Small ruminant genetic testing and diseases

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Abstract

Genetic testing can play an important role in management of small ruminants. There are four classes of genetic testing currently available to producers and veterinarians. Parentage identification allows keeping of accurate pedigrees, and therefore evaluation of offspring for desirable production traits. Genetic markers for specific production phenotypes can help producers to select animal with desired production traits. There are several genetic diseases identified in sheep and goats. Genetic testing for known gene mutations associated with a disease phenotype can be used to control the prevalence of disease and any resulting production losses. Lastly, testing has been developed for genetic mutations that have been identified that confer increased resistance to certain diseases. Increasing commercial availability of genetic testing for small ruminants has become an integrated part of herd management.

Key words: sheep, goat, genetic testing, disorders

Introduction

Identification of genetic traits and known causal mutations have increased substantially in sheep and goats in the last 10 years, however, they still lag considerably behind cattle. According to the compendium of inherited disorders, traits and genes in animal species (Online Mendelian Inheritance in Animals, OMIA), sheep have 49 and goats have 17 genetic traits in which the causal mutation is known, whereas cattle have 268.[19] The entire sheep and goat genomes have been sequenced and there are 50K SNP chips available for both species allowing easier identification of genetic traits using techniques such genome-wide association studies.[25] Whole genome sequencing has also allowed for the identification of microsatellite markers which can be used in parentage evaluation.[15,22]

Production phenotypes often follow a pattern of incomplete dominance where heterozygotes demonstrate an intermediate phenotype as compared to homozygotes.[16–18] Callipyge muscular hypertrophy phenotype in sheep is unique as it is expressed only if the mutant allele is contributed by the sire and the normal allele by the dam in an inheritance pattern called paternal polar over-dominance.[8] Most of the identified genetic disease phenotypes are produced in a simple autosomal recessive pattern.[14] These diseases are easily controlled with testing and selective breeding.

Parentage testing

Understanding DNA structure is key to understanding DNA-based parentage testing. DNA is made up of 4 bases: adenine(A), cystine (C), guanine (G) and thymine (T), put together in a linear structure to form chromosomes. Specific combinations of these bases form genes. Additionally, the animal genome contains sequences of bases that repeat in a tandem manner called microsatellite markers. Most parentage testing uses a specific type of microsatellite called short tandem repeat (STR) which has 2 bases repeat in tandem.[15,22] Many STR demonstrate length diversity within a population, allowing them to be used as markers for parentage. By using several STR, most parentage can be resolved with a high degree of certainty. The Veterinary Genetic Lab at the University of California-Davis currently uses 15 STR for sheep and 16 STR for goats,[26] although more STR can be used if potential parents are highly related. The sensitivity of parentage exclusions is 100%, whereas inclusion sensitivities range from 95-99%, depending what genetic material is available for testing.[26]

Production trait genetic testing

Several genetic variants affecting muscling in sheep have been identified. The features found in animals with the high-muscling phenotypes are similar regardless of the genetic mutation. These animals demonstrated increase in muscularity, particularly of the loin and hindquarter, and leanness/low fat content. These animals also have different development and growth trajectories.[24] The most well-known mutations are in the myostatin (GDF8) gene and the Callipyge (CLPG1) gene.[7,8,13] The myostatin gene mutation is common in the Texel breed, which is the major breed used for creating terminal crosses in Europe. The CLPG1 gene was identified in the American Dorset and all animals carrying this gene descend from a ram born in 1983 that demonstrated an extreme muscling phenotype. The GDF8 mutation is point mutation, G to A transition, which creates a target site for microRNA highly expressed in skeletal muscle which block translation of myostatin.[7] The CLPG1gene variant is an A to G point mutation, however, it is only inherited if the ram carries the mutation and passes it on to his offspring. Offspring of females carrying the mutation never express the hypertrophic muscling phenotype.[24] This mode of inheritance is referred to as paternal polar over-dominance.[8] Genetic testing for the mutations associated with GDF8 and CLPG1genes are commercially available in the US (GDF8–**https://www.neogen.com/categories/livestock-genetic-traits-conditions/ovine-myostatin**/, Callipyge - **http://genecheck.com/callipyge-gene/**). Genotyping for hypertrophic muscling can play a complementary role in genetic selection in the sheep meat industry.

There are significant polymorphisms in the gene responsible for the production of alpha-S1 casein in milk. These polymorphisms result in variants associated with high and low production of casein.[16–18] Animals carrying the high-casein variants also tend to have higher fat content in their milk;[5] together these traits are desirable for cheese producers as they result in higher cheese yield. On the other hand, some research suggests that lower casein content is better for people with milk sensitivities.[1] Many cheese producers are starting to use genetic testing to select for goats carrying the specific variants that suit their production needs.

There are two high-casein variants, A and B, and three low-casein variants, E, F and N, and 1 null variant, O1, that produces no alpha-s1 casein.[28] Animals expressing a high variant and a low/null variant will have an intermediate level of casein production. In the U.S., the high alleles are found most commonly in Nubian, La Mancha and Nigerian Dwarf goats, whereas Toggenburgs, Alpines, Saanens and Oberhaslis predominantly

express the low alleles,[16] although genetic testing and selection of bucks carrying high alleles can have a significant impact on frequency of alleles within a breed as was found in a Italian study.[10] Alpha-s1 casein testing is available in the U.S. for all known variants (**https://vgl.ucdavis.edu/test/alpha-s1-casein**). Testing and selection for alpha-s1 casein variants can have a significant economic impact for farms producing milk primarily for cheese production.

Genetic diseases

There are several genetic disorders identified in both sheep and goats. There is currently commercial testing available for ovine hereditary chondrodysplasia (spider lamb syndrome), dermatosparaxis (skin fragility), ectodermal dysplasia (hairy lamb syndrome) and caprine N-acetylglucosamine-6-sulphatase (G6S) deficiency (mucopolysaccharidosis type IIID). For these proceedings, I will focus on spider lamb syndrome and G6S deficiency.

Spider lamb syndrome is an autosomal recessive genetic disorder that results in skeletal deformities in young sheep. Lambs may be normal at birth, but the deformities typically manifest by 4-6 weeks of age, including facial defects, kyphosis and scoliosis, overly long, bent and/or splayed legs, flat ribcage and poor musculature. Lambs with these defects were first observed in black-faced lambs in the 1970s.[21,23] A mutation in the fibroblast growth factor receptor 3 (FGFR3) gene is responsible for the disorder.[2] Breeds that have been identified as carrying the mutation are Suffolk, Hampshire, Southdown, Shropshire, Oxford and crossbreds derived from those breeds in the U.S.[9]

G6S deficiency affects Nubian goats and their crosses.[4] It is also an autosomal recessive genetic disorder characterized by accumulation of catabolized heparin sulphate glycosaminoglycans in lysosomes particularly in the central nervous system and somatic cells due to lack of G6S enzyme activity.[4] Affected animal exhibit growth retardation, neurologic deficits, stilted gait and are generally poor doing animals.[4,12] The genetic defect is a nonsense mutation in codon 102 of the 559-amino-acid G6S coding sequence changing a C to T and resulting in production of a nonfunctional, truncated protein.[4] G6S deficiency should be considered as a differential diagnosis in poor-doing adult Nubian/Nubian-Cross goats.

Genetic susceptibility/resistance testing

Genotypes have been identified in both goats and sheep that confirm greater resistance to classical scrapie, not only limiting disease development, but also likely limiting transmission to other animals in breakthrough cases. Genetic testing is readily available for both sheep **(http://genecheck.com/, https://www.neogen.com/, https://ag.colorado.gov/labs/animal-health-laboratory) and goats (https://vgl.ucdavis.edu/test/goat-scrapie-susceptibility)**. Protection is conferred by an amino acid change in the prion protein. In sheep, the main determinants of scrapie resistance are at amino acid 171 and amino acid 136.3,11,29 Likely because of evolutionary timing, an arginine (R) at 171 is always accompanied by an alanine (A) at 136, which are both considered resistant variants. A glutamine (Q) or histidine (H) at 171 and a valine (V) at 136 are considered susceptible allele s.[11,29] Heterozygotes are more resistant to the development of clinical scrapie.[3]

In goats, there are 2 amino acid modifications that confer resistance to classical scrapie: Serine (S) at position 146, and lysine at position 222, whereas the susceptible alleles are asparagine (N) at 146 and Q at 222.20,27 Similar to sheep, heterozygotes are also considered to have increased resistance to classical scrapie.[6,31] S146 is found in ~12% of goats in the U.S., with the highest frequency in Boer and Nubian goats; K222 is much rarer and was only found in Toggenburgs and La Manchas.30 Scrapie genotype results from the 2019 NAHMS Goat study which sampled many goats across the U.S. should be available soon. Selection for resistant genotypes can be use a management tool to protect sheep and goat populations from developing and potentially spreading classical scrapie.

Conclusion

The development of genetic testing for pedigree integrity, production traits, genetic disorders and disease resistance can all play an important role in the management and genetic selection of small ruminants.

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