[2] Peden AH, Head MW, Ritchie DL, et al. Mok TPreclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet. 2004;364 (9433):527–9.

66. Scrapie strain typing of brain and lymph node-derived isolates in ovinized models reveals mixture of substrains with distinct pathobiological properties

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ABSTRACT

Phenotypic variability has been observed in several prion diseases, including human TSEs and scrapie of sheep of goats. This heterogeneity has been associated with distinct prion strains. The existence of strains in prion biology can be accommodated within the protein-only hypothesis by supporting the view that several conformational variants of PrP^{Sc} exist, which encode distinct pathobiological properties. Within this framework, the conformational selection model proposes that a given amino acid sequence for PrP^{C} allows a limited portfolio of PrP^{Sc} conformations, such that the degree of overlapping between host and donor *Prnp* sequences determines the capability of the isolate to cause disease.

Transmission barrier occurs upon heterologous interaction between incompatible PrP sequences, giving rise to a variety of new prion conformers. Therefore, transgenic models expressing homologous PrP^{C} are crucial to faithfully study the actual variety of prion strains. Ovinized models show enhanced susceptibility to infection with scrapie prions and have been employed to characterize strains in natural sheep isolates.

In the present study, we used the transgenic murine lines TgShp and Tg338, which express ovine PrP^{C} ARQ and VRQ, respectively, to bioassay 22 sheep scrapie isolates from distinct outbreaks within the Spain-France-Andorra transboundary territory. Animals were intracerebrally inoculated and survival periods, lesion profiles, PrP^{Sc} distribution, and glycosylation patterns were studied.

In all cases but one, Western blot from sheep tissues disclosed glycosylation patterns compatible with a low molecular weight (Mw) scrapie strain (~19 kDa). Only Inoculum 8L showed PrP^{res} of higher Mw (~21 kDa).

On bioassay, all inocula caused on second-passage TgShp mice similar survival periods together with high attack rates. While most TgShp mice accumulated 19-kDa PrP^{res} in their spinal cords, a number of isolates (including inoculum 8L) triggered deposition of the 21-kDa isoform.

In Tg338 mice, a majority of isolates induced survival times similar to those seen in TgShp, together with high attack rates and 19-kDa PrP^{res} in the spinal cord. However, a group of isolates showed different features consisting in very long survival periods with low attack rates and presence of 21-kDa PrP^{res}. Additionally, these animals showed lower vacuolization scores in all evaluated brain areas and occasional presence of amyloid plaques.

These results suggest that some scrapie isolates contain mixtures of substrains that are resolved distinctly in different transgenic lines. A number of isolates seemed to comprise a major 19-kDa component and a minor 21-kDa component that is specifically amplified by the TgShp, but not the Tg338 line. In contrast, some other isolates contained low titers of a 21-kDa, low pathogenicity isoform that seemed to interfere with the propagation of the major 19-kDa substrain exclusively in Tg338 thanks to its amyloidogenic properties, that sequester neurotoxic PrP monomers delaying the onset of clinical signs and restraining the development of neuropathology.

67. Diagnostic accuracy of cerebrospinal fluid RT-QuIC in cases of suspected prion disease and the potential utility of using RT-QuIC for public health surveillance

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ABSTRACT

Background: The clinical heterogeneity, potential mimickers, and rapid progression make prion diseases