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Ovine Scrapie disease: Do we have to live with it?☆

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Abstract

Scrapie has persisted in sheep for centuries, and most sheep-producing countries worldwide, with few exceptions, are, or may be, affected by the disease. Why is it that the Scrapie status in many countries is not known with certainty, why has the disease appeared "in waves" from time to time in others, and why has it been so difficult to combat and eradicate ovine Scrapie disease? In this article, bits of old and new knowledge are put together, in an effort to answer some of these questions and explain why it probably will be impossible, at least in the nearest future, to eradicate all variants of prion disease in sheep. The question is also: "how can we live with the disease, reduce losses in sheep due to a lethal disease, and at the same time ensure safe food or food free of prions transferable to man?" The significance of continuing research, as well as prevailing focus on diagnosis and surveillance is vital in the foreseeable future. Artificial selection based on PrP genotyping and various strategies for eliminating the VRQ allele, which is associated with a higher risk of classical Scrapie than any other allele, can be seen as accelerating a natural process, and there is a possibility that classical Scrapie may eventually disappear from the sheep population.
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1. Background

Scrapie belongs to the most intriguing group of diseases, the prion diseases, comprising slowly developing fatal neurodegenerative conditions in sheep and other animal species, as well as humans. Scrapie in sheep is the oldest of these diseases, being known in Europe for more than 250 years, and is often characterized as the prototype of prion disease. The fact that Scrapie has prevailed in sheep for so many years, without having disappeared in spite of intense efforts to eradicate it in many countries, leaves us with surprise for what the agents, the prions, are or can do. The inter-species jump of the bovine spongiform encephalopathy-prion to humans, whether it originally came from sheep, goats or cattle, is a warning of the agents' potential. And, despite an impressive pace of prion research in recent years, numerous issues remain unresolved and new variants of disease continue to appear.

Through history, ovine Scrapie was at times regarded as a genetic disease, as the familial link was very strong (Parry, 1984). The disease would appear in waves in certain family lines, disappear and then, emerge again. It became clear, however, that for an animal to develop Scrapie, it had to be both genetically susceptible to the disease and exposed to an infecting agent (Hunter et al., 1997). Early experimental transmission studies using sheep often yielded confusing results; however, the infection rates might vary between 3% and 35% and there was as much variation in rates of susceptibility between individual sheep, as well as between breeds (Gordon, 1966). Sheep lines were selected for resistance and susceptibility to Scrapie, and studies in Cheviot-breed sheep

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and in mice, gradually revealed the PrP gene and the genetics of Scrapie, as outlined in the review by Hunter (2007).

2. Genetic susceptibility: PrP genotypes

The association between Scrapie susceptibility and sheep encoding the prion protein (PrP) $V_{136}R_{154}Q_{171}$ allele is very strong. In the UK, sheep with a homozygous VRQ/VRQ genotype is, in most outbreaks, almost guaranteed to develop Scrapie (Hunter, 2007). However, in countries like New Zealand, Australia (Bossers et al., 1999) and Norway (Tranulis et al., 1999), there are sheep of homozygous VRQ/VRQ genotypes which are clinically healthy. In breeds like Cheviot and Texel, the VRQ allele is highly associated with Scrapie (Goldman et al., 1991), while in Suffolk-breed sheep and in other breeds, homozygosity for prion protein alleles encoding glutamine-171 (Q_{171}) renders sheep susceptible (Westaway et al., 1994; Hunter et al., 1999). The susceptibility of the PrP genotypes may be modified by both the breed and the prion strain (Goldman et al., 1994). For breeds with the VRQ allele, the susceptibility is like that of Cheviot-breed sheep (VRQ-Scrapie), for breeds where the VRQ allele is very rare or absent, the susceptibility is like that of Suffolk-breed sheep (ARQ-Scrapie). The $A_{136}R_{154}R_{171}$ allele generally renders sheep more resistant to Scrapie, the most resistant sheep being homozygous ARR/ARR. Sheep with the "ancestral" or "wildtype" ARQ allele are less susceptible, but they may get Scrapie (Tranulis et al., 1999; Tranulis, 2002). In most circumstances, the VRQ allele is associated with a markedly higher risk of disease than any of the other alleles (Woolhouse et al., 2001; Gubbins and Roden, 2005).

The close association between PrP genotype and Scrapie susceptibility has led to the "biggest genetic selection process ever attempted", in the UK [by means of adopting the National Scrapie Plan (NSP) and the Compulsory Ram genotype Scheme (CRGS)] (Table 1) and in other European countries (EC, 2007; Hunter, 2007).

The distribution of PrP genotypes in randomly sampled sheep within the EU reveals large differences between the countries. In some countries (e.g., The Netherlands, Germany, Lithuania, Luxembourg, Hungary, France) over 20% and up to 65% of samples are within the group NSP1 (more resistant), whilst in other countries (e.g., Denmark, Ireland, Austria, Slovenia, Sweden, Norway) more samples are within groups NSP4 and 5 (susceptible) (EC, 2005; Sviland et al., 2006). The distribution could be incidental or one may speculate whether the first group of countries, with more resistant sheep, may have lost susceptible sheep due to Scrapie in earlier times and hence have been exposed to natural selection (Woolhouse et al., 2001). The prevalence of susceptible sheep in NSP4 and 5 could then illustrate less infectivity among the sheep. In some countries (e.g., France, Spain, Portugal, Greece, Italy, Slovakia, Germany), a policy of breeding has been adopted. Iceland has difficulties to adopt a breeding policy, because of the apparent complete lack of ARR/ARR sheep (Thorgeirsdottir et al., 1999).

Recently, a protective effect of the amino acid substitution M137T, I142K or N176K on the ARQ allele in sheep experimentally challenged with either Scrapie or BSE has been reported (Vaccari et al., 2007). Polymorphism at codon 154 (R/H) has also been perceived to play a role in susceptibility to Scrapie. A recent study in Greece suggested that presence of H_{154} is likely to confer higher susceptibility to Scrapie in Chios-breed sheep (Ekateriniadou et al., 2007), which lack V_{136}. The influence of H_{154} to enhance susceptibility to Scrapie is not well understood, thus further studies are needed to address this issue. These observations suggest the existence of additional PrP alleles that significantly affect

Table 1
Listings in the National Scrapie Plan (NSP) applied in Great Britain (DEFRA, 2007)

PrP genotype	NSP type	Degree of resistance
ARR/ARR	1	Most resistant to Scrapie
ARR/AHQ, ARR/ARH, ARR/ARQ	2	Genetically resistant to Scrapie but need careful selection when used for breeding
ARQ/ARQ, AHQ/ARH, AHQ/ARQ, ARH/ARH, ARH/ARQ	3	Little resistance to Scrapie and need careful selection when used for breeding
ARR/VRQ	4	Genetically susceptible, should not be used for breeding, unless in the context of a controlled breeding programme
VRQ/AHQ, VRQ/ARH, VRQ/VRQ	5	Highly susceptible, should not be used for breeding

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