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Jacob sheep breeders find more Tay-Sachs carriers

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The American Livestock Breeds Conservancy and Jacob conservators have played a significant role in identifying the source and limiting the spread of a lethal mutation in Jacob sheep (*ALBC NEWS*, Vol.26, Issue 1; Vol.27, Issue 2). The mutation, now known as the G444R mutation in the *hexa* gene, was first suspected in 1999 in two affected sheep which were presented to Texas A&M's veterinary clinic. The initial diagnosis, reported to Jacob breeders in 2002, was gangliosidosis - defective lysosomes not processing and expelling nerve cell lipid and fat waste residue. New York University Medical Center's Department of Neurology (NYU) got involved with the project and did extensive DNA testing on Jacob blood and tissue. They compared the Jacob sheep DNA to sheep, cattle, and human DNA and found a specific genetic mutation that caused the skipping of a critical part of a gene that produces Hex A, the enzyme that processes a vital lipid in nerve cells. The initial gangliosidosis diagnosis was now specifically identified as the G444R mutation that causes a form of Tay-Sachs disease (TSD) in Jacob sheep.

NYU also discovered that the DNA sequence of nucleotides and amino acids in the Jacob is 86% and 89% similar, respectively, to human DNA. This discovery presented a unique opportunity not only to eradicate a fatal, autosomal recessive mutant gene in a rare breed but also provided a large animal model to address the fatal human disease, Tay-Sachs. Affected Jacob sheep die at about eight months; affected children die at about five years.

Either Jacob parent can carry the mutant autosomal recessive gene. Carriers appear normal and live a normal life. But breeding a mutation-carrying Jacob to a normal Jacob results in a 50/50 chance of producing another carrier lamb. A carrier Jacob bred to a carrier Jacob results in 25% chance of an affected lamb, a 25% chance of a normal lamb, and a 50% chance for additional carriers. Identification of carriers helps avoid the loss of foundation bloodline Jacob genetics. To identify carriers, the Neurogenetics lab at NYU offered free DNA testing for the mutant gene for any Jacob sheep breeders who wished to identify carriers in their flock, reduce the number of carriers in the Jacob population, and prevent the production of affected sheep (*ALBC NEWS*, JSBA Newsletter, 6/10). The NYU lab sent test supplies, instructions, and did the testing at no cost to the Jacob breeders.



Photo by SVF Foundation
Courtesy of the American Livestock Breeds Conservancy

Dr. Bai Zeng and Paola Torres processed 443 DNA samples from 10 participating shepherds located across the U.S. They identified 51 mutation carriers, a carrier incidence of 11%; 17 different flock names appeared in the names of carriers, and 90% of the shepherds' flocks had one or more mutation carriers. NYU spent about \$45,000 on testing supplies, mailings, and DNA testing. Participants received a report of mutant gene/normal gene for each Jacob tested. In many cases, breeders with identified carriers also received corrected and extended pedigrees based on complete Jacob ancestry records, including the AMBC (now ALBC) records held by the USDA Library in Beltsville, MD. These bloodline ancestry records helped point to the source and spread of the mutation. Turner 183K, a bloodline foundation ram and the apparent source of the mutation in North America, was born of imported Jacobs and the primary suspect is Turner's Supermom. Over the past two months, the lab has received few new requests and some breeders who requested and received testing materials have not submitted DNA specimens to the NYU lab. Since most concerned Jacob breeders have responded and the Jacob Sheep Breeders Association judged the mutation as "by no means a common problem" and "very unlikely that any breeder will ever see a problem," the two-year period for free testing will be curtailed.

The G444R mutation in Jacobs has not been eradicated but over 40 carriers have been identified by DNA testing and the source and spread of the problem has been documented. The knowledge gained by testing and identifying carriers will benefit the breed in general and, moreover, is critical knowledge for conserving the original bloodline. Knowing which Jacobs are carriers opens two courses of action: avoid selecting carriers for the Jacob gene 'puddle' or, breed a known carrier to retain the foundation bloodline genetics and test the offspring of carrier matings until a clear, better replacement is produced. This conserves the genetics and diversity of the breed. In fact, several sites that collected Jacob semen and embryos for cryo-preservation were notified of the mutation so they can take appropriate action in the future. Conversely, mutant gene semen and embryos are being cryo-preserved so the mutation will be available in the future.

The G444R mutation in the Jacob has taken several steps forward as a large animal model of the human form of TSD. Four TSD-affected Jacob sheep were placed in a clinical program similar to the program used for TSD cats, the small animal model. Two treated Jacobs have passed a longevity milestone but the final results and significance of this first clinical program for Jacobs will not be known for months. These tests will then have to be repeated and results confirmed, a process that will consume the next few years.

In concluding this final article on a congenital mutation in Jacob sheep, the authors wish to acknowledge and thank the Jacob shepherds who collaborated on this project and whose contribution toward identifying carriers and the source will help conserve foundation Jacob genetics. The consortium of scientists and doctors extend their gratitude to the Jacob breeders who have offered to donate carriers to this research project, and the New York University School of Medicine, the National Tay-Sachs and Allied Diseases Association, Cure Tay-Sachs Foundation and the Tay-Sachs family foundations that supported the testing and research.

(For more information, see the following resources: ALBC's "Managing Breeds for a Secure Future," Chapters 5 and 6, "Tay-Sachs disease in Jacob sheep" in Molecular Genetics and Metabolism , and "The pathology of GM2 gangliosidosis in Jacob sheep" in Veterinary Pathology.)

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