



## EVOLUTION OF THE SHEEP PRION PROTEIN GENE

### ISSUE

1. To consider a recent paper on molecular evolution of the sheep prion protein gene<sup>1</sup>.

### BACKGROUND

2. The susceptibility of sheep to scrapie is known to be influenced by polymorphisms in the prion protein gene (PRNP) especially at codons 136, 154 and 171. Fifteen genotypes resulting from variation at these codons have been identified. The genotypes occur at widely differing frequencies in different breeds of sheep.
3. The National Scrapie Plan (NSP) for Great Britain consists of a breeding programme to increase the number of sheep that genetically are naturally resistant to transmissible spongiform encephalopathies (TSEs). Its primary aims are to protect animal health by reducing and eventually eradicating scrapie and to protect public health from the theoretical risk of BSE (if it is present and being masked by scrapie) by increasing levels of genetic resistance to TSEs. The breeding programme consists of different schemes and initiatives, based on various considerations including the relative resistance of sheep carrying the ARR allele to scrapie.
4. The NSP implements a recommendation from the SEAC Sheep Subgroup for a long-term control and eradication programme for scrapie. At its most recent meeting in July 2004 the Subgroup concluded that the underlying strategy of the NSP to breed for scrapie resistance remains appropriate. However, it was considered that the basis for the strategy should be continue to be kept under review in the light of emerging scientific findings with respect to the possible detection of scrapie infections in animals of genotypes currently thought to be most resistant to infection.

---

<sup>1</sup> Slate (2005) Molecular evolution of the sheep prion protein gene. *Proc. R. Soc. B.* 272, 2337-2344.

5. At SEAC 88, SEAC was informed about a range of studies on atypical scrapie in sheep. The committee agreed that, now that a number of issues around atypical scrapie are becoming clearer, the SEAC Sheep Subgroup should consider the emerging scientific information in more depth and the possible implications for the NSP. The Subgroup will meet in January 2006.

## **SLATE PAPER**

6. A paper by Jon Slate (see Annex 1) investigated the evolutionary selection pressures acting on ruminant PRNP using a theoretical approach of molecular evolution analyses of ruminant PRNP sequence data. On the basis of these analyses, the author concluded that PRNP in sheep has evolved by balancing selection rather than positive selection. In other words, the natural evolution of sheep PRNP has resulted in variation in the coding sequence to include genotypes that are relatively susceptible to scrapie because variation in the gene is favourable.
7. The author proposes a number of possible hypotheses for the variation in sheep PRNP:
  - (i) susceptible genotypes confer some advantage(s) to sheep in the absence of scrapie thereby maintaining PRNP variation over time.
  - (ii) heterozygote genotypes are advantageous because they confer relative resistance to scrapie compared with homozygous genotypes.
  - (iii) relative susceptibility to scrapie is determined by the compatibility of PRNP genotype of the host and the scrapie strain such that incompatibility leads to a barrier to infection. Thus, variation in PRNP could be maintained by exposure over time to scrapie strains with different compatibilities, and therefore infection efficiencies, with sheep genotypes.
  - (iv) variation in an untranslated region linked to PRNP influences the expression levels of prion protein and therefore, susceptibility to scrapie, which helps to maintain variation in the coding region.
8. The author suggests that hypotheses (ii) and (iii) appear to be the most likely. This because there is evidence from humans and sheep that heterozygote genotypes are more resistant to TSEs. In addition, there is evidence that conversion of normal prion protein to an abnormal form is most efficient when the genotype of the

host from which infection is transmitted and the recipient host is the same.

9. The author notes that the aim of the NSP breeding programme is to induce positive selection of a single relatively resistant genotype to scrapie infection. Since this results in depletion in genetic variation, it runs counter to the natural evolution of PRNP in sheep that appears to favour variation. One possible implication is that the NSP may produce a genetically uniform population of sheep that could be susceptible to rare scrapie strain(s). In view of this, the author recommends that further investigations of the role of PRNP variation on resistance to rare scrapie strains and on fitness and production traits be conducted. In addition, it would be prudent to preserve existing PRNP variation, as frozen semen and in managed populations.

#### **INDEPENDENT REVIEWS OF THE SLATE PAPER**

10. Due to the specialist nature of the molecular evolution approach and analyses undertaken, the paper by Slate was sent to two independent genetics experts. The experts were asked to review the paper and to comment on the methodology used and the implications for the NSP. The reviews have been anonymised and are given at Annex 2.

#### **ADVICE SOUGHT FROM THE COMMITTEE**

11. The committee is requested to comment on the findings of the Slate paper and the possible implications for the NSP.



**Slate (2005) Molecular evolution of the sheep prion protein gene.  
*Proc. R Soc B.* 272, 2337-2344.**



**Independent expert reviews of the paper by Slate**