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

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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

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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/M_{142}, N/D_{146} or S/D_{146}, R/H_{154}, R/Q_{211} and Q/K_{222}. 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 $M_{142,}$ Q_{211} and K_{222} *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: $I_{142}R_{211}Q_{222}$), or M_{142}, Q_{211} or K_{222} variants. On the other hand, three transgenic mouse lines expressing similar levels of wt goat cellular prion protein (PrP^C), M_{142}-PrP^C variant or K_{222}-PrP^C variant were generated and IC inoculated with the same panel of scrapie and BSE isolates.

Goats and transgenic mice harboring the M_{142} *prnp* variant developed scrapie or BSE with similar incubation periods than their homologous wt goats or transgenic mice. Q_{211} 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 K_{222} 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 K_{222}–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 K_{222}-goats aforementioned.

These results indicate that M_{142}-PrP^C variant does not provide substantial resistance to scrapie or BSE agents, whereas the Q_{211} effect depends on the prion strain and the inoculation route. Interestingly, the K_{222}-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

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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 extratranasally. 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

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The recent report[1] 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.