GENETICS OF SCRAPIE

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Scrapie is a slowly progressive infectious disease of sheep and goats, which causes degeneration of the central nervous system. Scrapie is one of several diseases known as transmissible spongiform encephalopathies (TSE) that affect animals and humans. Bovine Spongiform Encephalopathy (BSE), or "mad cow disease", is a TSE that degenerates the nervous system in cattle. In humans, Creutzfeldt-Jakob disease and Kuru are two known TSE diseases. Although these TSEs are similar, there is no evidence that the diseases are transmitted between species.

Transmission of scrapie from sheep to sheep is thought to occur through direct contact (lateral transmission). Vertical transmission, or from the ewe to developing fetus, is unlikely. The scrapie agent is most commonly transmitted from an infected ewe to her own or other lambs during the first few months of life. This lateral transmission may occur orally or nasally, as the scrapie agent has been found in various sheep tissues and body fluids including central nervous system tissue and the placenta. The role of environmental contamination with the scrapie agent (feed, water, bedding) is not known. However, the scrapie agent is very resistant to heat and common disinfectants.

The incubation period for scrapie is relative long, ranging from two to five years. Due to this long incubation period, many sheep die from natural or other causes prior to developing clinical signs of the disease. The long incubation period also contributes to the difficulty of assessing the prevalence of the disease. Early symptoms of scrapie include anxiousness and excitability, with head/neck tremors and uncoordinated movement. Advanced stages of the disease are characterized by progressive weight loss, and intense rubbing and scraping against anything to relieve itching of the skin, as well as uncoordinated movement and violent shaking. Rubbing, and scratching with legs or wool biting, results in broken wool and loss of wool. These clinical signs are similar to those found with other diseases including external parasites and listeriosis. Presence of scrapie must be confirmed with brain tissue samples after death. A live-animal test using lymphoid tissue from the third eyelid is currently under development, and shows great promise. No blood tests or other procedures are currently available for diagnosis of the disease in the live animal, and there is no treatment for the disease.

Current research supports that scrapie is caused by an infectious protein particle called a prion or prion protein. These scrapie prions differ from normal proteins only structurally (in the way they are folded). These scrapie prions appear to have the ability to recruit other normal proteins and induce them to alter their structure to become scrapie prions. This is quite different from other infectious diseases, commonly caused by bacteria or viruses which replicate themselves and multiply. In the case of scrapie, the infectious agent (prion) is a conversion of the sheep’s own protein that causes disease. This scrapie prion also has another unique attribute- no antibodies are formed since the infectious prion protein is formed by the host itself. Since no antibodies are produced as a means of
fighting the infection, common live-animal blood tests that rely on detection of antibodies for a specific pathogen are not applicable. For this reason, detection of scrapie in the live animal is difficult and limited.

The relationship between scrapie and genetics is becoming clearer. In 1979, a British researcher published results of a twenty-year study investigating the genetics of scrapie. In his research, Perry studied flocks with high levels of scrapie and selected rams whose progeny did not die of the disease (even though they were exposed). The research identified rams whose progeny never developed the disease despite continuous exposure, with many of the lambs reared by dams that developed clinical signs during or after lactation. Today, we know these rams must have been “RR” genotype.

In the last twenty years, the scientific understanding of the relationship between scrapie and genetics has grown tremendously. It is important to recognize that scrapie is not transmitted genetically (and therefore not a genetic disease), rather the susceptibility to scrapie appears to be genetic.

Proteins are manufactured by the joining together of amino acids. Genes code for the sequences of amino acids that form a protein. Genes are made up of stretches of DNA, which is the basic hereditary material of organisms. Variations in proteins (amino acid sequences) are coded for by different forms of genes, known as alleles. In the case of scrapie, the amino acid of interest is located at codon 171 (codons are stretches of DNA that code for a single amino acid). There are two basic alleles at codon 171 that have been found to be related to scrapie susceptibility or resistance. The “Q” allele is known to produce proteins that are susceptible to conversion to scrapie prions. The “R” allele is thought to produce proteins that are not susceptible to this conversion to the scrapie prion (resistant). A sheep will have two copies of the prion gene in each cell. These copies may be the same or different alleles (i.e. “Q” or “R”), and each cell will contain the same copies. Therefore, a sheep may have a genotype of “QQ”, “QR”, or “RR” at codon 171. “QQ” would indicate the sheep has two copies of the “Q” allele, “RR” two copies of the “R” allele, and “QR” one copy of each allele.

So how do “Q” and “R” relate to scrapie susceptibility? Research conducted at Washington State University and USDA found that 30 out of 30 scrapie-affected sheep had a genotype of “QQ” at codon 171. A total of 565 sheep were studied. Of the normal (unaffected) sheep, 56% also had the “QQ” genotype. It is important to recognize that sheep with the “QQ” are not necessarily carriers of scrapie or infected with the disease. To be a carrier, a sheep must be exposed to the scrapie agent. The genotype “QQ” is associated with higher susceptibility to the disease. This has been demonstrated experimentally with sheep that were inoculated with the scrapie agent and monitored for up to 10 years for clinical signs of the disease. Of the 105 sheep inoculated, 63 developed clinical signs of scrapie. All infected sheep had the “QQ” genotype. No sheep with the “QR” or “RR” genotype developed the disease. This also is evidence that the “R” is dominant, as the presence of one “R” was associated with resistance.
As mentioned before, “Q” and “R” alleles code for a specific amino acids in the protein’s structure. For the sheep prion protein, changing the 171st amino acid (coded for by codon 171 of the gene) from “Q” (glutamine) to “R” (arginine) changes the prion’s ability to convert to a scrapie prion. A prion protein with an “R” at codon 171 appears to be resistant to conversion to scrapie prion.

With this evidence, it makes sense to avoid “QQ” genotypes that are more susceptible to scrapie. Genotype at position 171 of the prion gene can be determined from a blood sample on any sheep. This genotype can be used as a selection tool to enhance resistance to the disease within a flock. Since “RR” and “QR” sheep have never been diagnosed with a clinical case of scrapie, genetics may play an important role in the eradication of the disease as well. There has been some concern that “RR” and/or “QR” sheep may be carriers but never show clinical signs, or have extended incubation periods which are beyond the normal life of a sheep (and therefore are not diagnosed with the disease). However, it has never been demonstrated that a sheep can carry the scrapie agent without becoming infected itself (i.e. sheep that transmit the disease also will exhibit clinical signs at some time).

So how can codon 171 genotype be used in selection? Keep in mind that each ram or ewe will pass on one copy of each chromosome to its offspring. For sheep that are “QQ” or “RR”, only “Q” or “R” sperm or eggs will be produced. For sheep that are “QR”, either a “Q” or an “R” may be passed on. By knowing the genotype of the two sheep in any mating, the probability of the resulting progeny genotype can be predicted. As an example, assume we have a “RR” ram that we mate to a “QQ” ewe. A Punnett square can be set up to determine the possible resulting progeny genotypes.

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<tr>
<th>Ram</th>
<th>R</th>
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<tbody>
<tr>
<td>Ewe</td>
<td>Q</td>
<td>QR</td>
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<td></td>
<td>Q</td>
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In this example, the ram only produces “R” sperm and the ewe only produces “Q” eggs. The resulting genotype of every lamb from the mating will be “QR”.

Assume a “QR” ram is mated to a “QR” ewe. In this case, both the sire and dam can pass either the “Q” or “R” gene.

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<thead>
<tr>
<th>Ram</th>
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<tbody>
<tr>
<td>Ewe</td>
<td>Q</td>
<td>QQ</td>
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<td></td>
<td>R</td>
<td>QR</td>
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From this mating, three genotypes are possible in the resulting progeny. One-fourth of the lambs will be “QQ”, half will be “QR”, and one-fourth will be “RR”. In other words, three-fourths of the lambs will carry an “R” and be resistant.
A “QR” ram mated to “QQ” ewes will result in 50% of the progeny carrying an “R”.

<table>
<thead>
<tr>
<th>Ewe</th>
<th>Q</th>
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<tbody>
<tr>
<td></td>
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Codon 171 genotype should be a selection tool for all seedstock producers who sell rams and/or ewes. This selection should start with stud rams. Rams that are “RR” or “QR” should be utilized so that a high percentage of the resulting offspring carry the “R” factor. So what is the frequency of “Q” and “R” in the current sheep population in the U.S.? To date, most of the scrapie work relative to genetics has been conducted with the Suffolk breed. The Suffolk breed is know to have the highest incidence of scrapie, although the disease has also been diagnosed in Border Leicester, Cheviots, Corriedales, Cotswold, Dorset, Finn, Hampshire, Merino, Montadale, Rambouillet, Shropshire, Southdown, and several crossbreds. Before testing was available, it was estimated that approximately 40% of black face sheep in the U.S. were “QR”. It is likely that the frequency of “R” has increased in recent years due to selection. One only needs to attend shows and sales to recognize the importance codon 171 genotype has to seedstock breeders. “RR” sheep often are sold at a premium, and “QQ” sheep are often penalized. There are certainly a number of “RR” and “QR” rams available, and scrapie resistance can be incorporated into a selection scheme without sacrificing other economically important traits.

For seedstock breeders, starting with “RR” or “QR” rams is the first step, regardless of the genotype of the ewes. The genotyping blood tests cost from $16-17, depending on the number of sheep tested. Initially, whole-flock testing may be cost prohibitive especially if the genotype of the ewe flock is unknown. Once “R” has been introduced through the use of rams with known genotype, potential replacements can be screened. It may be most advantageous to use the genotype as a selection tool, rather than a culling tool. Remember that “QQ” ewes can be mated to “RR” rams and produce progeny that are 100% resistant. It would not make sense to cull the ewe flock of productive “QQ” ewes based solely on their codon 171 genotype. However, these ewes need to be mated to produce lambs that are “QR”. Seedstock breeders need to remember that if a sheep you sell is ever diagnosed with scrapie on another producer’s farm, your flock will be considered a source flock. For this reason, many seedstock breeders only sell “QR” and “RR” sheep.

So what are the implications for commercial producers? Commercial producers are in a different position than seedstock breeders, assuming that they do not sell breeding stock. However, scrapie can infect crossbred commercial flocks just as it can purebred flocks. Therefore, when replacements are being kept, “QQ” rams should be avoided. Utilizing “RR” and “QR” rams will have the impact of adding resistance to the ewe flock.
Scrapie is a disease that poses great threat to the U.S. sheep industry. For the U.S. industry to remain viable and competitive, programs that reduce and eliminate the disease must be embraced. Genetic selection for reduced susceptibility to the disease is a viable tool for the industry to utilize to reduce the incidence of clinical scrapie in sheep.

**References**


