



The cellular prion protein controls Notch signalling and neuroectodermal stem cell architecture

Severine Martin-Lannere, Julia Hernandez-Rapp, Sophie Halliez, Theo Z. Hirsch, Bruno Passet, Hector Ardila-Osorio, Jean-Marie Launay, Vincent Béringue, Jean-Luc Vilotte, Sophie Mouillet-Richard

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disease (CJD). All cases were tested for PrP^{Sc} and for Aβ1-42. A 22.6% overlap was found between all prion diseases and AD neuropathological changes. Based on the yearly incidence of CJD and AD in the United States, the probability of a random occurrence of CJD and AD in a single patient is negligible. Therefore, the 22.6% overlap of CJD with AD indicates a causal linkage of the two diseases. Because hyperphosphorylation of tau (Hτ) may be the cause of dementia in AD, we quantified Hτ in the locus coeruleus and raphe nuclei (LC/RN) of the pons and the medial temporal lobe (MTL) of brains from 37 patients with dementia recently sent to UCSF for evaluation of prion disease. We noted Hτ accumulation in 20 cases determined to be “Prion-only”, significantly more in 7 “Prion-AD” cases, and even more in “AD-only” cases: 4 cases of other neurodegenerative disorders contained little or no Hτ. To test whether prion disease induces Hτ, brain aggregates (BrnAgg) constructed from transgenic (Tg) mice expressing mutated tau (P301L). They were exposed to a homogenate of mouse brain expressing the APP Swedish mutation and a homogenate from scrapie prion-infected mouse brain. The AD-like homogenate increased the number of nerve cell bodies containing Hτs by ~2-fold and the scrapie prion homogenate, by 10-fold. Then Human (Hu) BrnAggs exposed to Hu CJD prions were tested for increased expression of the Fyn and Cdk5 kinase pathways known to phosphorylate tau. CJD prions induced a 1.6-fold and 3.4-fold increase in Fyn and Cdk5 respectively. The overlap of neurodegenerative processes is a common occurrence among neurodegenerative diseases. This study provides mechanisms for the overlap of prion disease and AD.

O.08: Gerstmann-Sträussler-Scheinker disease associated with P102L, A117V and F198S *PRNP* mutations are transmissible prion diseases

Laura Pirisinu,¹ Michele A Di Bari,¹ Claudia D'Agostino,¹ Stefano Marcon,¹ Geraldina Riccardi,¹ Anna Poleggi,² Pierluigi Gambetti,³ Umberto Agrimi,¹ and Romolo Nonno¹

¹Department of Veterinary Public Health and Food Safety; Istituto Superiore di Sanità; Rome, Italy; ²Department of Cell Biology and Neurosciences; Istituto Superiore di Sanità; Rome, Italy; ³Case Western Reserve University; Cleveland, OH USA

Introduction. Gerstmann-Sträussler-Scheinker (GSS) disease is an inherited prion disease associated with several mutations in the human PrP gene (*PRNP*). Despite their variability in the clinical presentation, all GSS cases show an atypical protease-resistant PrP^{Sc} (PrP^{res}) pattern, characterized by a small internal fragment of 7-8 kDa. Historical attempts to transmit GSS in rodent models showed that only those few cases also accompanied by a CJD-like 21 kDa PrP^{res} fragment were transmissible, leading to the suggestion that GSS cases with only 7-8 kDa PrP^{res} are non-transmissible proteinopathies rather than true prion diseases.

In this study we investigated the transmissibility of GSS cases to bank voles, which have been shown to be highly susceptible to human and animal prion diseases.

Materials and Methods. GSS cases with P102L (n = 3), A117V (n = 2) and F198S (n = 1) mutations were inoculated i.c. in two lines of bank voles, carrying either methionine (Bv109M) or isoleucine (Bv109I) at codon 109 of PrP. Among P102L cases, 2 cases had both 7-8 kDa and 21 kDa PrP^{res} fragments, while another had 7-8 kDa PrP^{res} only. Clinical diagnosis in voles was confirmed by brain pathological assessment, immunohistochemistry and western blot for PrP^{Sc}.

Results. To date, all cases transmitted the disease to Bv109I, but not to Bv109M. In Bv109I, the efficiency of transmission was dependent on the PrP mutation. Indeed, by 3 months p.i. clinical disease was evident in all voles infected with A117V cases and by 4-5 months p.i. in voles infected with GSS F198S. Among cases with P102L, the case with 7-8 kDa PrP^{res} was transmitted in all voles by 6 months p.i., while transmission of cases with both 7-8 and 21 kDa PrP^{res} was less efficient, resulting in partial attack rate and longer incubation time.

All clinically affected Bv109I faithfully reproduced the 7-8 kDa GSS-like PrP^{res} signature and showed brain spongiform degeneration, neuronal loss and gliosis mainly in cerebral cortex, hippocampus and cerebellum.

Conclusions. These findings show that P102L, A117V and F198S GSS are transmissible to bank voles and that transmissibility of P102L cases is not dependent on the presence of CJD-like 21 kDa PrP^{res}. These data support the notion that GSS are not mere proteinopathies but genuine transmissible prion diseases. Finally, Bv109I was previously observed to be susceptible to human VPSPr and sheep Nor98, and thus represents the first animal model available for the biological characterization of these atypical prions.

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O.09: Influence of *Prnp* variants on the susceptibility of goats to scrapie and BSE

Patricia Aguilar-Calvo,¹ Olivier Andréoletti,² Christine Fast,³ Juan-Carlos Espinosa,¹ Caroline Lacroux,² Martin H Groschup,³ and Juan María Torres¹

¹Centro de Investigación en Sanidad Animal (CISA-INIA); Valdeolmos, Madrid, Spain; ²INRA, UMR 1225, Interactions Hôtes Agents Pathogènes, Ecole Nationale Vétérinaire de Toulouse; Toulouse, France; ³Institute for Novel and Emerging Infectious Diseases; Friedrich-Loeffler-Institut; Greifswald-Insel Riems, Germany

Goats can be affected by scrapie and Bovine Spongiform Encephalopathy (BSE), both belonging to the group of Transmissible Spongiform Encephalopathies (TSEs). Scrapie occurrence in small ruminants is strongly determined by the host

prion-encoding protein gene (*Prnp*) and for goat some polymorphisms have been associated with resistance to scrapie: I/M₁₄₂, N/D₁₄₆ or S/D₁₄₆, R/H₁₅₄, R/Q₂₁₁ and Q/K₂₂₂. However, more information is still needed to conclude in the influence of *Prnp* on susceptibility of goats to scrapie and BSE.

In this work, we analyzed the effect of M₁₄₂, Q₂₁₁ and K₂₂₂ *Prnp* variants on the susceptibility of goats to TSEs by experimental inoculations in both goats and transgenic mice. On one hand, intracerebral (IC) and/or oral inoculations with either one natural scrapie isolate or one goat-BSE isolate were performed in goats with different *prnp* genotypes: wild type (wt: I₁₄₂R₂₁₁Q₂₂₂), or M₁₄₂, Q₂₁₁ or K₂₂₂ variants. On the other hand, three transgenic mouse lines expressing similar levels of wt goat cellular prion protein (PrP^C), M₁₄₂-PrP^C variant or K₂₂₂-PrP^C variant were generated and IC inoculated with the same panel of scrapie and BSE isolates.

Goats and transgenic mice harboring the M₁₄₂ *prnp* variant developed scrapie or BSE with similar incubation periods than their homologous wt goats or transgenic mice. Q₂₁₁ goats showed a high protective effect against the oral inoculation of the scrapie agent; while only short delays in the incubation times were registered when orally inoculated with goat-BSE agent. A clearer protective effect was observed in K₂₂₂ goats inoculated with either scrapie or Goat-BSE agents where no evidence of disease was found following oral inoculation, and traces of infectivity were only detected in a few numbers of BSE-inoculated goats after very long incubation times. Interestingly, transgenic mice expressing the K₂₂₂-PrP^C variant were resistant to the IC transmission of a variety of scrapie isolates and to cattle-BSE isolate. However, no protective effect was observed in these transgenic mice after IC inoculation of goat-BSE, contrasting with the high resistance to this agent in orally K₂₂₂-goats aforementioned.

These results indicate that M₁₄₂-PrP^C variant does not provide substantial resistance to scrapie or BSE agents, whereas the Q₂₁₁ effect depends on the prion strain and the inoculation route. Interestingly, the K₂₂₂-PrP^C variant exhibits a high protective effect against scrapie and BSE transmission in both goats and transgenic mice, appearing as a very good candidate for selective breeding programs for controlling TSEs in goat herds.

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O.10: In vitro temporal assessment of CWD and TME blood-borne prions

Alan Elder,¹ Davin M Henderson,¹ Amy V Nalls,¹
Jason M Wilham,² Byron Caughey,² Edward A Hoover,¹
Anthony E Kincaid,³ Jason C Bartz,³ and Candace K Mathiason¹

¹Colorado State University; Fort Collins, CO USA, ²NIH-Rocky Mountain Laboratory; Hamilton, MT USA, ³Creighton University; Omaha, NE USA

Blood-borne prion transmission is remarkably efficient and is known to occur during the asymptomatic or pre-clinical phase of disease for both human and animal transmissible spongiform

encephalopathies (TSEs). We have recently reported the detection of amplification competent hematogenous prions in blood harvested from TSE-infected hosts during pre-clinical infection. Detection was realized by using a modified version of the real time quaking induced conversion assay, whole blood optimized RT-QuIC (wboRT-QuIC), which provides 100% specificity and >92% sensitivity. To better understand the temporal course and biological significance of prionemia, we have employed wboRT-QuIC to assess longitudinal blood samples harvested from chronic wasting disease (CWD)-infected deer and transmissible mink encephalopathy (TME)-infected hamsters. We have demonstrated the presence of an initial spike and decline in amplifiable prions during the first 72 hours post inoculation, which was followed by a subsequent resurgence of amplifiable prions prior to the midpoint of TSE terminal disease. This temporal presence of prionemia was recapitulated in cervids that were exposed to CWD by intravenous and oral routes, as well as in hamsters exposed to TME extraranasally. These findings lend credence to the existence of an initial dissemination of prions via the circulatory system and the possibility that additional routes and TSEs may purvey prions in a similar manner. Further studies employing wboRT-QuIC are warranted to determine the mechanisms associated with trafficking and transmission of blood-borne prions, as well as to detect, mitigate and prevent prion spread.

O.11: Fatal myelopathy in primates exposed to prion contaminated blood products: Unmasking abnormal PrP

Emmanuel E Comoy,¹ Nina Jaffré,¹ Jacqueline Mikol,¹

Valérie Durand,¹ Christelle Jas-Duval,^{1,2}

Sophie Luccantoni-Freire,¹ Evelyne Correia,¹

Nathalie Lescoutra-Etcheagaray,³ Nathalie Streichenberger,⁴

Stéphane Haïk,⁵ Chryslain Sumian,³ Paul Brown,¹

and Jean-Philippe Deslys¹

¹CEA, Institute of Emerging Diseases and Innovative Therapies (iMETI), Division of Prions and Related Diseases (SEPIA); Fontenay-aux-Roses, France; ²EFS-Nord de France; Lille, France; ³MacoPharma; Tourcoing, France; ⁴Hospices Civils de Lyon, Prion Unit, Neurobiology department; Bron, France; ⁵Inserm, U 975 - CNRS, UMR 7225 - Université Pierre et Marie Curie-Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM); Paris, France

The recent report¹ of 16 appendices positive for abnormal PrP among 32,441 in British patients strongly suggests a high prevalence of silent vCJD carriers in the UK (almost 200- fold greater than the total number of clinical vCJD cases reported so far). This high prevalence might even be underestimated as suggested by the recent report of one case of vCJD with minimal PrPres deposition in lymphoid tissues.² There is thus a continuing cause for concern about the management of blood and blood products and surgical instruments that encourages further evaluation of BSE primary and vCJD secondary risks in relevant experimental models. We present here unexpected results of experiments evaluating blood transmission risk in a non-human primate model.