# Scrapie prions: an etiologic agent of sCJD in human?

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# Invited Speakers

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## Invited.24: Scrapie prions: an etiologic agent of sCJD in human?

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While the Bovine Spongiform Encephalopathy (BSE) is the cause of variant CJD in human, the zoonotic potential of Scrapie prions remains mostly unknown. Some rodent-adapted scrapie isolates were reported to propagate in non-human primates. However, because prions adaptation in rodents can profoundly alter their biological properties and no transmission was observed in chimpanzee inoculated with sheep scrapie, the significance of these results was considered low.

Mice genetically engineered to over-express the human prion protein (tgHu) have emerged as highly relevant models for gauging prions capacity to transmit in human. These models can propagate human prions without apparent transmission barrier and they were largely used to confirm the zoonotic ability of the BSE. Here we show that a panel of sheep scrapie prions transmit in several tgHu mice models with comparable efficacy than cattle BSE. The serial transmission of different scrapie isolates in these mice led to the propagation of prions that are phenotypically identical to those causing sporadic Creutzfeldt Jakob disease in humans.

These results demonstrate that scrapie prions have an intrinsic zoonotic potential and raise new questions about the possible links between animal and human prions.



## Invited.25: Transmissibility of human prion diseases

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For many years the notion has been accepted that human prion diseases can be divided as transmissible and non- (or only partially) transmissible. Commonly listed in the first group were all forms of Creutzfeldt-Jakob disease (CJD), fatal insomnia (FI) and the GSS subtype associated to the P102L mutation harboring CJD-like scrapie prion protein ($PrP^{Sc}$) generally identified as PrP27-30; the second group included subtypes of GSS lacking $PrP^{Sc}$ 27-30 and variably protease sensitive prionopathy (VPSPr), which also lacks significant amount of PrP27-30.

We have probed transmissibility of VPSPr using two sets of Tg mice: 1. Tg mice expressing human cellular PrP ($PrP^{C}$) in amounts ranging x1 to x8 the normal mouse level and harboring methionine or valine at position 129 [Tg(HuPrP$^{C}$129V) and Tg(HuPrP$^{C}$129M]; 2. Tg mice expressing glycan-free human PrP [Tg(HuPrP129MGlycKO)].

Following inoculations of a total of 12 cases of VPSPr of the three genotypes and controls to a total of 170 Tg(HuPrP$^{C}$129V) and Tg(HuPrP$^{C}$129M) mice none of the VPSPr-inoculated mice manifested clinical signs; 60% of challenged mice were positive at histopathological examination, on average 655 to 711 days post inoculation (dpi) showing PrP-positive plaques and, occasionally, focal spongiform degeneration in or around the hippocampus; about 34% harbored $PrP^{Sc}$ with properties similar to those of VPSPr $PrP^{Sc}$. Transmission occurred only when host and inoculum PrP 129 residue matched. Virtually, no prion disease was detected at second passage.

VPSPr-129M inoculation to Tg(HuPrP129MGlycKO) caused clinical signs and widespread, severe histopathological changes approximately 380 dpi in virtually all challenged mice. Second passage mice also were affected. Histopathological changes that followed VPSPr challenge were comparable to those that followed inoculation with brain homogenates from sCJD subtypes.

These findings suggest that the distinction of transmissible and non-transmissible prion diseases in principle is futile since by virtue of their common mechanism prion diseases are all likely to be proven transmissible when they are exposed to a suitable conversion substrate.

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