in Arabian horses, these TC67 malformations primarily occur in Warmbloods and Thoroughbreds.

Previous work in our laboratory has discovered the genetic cause for OAAM1 in Arabian horses. This genetic mutation resides in a regulatory area of a gene, HOXD3, that is involved in coding for the formation of body structures during embryonic development. This family of homeobox genes direct the formation of many body structures during early embryonic development. However, the OAAM1 variant does not explain all cases of malformation at the first few vertebrae in the neck. We have recently identified a family of Arabians with malformations of the second vertebrae and incoordination as a result of this malformation. These horses tested DNA negative for OAAM1. In Specific Aim 1, we will use whole-genome sequencing to investigate the genetic basis for this malformation in this family of Arabian horses. We hypothesize that a genetic variant in, or regulating, one of the HOX4 genes will be associated with this inherited malformation in Arabian horses.

Identifying the genetic basis for this malformation will provide a genetic test for Arabian breeders and expand our understanding of the genetic pathways involved in overall cervical spine malformations.

Current estimates of TC67 approximate that between 20-30% of Thoroughbreds and Warmbloods have this anatomic variant. The genetic cause for this was proposed to be similar to a disease in cattle, called Complex Vertebral Malformation. However, the phenotype in cattle is clearly distinct from TC67 in horses. In Specific Aim 2, we will use whole-genome sequencing of horses with TC67 to exclude the gene that is causing disease in cattle as the gene for TC67 in horses. We will then investigate if there is a genetic basis for TC67 by creating pedigrees of affected horses and examining whole-genome sequences for possible genetic changes.

Importance to the Equine Industry: Despite varying opinions on whether these malformations, specifically TC67, result in disease or not, young horses are being increasingly euthanized based on this x-ray diagnosis and without associated signs of disease. Once we have identified potential genetic causes for the second vertebrae malformations in Arabian horses and TC67 malformations in Thoroughbreds and Warmbloods, we will expand our study to genetically test horses for these malformations and begin to associate signs of disease and performance success with these genetic malformations. Our long-term goal is to provide diagnostic tests for these malformations in the horse, while working closely with clinicians to define the clinical relevance.

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