**PrP gene polymorphisms in Cyprus goats and their association with resistance or susceptibility to natural scrapie**

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In contrast to scrapie in sheep, the genetic basis of susceptibility to scrapie in goats is not well understood. To study the association of prion protein (PrP) alleles with susceptibility to scrapie in goats in Cyprus, the coding sequence of the caprine PrP gene was determined in 717 goats, including 218 scrapie positive animals. Several novel polymorphisms were detected, such as a novel octarepeat variant and a stop codon mutation. Amino acids at codons 146 and 154 were associated with susceptibility to goat scrapie. Animals heterozygous for serine (S) and aspartate (D) at codon 146 were significantly under-represented in scrapie positive animals and no positive animals were found that were homozygous for these amino acids at codon 146. These results might provide the basis for genetic control of scrapie in Cypriot goats.

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**Introduction**

Scrapie is a fatal neurodegenerative disease of sheep and goats which, together with bovine spongiform encephalopathy (BSE) in cattle and Creutzfeldt–Jakob disease (CJD) in humans, belongs to the group of transmissible spongiform encephalopathies (TSEs). The occurrence of natural scrapie is strongly influenced by alterations in the host gene that encodes the prion protein (PrP) (Hunter et al., 1997). Such polymorphisms might influence the conversion of PrP into the pathogenic isoform PrPSc (Bossers et al., 1997).

In sheep, several polymorphisms of **PrP** gene are associated with differences in the phenotypic expression of prion diseases, such as incubation period, pathology and clinical signs. While more than 30 polymorphisms have been described, only a few are closely associated with resistance or susceptibility to classical scrapie, in particular codons for amino acids 136 (A–V), 154 (R–H) and 171 (Q–R–H) (Hunter et al., 1989, 1994; Laplanche et al., 1993; Belt et al., 1995; Bossers et al., 1996).1

Although, the study of scrapie susceptibility is complicated by different PrP genotypes found in different breeds of sheep, almost all relevant studies suggest that the ARR/ARR genotype is the most resistant to classical scrapie. The recent finding of atypical scrapie (originally termed Nor98) in sheep, however, has shown that the genetic susceptibility can be remarkably different for other strains of scrapie (Moum et al., 2005; Saunders et al., 2006).

In goats, the association of genetic variability of **PrP** with resistance or susceptibility to classical scrapie remains uncertain. Studies in the UK revealed high variability of **PrP** in goats (Goldmann et al., 2004; Goldmann, 2008), and work in Italy suggested that the variant 222K had an association with scrapie resistance in Ionica breed goats (Vaccari et al., 2006). Moreover, the variants 143R and 154H may give some protection against natural scrapie in Greek goats (Billinis et al., 2002). A recent study in Cypriot goats suggested that the variants 146D and 146S may provide protection against scrapie (Papasavva-Stylianou et al., 2007). In the same study, the presence of the homozygous wild type (WT) allele 146N was strongly associated with susceptibility to natural scrapie.

The variant 142M has been associated with varying disease incubation periods in British goats (Goldmann et al., 1996). Furthermore, a PrP variant having three rather than the usual five copies of a short peptide repeat, was associated with an increased scrapie incubation period in goats (Goldmann et al., 1998). In total, 30 **PrP** amino acid polymorphisms and 16 ‘silent’ mutations have been described so far in the PrP gene of goats (Table 1), which shows a similar degree of genetic variability to its ovine counterpart.