S1-1-1 Diagnosis for Human prion disease

APPS2025 Abstract

Title: Recent advances in MRI-based approaches for the diagnosis of human prion diseases

Authors: Koji Fujita,[1] Masafumi Harada[2]

Affiliation:
[1]Department of Neurology, Tokushima University Graduate School of Biomedical Sciences,
[2]Department of Radiology, Tokushima University Graduate School of Biomedical Sciences

Abstract (300 words):
Magnetic resonance imaging (MRI) is a core biomarker within international diagnostic criteria for human prion diseases. Diffusion-weighted imaging (DWI) and corresponding apparent diffusion coefficient (ADC) maps are central, demonstrating diffusion restriction in characteristic cortical and deep gray matter regions and supporting early recognition and subtype differentiation in sporadic Creutzfeldt–Jakob disease. Fluid-attenuated inversion recovery (FLAIR) provides complementary information; combined assessment of DWI/ADC and FLAIR improves confidence and aids differentiation from autoimmune encephalitis, status epilepticus, metabolic disorders, and hypoxic-ischemic injury. Arterial spin labeling (ASL) can show cerebral blood flow reduction in regions with DWI abnormalities, supporting diagnostic interpretation and longitudinal assessment. In genetic prion diseases, subtle early changes on multimodal MRI may assist in surveillance of at-risk individuals. Quantitative MRI and emerging computational approaches are being explored to improve sensitivity and interpretation. These advances support timely diagnosis, facilitate early clinical trial enrollment, and align with efforts toward earlier therapeutic intervention in prion diseases.

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Park HY, et al. Eur Radiol 2021;31:9073-9085.

S1-1-2 Diagnosis for Human prion disease

APPS2025 Abstract

Title:

Boosting Skin/CSF RT-QuIC Assay Sensitivity for Prion Disease with CSF Biomarkers 14-3-3 and Total Tau

Authors:

Zihao Zhang[1#], Pingping Shen[2#], Kuang Ning[1#], Pengcheng Huang[3], Yirong Yang[1], Hailun Wu[1], Weiguanliu Zhang[2], Xuerui Yao[1], Hancun Yi[3], Ziyi Chen[1], Yijia Chen[1], Yuhe Wu[1], Jingwei Huang[3], Li Cui[2], Daojun Hong[3*], Wen-Quan Zou[1*]

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Abstract (300 words):

The definitive diagnosis of Creutzfeldt‑Jakob disease (CJD) relies on the postmortem detection of pathological prion protein (PrP^{Sc}) in the brain. Antemortem diagnosis commonly uses the real-time quaking-induced conversion (RT-QuIC) assay to detect PrP^{Sc} seeding activity in cerebrospinal fluid (CSF). Despite its utility, there remains a need for less invasive and more sensitive diagnostic biomarkers. In collaboration with the Caughey laboratory, we previously demonstrated that PrP^{Sc} is present in the skin of CJD patients, establishing skin RT-QuIC as a novel, minimally invasive diagnostic tool. Using animal models, we further showed that skin PrP^{Sc} seeding activity can be detected earlier than brain PrP^{Sc} by western blotting or neuropathological analysis, preceding the onset of clinical symptoms. While both CSF RT-QuIC and skin RT-QuIC exhibit near-perfect specificity (~ 95%) and high sensitivity (~90%), a small proportion of cases remain false-negative. In the present study, we evaluated whether combining these seeding assays with established CSF biomarkers−14-3-3 protein and total tau− could improve diagnostic performance. According to the current results, the CSF RT-QuIC + skin RT-QuIC model achieved an AUC of 0.982, with 96.9% sensitivity and 94.1% specificity, representing the highest diagnostic accuracy among dual-marker combinations. When CSF total tau was incorporated, the model (Skin RT-QuIC+ CSF RT-QuIC + Tau) further improved to an AUC of 0.989, with 97.3% sensitivity and 100% specificity, indicating superior diagnostic efficiency. In contrast, adding CSF 14-3-3 to this model (Skin RT-QuIC+ CSF RT-QuIC + Tau + 14-3-3) yielded only marginal benefit (AUC 0.989, sensitivity 97.3%, specificity 100%), suggesting that total tau provides the principal additional diagnostic value. Overall, integrating skin RT-QuIC with CSF RT-QuIC and total tau markedly enhances diagnostic performance for CJD, offering a robust, minimally invasive, and clinically practical framework for early and reliable diagnosis.

S1-1-3 Diagnosis for Human prion disease

APPS2025 Abstract

Title: Specific early electroencephalogram analysis for the early diagnosis of sporadic Creutzfeldt-Jakob disease

Authors: Nobuo SANJO[1,3)], Taiki MATSUBAYASHI[2)], Hirokazu NATSUI[3)]

Affiliation:

1) Joint Research Department of Rare Intractable Neurological Disease Therapeutics Development, Institute of Biomedical Engineering, Institute of Science Tokyo

2) Department of Neurology, National Hospital Organization Disaster Medical Center, Tokyo, Japan

3) Department of Neurology and Neurological Science, Institute of Science Tokyo Graduate School of Medical and Dental Sciences, Tokyo, Japan

Abstract (300 = 300 words):

[Aims] Early diagnosis is necessary for timely interventions in prion diseases. To elucidate the specificity of the early electroencephalography (EEG) discharges in sporadic Creutzfeldt-Jakob disease (sCJD), we analyzed epileptiform discharges associated with early stages of sCJD.

[Methods] Nine patients with MM1/classic sCJD and 20 patients with status epilepticus (SE), consisting of 11 with convulsive SE and 9 with nonconvulsive SE, were included. We evaluated epileptiform discharges, such as generalized periodic discharges (GPDs), lateralized periodic discharges (LPDs), and central sagittal sporadic epileptiform discharges (CSSEDs) on EEGs in both MM1/classic sCJD and SE groups. CSSEDs were defined as nonrhythmic and nonperiodic waveforms showing generalized spike-and-wave complexes and/or sharp waves predominantly in the central sagittal region of the brain [1].

[Results] In the MM1/classic sCJD group, CSSEDs, LPDs, and GPDs were observed in five (55.6%), one (11.1%), and eight (88.9%) patients, respectively. The average duration from onset to the appearance of the discharges on EEGs were 1.6, 1.0, and 2.44 months, respectively. In the SE group, CSSEDs, LPDs, and GPDs were detected in one (5.0%), six (30.0%), and six (30.0%) patients, respectively. Incorporating CSSEDs and LPDs into the World Health Organization (WHO) diagnostic criteria, alongside GPDs, significantly shortened the average duration from onset to the diagnosis of probable sCJD (2.06 months vs. 2.44 months; $p = 0.02$). Furthermore, when CSSEDs were included in the EEG criteria of the WHO diagnostic criteria, the disease severities, which were measured using the Medical Research Council Prion Disease Rating Scale, were significantly lower at the time of diagnosing patients as probable sCJD (4.57 vs. 9.0; $p = 0.04$).

[Conclusions] Epileptiform discharges in the central sagittal region were detected early in MM1/classic sCJD, whereas those in the lateral region were more frequent in SE than in MM1/classic sCJD. CSSEDs could be a useful potential biomarker for early-stage diagnosis of sCJD, facilitating earlier intervention [2].

References:

[1] Matsubayashi T, et al. J Neurol Sci. 2022;437:120265.

[2] Matsubayashi T, Hirokazu N, et al. Prion 2025; 19(1):17-24.

S1-1-4 Diagnosis for Human prion disease

APPS2025 Abstract

Title:
CSF biomarkers improve the accuracy of early diagnosis for human prion diseases: A 10-year prospective study (2011–2020)

Authors:

Katsuya Satoh

Affiliation:

Department of Health Sciences, Unit of Medical and Dental Sciences, Nagasaki University Graduate School of Biomedical Sciences

Abstract (300 words):

Abnormal prion protein (PrP^Sc) is the pathogenic isoform responsible for human prion diseases (HPDs), a group of fatal and transmissible neurodegenerative disorders characterized by rapidly progressive dementia, motor dysfunction, and widespread neuronal loss. Establishing an accurate and reliable early diagnosis, ideally within four weeks before or after disease onset, is essential for enabling early therapeutic intervention and for the development of effective disease-modifying treatments. Although cerebrospinal fluid (CSF) and MRI biomarkers have been used in clinical settings, their diagnostic accuracy has not been fully validated in large-scale prospective studies.

We conducted a nationwide 10-year prospective investigation (2011–2020) in Japan involving 4,153 patients with suspected HPDs who presented with rapidly progressive dementia. Each case was analyzed using CSF biomarkers, including 14-3-3 protein (Western blot and ELISA), total tau, and real-time quaking-induced conversion (RT-QuIC) assay, in addition to MRI, EEG, and prion protein gene polymorphism analyses. Clinical and laboratory findings were systematically reviewed by the Japan Prion Disease Surveillance Committee. Among all cases, 2,030 were classified as definite, probable, or possible HPDs (1,592 sporadic, 37 genetic, and 2 acquired), whereas 2,123 were diagnosed as non-HPDs. The sensitivities of 14-3-3 WB, 14-3-3 ELISA, total tau, RT-QuIC, and MRI were 79.3%, 81.4%, 80.1%, 70.6%, and 97.7%, with specificities of 81.2%, 80.4%, 86.8%, 98.8%, and 88.6%, respectively. In sporadic HPDs, biomarker sensitivities were markedly higher at the early disease stage, and all markers were positive even before symptom onset.

These findings demonstrate that the combined use of MRI and CSF biomarkers, particularly RT-QuIC, 14-3-3, and total tau, provides a powerful and practical diagnostic strategy for accurate identification of human prion diseases during preclinical and early symptomatic phases. This integrative approach will enhance early diagnosis, facilitate patient stratification, and accelerate the development of targeted therapeutic interventions for these devastating disorders.

Oral Presentation

S1-2-1 Educational lecture

APPS2025 Abstract

Title:
Development of Brain-Targeted Drug Delivery Systems for Nucleic Acid Drugs

Authors:
Shigeru Kawakami

Affiliation:
Department of Pharmaceutical Informatics, Graduate School of Pharmaceutical Sciences, Nagasaki University, Japan

Abstract (300 words):

Nucleic acid therapeutics offer great promise for the treatment of intractable brain disorders. However, drug penetration into the brain is severely restricted by the blood–brain barrier (BBB), highlighting the need for innovative brain-targeted drug delivery systems[1)]. To date, we have advanced brain drug delivery research in three major directions: i) exploiting transcytosis by conjugating BBB-permeable ligands to DDS carriers[2)], ii) transient BBB opening via focused ultrasound irradiation[3)], and (iii) brain-targeted delivery methods using cell-permeable DDS[4)] that interact with heparan sulfate proteoglycan–expressing cells, as well as antibody-modified DDS approaches[5,6)]. In this presentation, I will introduce our recent progress in brain-targeted DDS systems for nucleic acid delivery.

References:

1) K. Ogawa and S. Kawakami* *et al.*, *Chem Pharm Bull*, **2020**;68(7):567-582
2) N. Kato and S, Kawakami* *et al.*, *Drug Deliv*, **2023**;30(1):2173333.
3) K. Ogawa and S, Kawakami* *et al.*, *J Control Release*, **2022**;348:34-41
4) Y. Sugimoto and S. Kawakami* *et al.*, *Drug Deliv*, **2023**;30(1):2191891
5) N. Kato and S. Kawakami* *et al.*, *Eur J Pharm Biopharm*, **2024**;203:114468
6) A. Matsuo-Tani and S. Kawakami* *et al.*, *Pharmaceutics*, **2025**;17(10):1298

S1-3-1 Development of Treatment and Their Current Status for Human prion disease

APPS2025 Abstract

Title: Therapeutic Potential of FK506 in Prion Diseases

Authors: Takehiro Nakagaki

Affiliation: Department of Molecular Microbiology and Immunology, Graduate School of Biomedical Sciences, Nagasaki University

Abstract (300 words):

Inhibition of prion protein (PrP) conformational conversion has been a major therapeutic strategy for prion diseases. However, compounds such as pentosan polysulfate and quinacrine have failed to achieve sufficient efficacy in clinical trials[1)]. Since treatment in humans must inevitably begin after disease onset, it is difficult to adequately suppress the pathological conformational conversion of PrP. Activation of glial cells during disease progression is considered to be a crucial cause of neuronal death. Therefore, we have been attempting to establish another therapeutic approach for prion diseases by suppressing glial cell proliferation using the immunosuppressant FK506 (tacrolimus)[2)3)]. In this presentation, we will introduce our recent studies and ongoing efforts toward this goal.

References:

1) Shim KH et al., *Prion.* 2022 Dec;16(1):265-294.
2) Nakagaki T et al., *Autophagy*. 2013 Sep;9(9):1386-94.
3) Nakagaki T et al., *Neurotherapeutics*. 2020 Oct;17(4):1850-1860.

S1-3-2 Development of Treatment and Their Current Status for Human prion disease

APPS2025 Abstract

Title:
Therapeutic Development for Human Prion Diseases: Current Progress and Challenges

Authors:
Eun-Kyoung Choi[1,2]

Affiliation:
[1]Ilsong Institute of Life Science, Hallym University, Seoul 07247, Republic of Korea,
[2]Department of Biomedical Gerontology, Graduate School of Hallym University, Chuncheon 24252, Republic of Korea

E-mail:

Abstract (300 words):
Human prion diseases remain universally fatal neurodegenerative conditions characterized by the misfolding and propagation of the prion protein (PrP). Despite significant advances in understanding prion biology, no disease-modifying therapy is currently available. This presentation summarizes current progress in therapeutic development for human prion diseases, with a particular focus on PrP-lowering strategies, immunotherapeutic approaches, gene-editing platforms, and small-molecule inhibitors. Recent preclinical results—especially those involving antisense oligonucleotides and in vivo base editing—highlight the emerging potential for meaningful intervention. However, substantial environmental and systemic challenges continue to impede translation into clinical practice. Barriers include limited patient populations, late-stage diagnosis, lack of validated biomarkers for therapeutic monitoring, biosafety and infrastructural constraints, regulatory complexity, and the biological heterogeneity of prion strains. Addressing these multi-layered obstacles will require coordinated international efforts, improved preclinical models, innovative clinical trial designs, and strengthened translational frameworks. This talk evaluates both scientific progress and system-level limitations, offering perspectives on future directions essential for advancing prion therapeutics.

References:

S2-1-1 Keynote lecture

APPS2025 Abstract

Title:
Food Safety Framework in Japan
-Role and Future Challenges of Food Safety Commission of Japan

Authors:
Shigeki Yamamoto

Affiliation:
Food Safety Commission, Government Office of Japan, Tokyo, Japan

Abstract (300 words):
Since the first case of BSE was identified in September 2001, the Japanese government initiated discussions to introduce a risk analysis framework for food safety management, aiming to restore consumer confidence. According to this policy, the Food Safety Basic Law was established in May 2003. The Food Safety Commission was established in the Cabinet Office. The Food Safety Commission (FSC) serves as a risk assessor and advisor to support the risk management authorities, including the Ministry of Health, Labor and Welfare, the Ministry of Agriculture, Forestry and Fisheries, the Consumer Affairs Agency, and the Ministry of Environment. The Food Sanitation Law was also revised at the same time. The FSC conducts risk assessment at the request of the risk management authorities. Risk assessment consists of four steps. These are 1. Hazard identification, 2. Hazard characterization, 3. Exposure assessment, and 4. Risk characterization. The FSC comprises 16 expert committees and 6 working groups, with more than 200 experts. More than 3,300 risk assessment reports were published over approximately 20 years. For the future, FSC plans to introduce the DX system to collect scientific evidence, and introduce an *in silico* approach of risk assessment.

FSC proceeds with international cooperation, sharing information about the risk of food safety

S2-2-1 Cellular and Molecular Biology, Biophysics for neurodegeneration disease including prion disease

Oral Presentation

APPS2025 Abstract

Title:

How prion protein monomer conformation and amyloid fibril polymorphism determine yeast strain phenotypes

Authors:

Takashi Nomura[1], David R. Boyer[2], Yusuke Komi[1], David S. Eisenberg[2], and Motomasa Tanaka[1]

Affiliation:

[1] Laboratory for Protein Conformation Diseases, RIKEN Center for Brain Science

[2] Department of Biological Chemistry, University of California, Los Angeles

Abstract (300 words):

In the [*PSI*$^+$] prion system, the yeast prion protein Sup35 can form structurally distinct amyloid fibrils that lead to distinct transmissible prion states, or strains. However, our understanding of how different Sup35 fibril structures arise and translate to phenotypic variations is limited. Here, using cryo-EM and single-monomer force spectroscopy with optical tweezers, we reveal the structural basis of yeast prion propagation in four wild-type and S17R mutant variants of Sup35 that underlie different [*PSI*$^+$] strains. Cryo-EM structures show that the four variants form strikingly distinct fibril structures, which exhibit varying stability and chaperone-accessibility. Force spectroscopy suggests the different distinct fibril structures are derived from distinct monomer conformational ensembles. Further, cryo-EM structures indicate that prion strain strength is correlated with enhanced fibril propagation caused by a combination of low fibril stability and a large separation between the Sup35 fibril core and the Ssa1/Sis1 chaperone-binding region. These results provide a structure-based mechanism for the yeast prion strain phenomenon with implications for understanding amyloid propagation in human neurodegenerative diseases.

References:

(1) Ohhashi, Y. *et al.* Molecular basis for diversification of yeast prion strain conformation. *Proc Natl Acad Sci U S A* **115**, 2389–2394 (2018).

(2) Nakagawa, Y. *et al.* Amyloid conformation-dependent disaggregation in a reconstituted yeast prion system. *Nat Chem Biol* **18**, 321–331 (2022).

(3) Shen, C.-H. H. *et al.* Exposed Hsp70-binding site impacts yeast Sup35 prion disaggregation and propagation. *Proc Natl Acad Sci U S A* **121**, e2318162121 (2024).

APPS2025 Abstract

Title:
Activation of Aggrephagy as a Novel Therapeutic Approach to Degrade Protein Aggregates

Authors:
Gen Matsumoto

Affiliation:
Department of Neuronal Disease Control, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

Abstract (300 words):
Prion-like self-propagating protein aggregation is a fundamental pathogenic principle shared by many neurodegenerative diseases including Alzheimer's and Parkinson's disease. In these disorders, soluble proteins such as tau and α-synuclein undergo abnormal conformational changes to form nucleating "seeds," which then convert innate monomers into amyloid fibrils through prion-like templated conformational conversion. These seeds can spread between cells, propagating along neural circuits and thereby expanding the pathological domain. Thus, eliminating pathogenic protein aggregates represents the most direct and rational therapeutic strategy. We have focused on aggrephagy, an intrinsic cellular mechanism for degrading protein aggregates, and demonstrated that this pathway participates in the elimination of protein aggregates and the suppression of neuronal cell death in a tauopathy mouse model (PS19). Aggrephagy is driven by phosphorylation of p62 at serine 403, which facilitates efficient autophagosomal engulfment of aggregates. Through a chemical screen for activators of p62-S403 phosphorylation, we developed a class of small molecules termed Aggregate Degradation Inducers (ADIs). Oral administration of ADI compounds to PS19 mice showed that they cross the blood–brain barrier, enhance neuronal aggrephagy, and suppress tau fibril accumulation, neuronal loss, and brain atrophy. Our study demonstrates that activation of the aggrephagy system by small molecules enables degradation of protein aggregates and protects neurons from cell death caused by aggregation-prone proteins.

References:

APPS2025 Abstract

Title: Elucidation of the pathogenesis of human prion diseases using mouse models

Authors: Atsushi Kobayashi

Affiliation: Department of Biomedical Models, Graduate School of Biomedical Sciences, Nagasaki University

Abstract (300 words):

The mouse models of human prion diseases have made significant contributions to elucidate the pathogenesis of prion diseases. In particular, the mouse models of acquired prion diseases faithfully reproduced the pathology in humans and have contributed to elucidating the mechanisms underlying the phenomenon observed in human cases. On the other hand, mouse model that spontaneously develop sporadic or genetic prion diseases has yet to be established. Establishing genuine mouse models of sporadic or genetic prion diseases will contribute not only to research into the pathogenesis, but also to the development of therapeutics. In my presentation, I will summarize our progress so far in elucidating the pathogenesis of human prion diseases using mouse models.

References:

1. Kishida H, Kobayashi A, Teruya K, Doi H, Ueda N, Tanaka F, Kuroiwa Y, Parchi P, Mohri S, Kitamoto T. Transmission experiments verify sporadic V2 prion in a patient with E200K mutation. *Acta Neuropathol*, 2024; 147: 89.

2. Kobayashi A, Hirata T, Shimazaki T, Munesue Y, Aoshima K, Kimura T, Nio-Kobayashi J, Hasebe R, Takeuchi A, Matsuura Y, Kusumi S, Koga D, Iwasaki Y, Kinoshita T, Mohri S, Kitamoto T. A point mutation in GPI-attachment signal peptide accelerates the development of prion disease. *Acta Neuropathol*, 2023; 145: 637-650.

3. Kobayashi A, Munesue Y, Shimazaki T, Aoshima K, Kimura T, Mohri S, Kitamoto T. Potential for transmission of sporadic Creutzfeldt-Jakob disease through peripheral routes. *Lab Invest*, 2021; 101: 1327-1330.

4. Takeuchi A, Mohri S, Kai H, Tamaoka A, Kobayashi A, Mizusawa H, Iwasaki Y, Yoshida M, Shimizu H, Murayama S, Kuroda S, Morita M, Parchi P, Kitamoto T. Two distinct prions in fatal familial insomnia and its sporadic form. *Brain Commun*, 2019; 1: fcz045.

5. Kobayashi A, Teruya K, Matsuura Y, Shirai T, Nakamura Y, Yamada M, Mizusawa H, Mohri S, Kitamoto T. The influence of *PRNP* polymorphisms on human prion disease susceptibility: an update. *Acta Neuropathol*, 2015; 130: 159-170.

PV1-1 Oral Presentation of Selected Posters

APPS2025 Abstract

Title: Monitoring Prion-like Tau Seeding Activity in an Alzheimer's Disease Mouse Model n

Authors:

Yuhe Wu1*, Yajie Liu2*, Ziyi Chen1*, Zihao Zhang1, Hailun Wu1, Xuerui Yao1, Yirong Yang1, Kuan Ning1, Mengting Li1, Yuejun Gu1, Yifan Wang1, Rui Xiong1, Pengcheng Huang2, Yifei Kong1, Hongxuan Wu3, Daojun Hong2#, Chengsi Wu2#, Wen-Quan Zou1#

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[2]Department of Neurology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, Jiangxi Province, China

[3]Department of Dermatology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, Jiangxi Province, China

Abstract (300 words):

Alzheimer's disease (AD) is neuropathologically defined by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau. The triple-transgenic AD mouse (3xTg-AD), which carries mutations in APP, PS1, and tau, recapitulates both hallmark pathologies and has been widely studied using behavioral tests, western blotting, and immunohistochemistry (IHC). Here, we applied the highly sensitive real-time quaking-induced conversion (RT-QuIC) assay to longitudinally quantify pathological tau seeding activity in 3xTg-AD brains at 3, 6, 9, and 12 months of age. Remarkably, tau seeding was already detectable at 3 months—preceding the onset of cognitive impairment in the Water-maze and Y-maze test and the appearance of Aβ and phosphorylated tau by IHC. Seeding activity increased progressively with age and was significantly higher in 3xTg-AD mice than in wild-type controls at all time points ($p < 0.01$). To our knowledge, this represents the first systematic mapping of tau seeding dynamics in the 3xTg-AD model using RT-QuIC. These findings establish RT-QuIC as a sensitive and specific approach for detecting early pathological tau seeds, far in advance of conventional readouts. This work not only strengthens the validity of the 3xTg-AD model for tauopathy research but also underscores the translational potential of RT-QuIC in monitoring disease progression and evaluating tau-targeted therapies.

Supported by the Startup Package and Developmental Funds of the First Affiliated Hospital of Nanchang University (#500021001 and #500021002), and by the National Natural Science Foundation of China (NSFC 82471499).

References:

1. Li L, Jiang Y, Hu W, Tung YC, Dai C, Chu D, Gong CX, Iqbal K, Liu F. Pathological Alterations of Tau in Alzheimer's Disease and 3xTg-AD Mouse Brains. Mol Neurobiol. 2019 Sep;56(9):6168-6183.
2. Barber AJ, Del Genio CL, Swain AB, Pizzi EM, Watson SC, Tapiavala VN, Zanazzi GJ, Gaur AB. Age, Sex and Alzheimer's disease: A longitudinal study of 3xTg-AD mice reveals sex-specific disease trajectories and inflammatory responses mirrored in postmortem brains from Alzheimer's patients. bioRxiv [Preprint]. 2023 Dec 24:2023.12.23.573209.
3. Javonillo DI, Tran KM, Phan J, Hingco E, Kramár EA, da Cunha C, Forner S, Kawauchi S, Milinkeviciute G, Gomez-Arboledas A, Neumann J, Banh CE, Huynh M, Matheos DP, Rezaie N, Alcantara JA, Mortazavi A, Wood MA, Tenner AJ, MacGregor GR, Green KN, LaFerla FM. Systematic Phenotyping and Characterization of the 3xTg-AD Mouse Model of Alzheimer's Disease. Front Neurosci. 2022 Jan 24;15:785276.

Stevens LM, Brown RE. Reference and working memory deficits in the 3xTg-AD mouse between 2 and 15-months of age: a cross-sectional study. Behav Brain Res. 2015 Feb 1;278:496-505.

PV1-2 Oral Presentation of Selected Posters

APPS2025 Abstract

Title:

Cellular prion protein exacerbates brain demyelination by activating microglia through the TREM2-TYROBP axis in cuprizone-treated animals

Authors:

Qing Li1ǂ, Pengcheng Huang1ǂ, Jinqiong Zhan2ǂ, Hancun Yi1, Zihao Zhang1, Pingping Shen3, Yuanjian Yang2, Yanming Wang4, Daojun Hong1, Jiyan Ma5,6*, Xiaomu Wu1,7*, Wen-Quan Zou1*

Affiliation:

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2. Jiangxi Mental Hospital & Affiliated Mental Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330029, Jiangxi, China;
3. Department of Neurology, The First Hospital of Jilin University, Changchun 130000, Jilin Province, China;
4. Institute of Nuclear Medicine Molecular Imaging, Binzhou Medical University Hospital, Binzhou 256603, Shandong Province, China;
5. Beijing Institute for Brain Research, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 102206, China;
6. Chinese Institute for Brain Research, Beijing 102206, China
7. Jiangxi Provincial Institute of Neurology, Nanchang 330006, Jiangxi Province, China

Abstract (300 words):

The cellular prion protein (PrPC), widely recognized for its role in prion diseases, is highly expressed in the central nervous system (CNS)1,2. While it has been reported to link to demyelination in the peripheral nervous system3,4, the function of PrPC in CNS demyelination remains unclear. We explored the role of PrPC in cuprizone-induced demyelination using wild-type and two PrP-deficient mouse models5. We observed significant upregulation of PrPC within demyelinating lesions of wild-type mice fed with cuprizone. In contrast, mice lacking PrPC (Prnp-KO) or with deletion of its octapeptide repeat region (OPR) (Prnp-OPRde) exhibited markedly reduced myelin loss and oligodendrocyte death, evidenced by luxol fast blue staining, myelin basic protein examination, and detection of OLIG2. RNA sequencing analysis indicated that this protection was associated with attenuated microglial activation and a downregulation of the TREM2-TYROBP signaling pathway. Accordingly, compared to wild-type mice, microglia-mediated neuroinflammatory responses were substantially reduced in Prnp-KO and Prnp-OPRde mice. Together, these findings demonstrate that PrPC exacerbates CNS demyelination by promoting microglia activation via the TREM2-TYROBP axis, and further identify OPR as a critical domain responsible for this neurotoxic activity. These findings reveal a novel pathogenic mechanism for PrPC in CNS demyelination and suggest that targeting PrPC or its OPR may offer new therapeutic opportunities for demyelinating disorders.

Supported by the Startup Package and Developmental Funds of the First Affiliated Hospital of Nanchang University (#500021001 and #500021002), and by the National Natural Science Foundation of China (NSFC 82471499).

PV1-3 Oral Presentation of Selected Posters

APPS2025 Abstract

Title: Development of therapeutic agents for prion diseases based on structural analysis of abnormal prion protein

Authors: Kazuki Kanemaru[1,2], Takeshi Ishikawa[3], Ryuichiro Atarashi[2]

Affiliation:

1) Division of Respirology Rheumatology, Infectious Diseases and Neurology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki

2) Division of Microbiology, Department of Infectious Diseases, Faculty of Medicine, University of Miyazaki

3) Department of Chemistry and Biotechnology, University of Kagoshima

Abstract (300 words):

Prion diseases are fatal neurodegenerative disorders caused by the accumulation of abnormal prion protein (PrP^{Sc}) in the central nervous system. Drug discovery has been based on the binding of compounds to normal prion protein (PrP^{C}), but no clinically effective treatments have been identified currently. Recently the analysis of the amyloid structure of PrP^{Sc} by cryo-electron microscopy(Cryo-EM) has been established, therefore the prospects of efficient search for compounds by virtual screening of drugs based on the detailed structure of the PrP^{Sc} was opened up. In this study, a model of human PrP^{Sc} was created by manually converting 16 amino acids on a computer based on the PrP^{Sc} of Chandler strain, whose structure has been analysed by Cryo-EM, and structure-based virtual screening was performed. Then the distribution of non-electrostatic interactions on the amyloid structure of the PrP^{Sc} was visualised and compound docking calculations were performed with the hypothesis that larger interactions would contribute to increased amyloid. Docking calculations were performed using 3430 compounds as drug repositioning, the top 53 compounds were extracted from those showing strong binding. When 32 of these compounds, which are presumed to have blood-brain barrier(BBB) permeability, were added to Neuro-2a persistently infected with Fukuoka-1 strain, several compounds showed reduced protease resistant PrP(PrP-res) in Western blots(WB), so further analysis is currently underway.

These results may indicate new possibilities of future drug discovery for conditions associated with abnormal aggregation of proteins such as α-synuclein, not only prion diseases.

References:

PV1-4 Oral Presentation of Selected Posters

APPS2025 Abstract

Title: Oligoadenylate synthetase 1a (Oas1a) as a Key Interferon-Stimulated Gene Limiting Prion Propagation

Authors: Takujiro Homma[1], Takehiro Nakagaki[2], Takuya Nishinakagawa[8], Yurie Morita[8], Ryuichiro Atarashi[3], Shigeru Kakuta[4,5,6], Yoichiro Iwakura[4,7], Noriyuki Nishida[2], and Daisuke Ishibashi[8]

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Abstract (300 words):
Prion diseases are fatal neurodegenerative disorders caused by the misfolding of the normal cellular prion protein (PrP^{C}) into its infectious, β-sheet-rich isoform (PrP^{Sc}). Traditionally, prions were considered incapable of eliciting robust immune responses because PrP^{C} and PrP^{Sc} share an identical primary structure. However, accumulating evidence indicates that type I interferon (IFN-I) signaling plays a crucial role in the host defense against prion propagation. Our previous studies demonstrated that interferon regulatory factor 3 (IRF3), a key transcriptional activator of IFN-I, limits prion replication and delays disease progression. Furthermore, IFN-I signaling itself confers resistance to prion infection. Yet, the precise mechanisms underlying this protection have remained unclear. Here, using both *in vivo* and *ex vivo* prion infection models, we identified 2′-5′ oligoadenylate synthetase 1a (Oas1a)—an interferon-stimulated gene downstream of the IFN-I receptor—as a key inhibitor of early-stage prion invasion. In Oas1a-knockout mice, prion disease progression was markedly accelerated and survival time significantly shortened, demonstrating the protective role of Oas1a *in vivo*. Consistently, mouse embryonic fibroblasts derived from Oas1a-deficient mice showed heightened susceptibility to 22L prion infection, thereby abolishing the anti-prion effects of IFN-I treatment. Moreover, recombinant Oas1a applied extracellularly suppressed prion propagation without activating the canonical RNase L pathway. Mechanistically, Oas1a directly binds to PrP^{C}, preventing its conversion into PrP^{Sc} and thereby limiting PrP^{Sc} accumulation in vitro. Collectively, these findings reveal a pivotal role of the IFN–Oas1a axis in restricting prion propagation and highlight Oas1a as a potential therapeutic target for prion diseases.

References:
Takujiro Homma, Takehiro Nakagaki, Takuya Nishinakagawa, Yurie Morita, Ryuichiro Atarashi, Shigeru Kakuta, Yoichiro Iwakura, Noriyuki Nishida, Daisuke Ishibashi. Oligoadenylate synthetase 1a suppresses prion infection through binding to cellular prion protein. *Brain* (2025), awaf193, doi: 10.1093/brain/awaf193.

P01

APPS2025 Abstract

Title: Elucidation of prion propagation mechanism in primary cultured neurons

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Background: Prion-infected cells are useful for clarifying the mechanism of prion propagation and pathogenesis in prion diseases. However, cellular localization of PrP^{Sc} in primary cultured neurons differs from that of PrP^{Sc} in neuroblastoma cells[1)] and primary cultured astrocytes. Therefore, we attempted to elucidate the mechanism of prion propagation in primary cultured neurons more precisely.

Methods: Primary cortical neurons were prepared from cortices of mouse fetus at 14 embryonic days. Primary cortical neurons were infected with prions using microsomal fractions from 22L strain-infected mouse brains. PrP^{Sc} was analyzed by immunofluorescence assay using Airyscan microscopy system that can acquire high-resolution images with better signal-to-noise ratio.

Results & Discussion: The elongation and increase of these stains were observed on the cell surface of primary neurons at 4–10 days post infection (dpi) when PrP^{Sc} was directly stained with Alexa Fluor 488-labeled anti-PrP mAb 8D5 at 4˚C. Average length of the string-like PrP^{Sc} stains were 1.41 μm and 1.62 μm at 4 and 10 dpi, respectively, indicating 1.2-fold elongation on the cell surface. In addition to the elongation, numbers of string-like PrP^{Sc} stains were increased 8.3 times at 10 dpi. When prion-infected primary cortical neurons were treated with anti-PrP mAb 31C6 for 17 days from 4 dpi, the average length of the string-like PrP^{Sc} stains was shortened to 73.1 % and numbers of the PrP^{Sc} stains were decreased to 5.4% of the cells treated with negative control antibody. Consistent with the decrease of PrP^{Sc} stains, the level of PrP^{Sc} was reduced to 33.5% of the cells treated with negative control antibody. The length was shortened to 72.3% and numbers of the string-like PrP^{Sc} stains were decreased to 25.0% of the cells treated with negative control antibody, even when the antibody treatment was started from 11 dpi, at which string-like PrP^{Sc} had already generated extensively. These results suggest that prion propagation mainly occurs on the cell surface of primary cortical neurons. However, PrP^{Sc} existing on the cell surface appeared to be degraded if generation of PrP^{Sc} was inhibited by the treatment with mAb 31C6.

References:

1) Tanaka et al., J. Gen Virol, 97: 2030-2042, 2016

P02

APPS2025 Abstract

Title: An autopsied case of plaque-type dura mater graft-associated Creutzfeldt-Jakob disease

Authors: Daisuke Tahara[1], Daichi Yokoi[2], Nao Tahara[1], Akio Akagi[1], Yuichi Riku[1], Jun Sone[1], Hiroaki Miyahara[1], Hirohisa Watanabe[3], Masahisa Katsuno[2], Yasushi Iwasaki[1]

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Abstract (300 words):

Dura mater graft-associated Creutzfeldt-Jakob disease (dCJD) is one of iatrogenic Creutzfeldt-Jakob diseases due to cadaveric dura mater used in neurosurgery[1]. Two subtypes exist in dCJD: non-plaque type and plaque type[2]. Plaque-type dCJD is uncommon form and is also referred to as MMiK (129M/M genotype, type i PrP^{Sc}, and kuru plaques) dCJD[2,3]. Patients with plaque-type dCJD exhibit slowly progressive clinical course, and some clinical symptoms such as myoclonus less frequently occur[2]. Herein, we report an autopsy case of plaque-type dCJD together with biochemical and genetic analyses. A 41 years-old male patient developed right hand paresthesia. He had received a dura mater graft in the right parietal region at 14 years of age. The symptoms slowly progressed. The paresthesia extended to extremities after seven months. He became unable to walk independently after 17 months. Voluntary speech and movement obviously decreased at 23 months after onset. At 24 months, myoclonus was firstly observed, and the patient developed akinetic mutism. He died at 26 months after the onset. Neuropathological investigations revealed mild to moderate spongiform changes with fine vacuoles throughout the brain and spinal cord. Synaptic, perineuronal, and plaque-type abnormal prion protein (PrP) deposition were also diffusely observed. One of characteristic findings was intense PrP deposition was observed throughout the spinal gray mater. Long disease duration may be associated the diffuse deposition in the spinal cord. Considering the initial symptom and spinal lesions, we speculated an indirect PrP propagation via cerebrospinal fluid. In addition, degeneration was prominent in the limbic system and cerebellum. This pattern resembled that of VV2 sporadic CJD. We thought that distribution of lesions reflected the source of infection in dCJD.

References:

1. Brown P, Brandel JP, Sato T, et al. Iatrogenic Creutzfeldt-Jakob disease, final assessment. Emerg Infect Dis. 2012;18(6):901–907.
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P03

APPS2025 Abstract

Title:

Role and mechanism of PrP^C in tolerance of mice to neuropathic pain

Authors:

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Abstract (300 words):

Introduction: Neuropathological pain causes serious trouble to patients' daily lives [1, 2]. Recent studies have indicated that certain neurodegenerative diseases, such as Creutzfeldt–Jakob disease (CJD), are associated with pain sensitization in the late stage [3, 4]. Notably, prion gene knockout (*Prnp*$^{-/-}$) mice exhibit reduced pain sensitivity, suggesting a role for the cellular prion protein (PrP^C) in pain regulation.

Objective: This study aims to elucidate the involvement of PrP^C in neuropathic pain and to investigate its underlying mechanisms.

Methods: A spared nerve injury (SNI) model was established in mice to evaluate pain and anxiety-like behaviors. Neuronal activity and cell types in the anterior cingulate cortex (ACC) were assessed via immunohistochemical staining. Genetic differences between *Prnp*$^{-/-}$ and wild-type (WT) mice were analyzed using RNA sequencing and qPCR, while Western blot was employed to measure PrP and KCNJ13 protein expression in the ACC before and after SNI. The roles of $CaMKII^+$ and $GAD67^+$ neurons in pain modulation were examined through chemogenetic manipulation. Additionally, adeno-associated viruses (AAVs) were constructed to overexpress *Kcnj13* in the ACC to explore its functional role in pain behavior.

Results: Neuropathic pain downregulated PrP expression in the ACC. Prnp$^{-/-}$ mice exhibited higher tolerance to both neuropathic and inflammatory pain compared to WT mice. In the SNI model, the number of $c\text{-}Fos^+$ neurons in the ACC was greater in Prnp$^{-/-}$ mice than in WT controls. Prnp knockout downregulated KCNJ13 expression in the ACC under basal conditions. Interestingly, SNI downregulated KCNJ13 expression in WT mice but upregulated it in Prnp$^{-/-}$ mice. Chemogenetic inhibition of $CaMKII^+$ neurons in the ACC reduced pain tolerance in Prnp$^{-/-}$ mice. Overexpression of *Kcnj13* enhanced pain tolerance in WT mice.

Conclusion: *Prnp* knockout may modulate neuronal activity in the ACC via KCNJ13, thereby enhancing pain tolerance.

Keywords Neuropathic pain; Anterior cingulate cortex; Prion protein; KCNJ13

[Supported by the startup package and developmental funds of the First Affiliated Hospital of Nanchang University (#500021001, #500021002), National Natural Science Foundation (NSFC) (82471499) to WQZ, and Jiangxi Key Laboratory of Neurological Diseases (2024SSY06072) to DH and WQZ.]

P04

APPS2025 Abstract

Title: Two Decades of Primate Prion Research in Japan: From Infection Model to Biobank

Authors: Fumiko Ono[1)], Hiroaki Shibata[2)], Nozomi Nakano[2)], Keiko Ohto[2)], Sachi Okabayashi[3)], Nene Miyamae[1)], Minoru Tobiume[4)], Yuko Sato[4)], Ken'ichi Hagiwara[4)], Morikazu Imamura[5)], Yuichi Murayama[6)],Tetsutaro Sata[4)], Keiji Terao[2)] and Motohiro Horiuchi[7)]

Affiliation: 1) Okayama University of Science, 2) The Corporation for Production and Research of Laboratory Primates, 3) Transgenic Group Inc., 4) National Institute of Infectious Diseases, 5)University of Miyazaki, 6) Independent Researcher, 7) Hokkaido University

Abstract:

Over the period from 2003 to 2023, our group established and maintained the only experimental system in Japan for prion infection using cynomolgus macaques. Over the past two decades, infection studies with classical (C-BSE) and atypical (L-BSE, H-BSE) bovine spongiform encephalopathy strains have been conducted to evaluate their zoonotic potential and pathogenic mechanisms.

A total of 32 macaques were inoculated via intracerebral, oral, intravenous, or intraperitoneal routes, followed by longitudinal sampling and comprehensive pathological examination. Approximately 2,500 biological and tissue specimens—including cerebrospinal fluid, blood fractions, saliva, urine, and multiple organs—have been preserved along with detailed experimental records, forming the foundation of the Primate Prion Biobank.

In addition to specimen preservation, a digital histopathological archive has been developed, comprising virtual slides of hematoxylin-eosin, PrP immunostaining, phosphorylated tau, and GFAP-stained sections. This database enables quantitative image analysis and facilitates secondary data utilization without the need for additional animal experiments.

Findings from this long-term study have provided valuable insights into the pathogenesis of prion diseases in nonhuman primates and have established a sustainable research platform integrating clinical, pathological, and digital data. As experimental prion infection in primates is unlikely to be conducted again, the accumulated materials and datasets now constitute an irreplaceable scientific resource to be inherited by the next generation of prion researchers.

References:

1)Imamura M, Hagiwara K, Tobiume M, Ohno M, Iguchi H, Takatsuki H, Mori T, Atarashi R, Shibata H, Ono F. Administration of L-Type Bovine Spongiform Encephalopathy to Macaques to Evaluate Zoonotic Potential. Emerg Infect Dis. 2025 May;31(5):986-990.

2) Shibata H, Ono F, Sato Y, Ohto K, Nakano N, Imamura M, Horiuchi M, Tobiume M, Hagiwara K. Lack of Evidence for Transmission of Atypical H-Type Bovine Spongiform Encephalopathy Prions (H-BSE Prions) by Intracranial and Oral Challenges to Nonhuman Primates. Microbiol Immunol. 2025 Jan;69(1):25-34.

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Jpn J Infect Dis. 2011;64(1):81-4.

P05

APPS2025 Abstract

Title: Specific early electroencephalogram for the diagnosis of sporadic Creutzfeldt-Jakob disease

Authors: Hirokazu Natsui[a], Taiki Matsubayashi[b], Katsuya Satoh[c], Tetsuyuki Kitamoto[d,e], Takanori Yokota[a], and Nobuo Sanjo [a,f]

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Abstract (300 words):

An early diagnosis is required for intervention in prion disease cases. To elucidate the specificity of early electroencephalography discharges in cases of sporadic Creutzfeldt-Jakob disease, we analysed epileptiform discharges through electroencephalography. Nine patients with methionine/methionine type 1/classic sporadic Creutzfeldt-Jakob disease and 20 patients with status epilepticus were included. Generalized periodic discharges, lateralized periodic discharges, and central sagittal sporadic epileptiform discharges were evaluated. Central sagittal sporadic epileptiform discharges were defined as nonrhythmic and nonperiodic waveforms showing generalized spike-and-wave complexes and/or sharp waves predominantly in the central sagittal region. In the sporadic Creutzfeldt-Jakob disease group, central sagittal sporadic epileptiform discharges, lateralized periodic discharges, and generalized periodic discharges were observed in five (55.6%), one (11.1%), and eight (88.9%) patients, respectively, with an average duration from onset to the appearance of the discharges of 1.6, 1.0, and 2.44 months, respectively. In the status epilepticus group, these discharges were detected in one (5.0%), six (30.0%), and six (30.0%) patients, respectively. The incorporation of central sagittal sporadic epileptiform discharges and lateralized periodic discharges into the World Health Organization diagnostic criteria, alongside generalized periodic discharges, significantly shortened the average lapse from symptom onset to sporadic Creutzfeldt-Jakob disease diagnosis (2.06 months vs. 2.44 months; $p = 0.02$). Central sagittal sporadic epileptiform discharges emerge as promising biomarkers for distinguishing sporadic Creutzfeldt-Jakob disease from status epilepticus, and together with lateralized periodic discharges provide an opportunity for early diagnosis of sporadic Creutzfeldt-Jakob disease. (232words)

References:

P06

APPS2025 Abstract

Title:
Abnormal RIG-I formation arising during the incubation period in prion-infected mouse brains

Authors:
Kazunori Sano

Affiliation:
Department of Physiology and Pharmacology, Faculty of Pharmaceutical Sciences, Fukuoka University

Abstract (300 words):

Prion diseases are characterized by prolonged asymptomatic incubation periods, followed by a rapidly progressive clinical phase. In mouse models, neuropathological changes occur during incubation periods that span several months. Despite this, the contribution of innate immune molecules to the pathogenesis of prion disease during the incubation period remains poorly understood. Previous studies reported that IRF3 deficiency leads to earlier onset and more severe pathology, while MyD88 deficiency does not significantly alter disease progression. These findings suggest that MyD88-independent, but not MyD88-dependent, signaling contributes to early host defense against prion infection. Here, we examined alterations in dsRNA-sensing molecules associated with MyD88-independent signaling during the incubation period and after disease onset. We found that among the dsRNA-recognition molecules, only retinoic acid-inducible gene I (RIG-I) showed aberrant formation in the brains of prion-infected mice during the incubation period. These results suggest that abnormal RIG-I formation is involved in the pathogenesis of prion disease even during the asymptomatic incubation phase.

Psoter Presentation

P07

APPS2025 Abstract

Title: **Novel CLEIA assay for total tau protein in cerebrospinal fluid (CSF) of human prion disease patients: evaluation and limitations**

Authors: KONG WEIJIE, Katsuya Satoh[1]

Affiliation:
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Abstract (300 words):

Background: Clinical trials for human prion diseases (HPD) have recently begun, and cerebrospinal fluid (CSF) biomarkers such as total tau (t-tau) protein are gaining attention. High reproducibility and accuracy are essential for biomarker studies. With the COVID-19 pandemic, measurement using automated chemiluminescent enzyme immunoassay (CLEIA) instruments has become widespread. We evaluated the performance of t-tau detection by CLEIA and compared it with the conventional ELISA method.

Methods: Ninety-one CSF samples from patients with rapidly progressive dementia were analyzed by both ELISA and CLEIA. The 14-3-3 protein was assessed by Western blotting, and prion conversion activity was examined by RT-QuIC assay. Correlation between ELISA and CLEIA was analyzed in 30 samples. In addition, three samples were used to evaluate CLEIA reproducibility, storage stability, dilution linearity, and freeze–thaw effects.

Results: Among 91 samples, 45 were RT-QuIC–positive HPD cases and 46 were non-HPD controls. Both ELISA and CLEIA showed 100% sensitivity and specificity for HPD detection. A strong correlation was observed between methods ($R^2 = 0.88$). CLEIA demonstrated superior reproducibility, stability, and tolerance to freezing and thawing. However, t-tau values above 2,000 pg/mL by CLEIA were unstable, and dilution tests showed reduced linearity and reproducibility.

Conclusion: CLEIA offers high reproducibility and stability compared to ELISA, but ELISA remains superior for dilution accuracy. Further optimization of dilution protocols is needed to establish CLEIA as a reliable tool for biomarker assessment in HPD clinical trials.

Reference

Kong Weijie, Toshiaki Nonaka, Katsuya Satoh. Evaluation and Limitations of the Novel Chemiluminescent Enzyme Immunoassay Technique for Measuring Total Tau Protein in the Cerebrospinal Fluid of Patients with Human Prion Disease: A 10-Year Prospective Study (2011-2020). Diagnostics (Basel). 2024 Jul 15;14(14):1520.

P08

APPS2025 Abstract

Title:
Validation of CSF Alpha-synuclein RT-QuIC in an Autopsy Cohort with Systemic Assessment of Lewy Pathology Including the Body

Authors:
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4. Department of Health Sciences, Unit of Medical and Dental Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Abstract (300 words):

Background and Objective:
Cerebrospinal fluid (CSF) real-time quaking-induced conversion (RT-QuIC) changed the diagnosis of prion disease [1]. RT-QuIC has been applied for other neurodegenerative diseases including Lewy body disease (LBD) defined by characteristic alpha-synuclein (α-syn) protein aggregates with prion-like properties [2,3]. While these α-syn aggregates are also observed in multiple organs in the body [4-8], the association between α-syn RT-QuIC and these pathology in the body remained undetermined. Based on the recent recommendations [9], we evaluated the association in our autopsy cohort with systemic assessment including the body.

Methods: α-syn RT-QuIC of stored CSF samples was carried out using previously published methods [10]. Regardless of the diagnosis, systemic Lewy pathology assessment including olfactory bulb, sympathetic ganglia, spinal cord, and multiple organs in the body, including esophagus, heart, and skin, was conducted [4-8].

Results: CSF from 30 patients were analyzed; symptomatic LBD (n=8), multiple system atrophy (MSA) (n=2), Alzheimer's disease (AD) (n=3), and other controls (n=17). Despite different clinical stages, autopsy revealed that six with symptomatic LBD were in diffuse neocortical and two were in limbic stage in the brain. All the eight patients showed widespread LBs in the body including those in olfactory bulb, esophagus, and sympathetic ganglia. Incidental LBs in the sympathetic ganglia were identified in one control. SAA was positive in all eight with symptomatic LBD, was weakly positive in one with AD, and was negative in all the others.

Conclusions: We confirmed high specificity (95%) and high sensitivity (100%) of our CSF α-syn RT-QuIC in symptomatic LBD with widespread pathology including the body. Negative results were observed in one with limited LBs in the body (sympathetic ganglia) and the two patients with MSA. Larger studies, including systemic Lewy pathology assessment including the body, may be necessary before fully implementing biomarker-based diagnosis of LBD.

References:

1. Hermann P, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Lancet Neurol. 2021; 20(3): 235-246.
2. Sano K, et al. Prion-Like Seeding of Misfolded α-Synuclein in the Brains of Dementia with Lewy Body Patients in RT-QUIC. Mol Neurobiol. 2018; 55(5): 3916-3930.
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P09

APPS2025 Abstract

Title:
Normal prion protein (PrPC) affects cellular adipogenesis by regulating Pparγ pathway

Authors:
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Abstract (300 words):

As is well known, Pparγ plays an indispensable role in adipocyte differentiation.

By comparing wild-type (WT) mice and prion gene knockout (PKO) mice of the same age, we found that PKO mice are smaller, weigh less, and exhibit reduced visceral fat accumulation compared with WT mice.

Adipose-derived mesenchymal stem cells (ADSCs) were isolated from the epididymal fat pads of 8-week-old male mice. After sufficient proliferation, the cells were subjected to a 14-day adipogenic induction culture using a standard cocktail method.

Isolation and in vitro adipogenic induction of mouse ADSCs demonstrated an increase in Prnp expression, accompanied by elevated expression of adipogenesis-related genes.

Similarly, 3T3-L1 preadipocytes were cultured to confluence and then induced to differentiate for 7 days using the same cocktail method. On day 4 of differentiation, siRNA was introduced to suppress prion gene expression.

Experiments using 3T3-L1 cells revealed that following lipid droplet formation, Prnp expression was upregulated, along with increased expression of CD36, Pparγ, and Pparα.

Conversely, suppression of Prnp expression by siRNA on day 4 led to a marked decrease in the protein levels of CD36 and Pparγ.

Taken together, these findings indicate that the absence of prion protein suppresses Pparγ expression, thereby inhibiting the expression of associated lipid metabolism factors and slowing the process of lipogenesis.

According to the above conclusion, we can infer that the expression of Pparγ is inhibited when there is no prion protein. The expression of lipid metabolism factors related to it is inhibited at the same time, resulting in the slow process of lipogenesis.

References:

P10

APPS2025 Abstract

Title: Electroencephalogram features in the very early phases of sporadic Creutzfeldt–Jakob disease (Interim Analyses by Prion Disease Surveillance Committee members)

Authors: ◎Ryoko Muramatsu[1)], Hirokazu Natsui[1)], Taiki Matsubayashi[2)], Ryusuke Ae[3)], Koki Kosami[3)], Katsuya Sato[4)], Sonoko Misawa[1)], Nobuo Sanjo[1)]

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2) Department of Neurology, National Hospital Organization Disaster Medical Center, Tokyo, Japan
3) Division of Public Health, Center for Community Medicine, Jichi Medical University, Shimotsuke, Tochigi, Japan
4) Department of Health Sciences, Unit of Medical and Dental Sciences, Nagasaki University Graduate School of Biomedical Sciences, Japan

Abstract (300 words):

【Background】In sporadic Creutzfeldt–Jakob disease (sCJD), it can be challenging to establish ‘probable’ diagnosis based on WHO criteria, because some patients do not display generalized periodic discharges (GPDs) on electroencephalography (EEG). Increasing numbers of patients have recently received ‘possible’ diagnosis due to lack of GPDs on EEG. We aim to clarify the periods of emerging prodromal EEG changes from onset, including central sagittal sporadic epileptiform discharges (CSSEDs) and lateralized periodic discharges (LPDs)[1)], and assess the sensitivity and specificity of those changes.【Methods】In Prion Disease Surveillance registry records from inception through 2025, 645 patients were diagnosed as ‘possible’ due to lack of GPDs on EEG. Among them, the committee continuously follow 382. Fifteen of these patients were re-diagnosed from ‘possible’ to ‘probable’ sCJD based on the emergence of GPDs. We reviewed EEG data from 9 of the 15 patients before and after GPD emergence. Six patients were excluded due to data unavailability.【Results】Among the nine reviewed patients whose EEG records were submitted to the committee, single EEGs were recorded in two patients. One patient showed GPDs, and another showed slow waves without GPDs. Among the remaining seven patients, GPDs were identified at the first recorded EEG in one patient, and no GPDs were identified even at the second recorded EEG in one patient. Conversion from prodromal EEG changes to GPDs was identified in five patients, with the median period of emergence between these discharges being 30 days (range, 11–164 days). Secondary diagnoses made by the primary physicians were concordant with those made by the committee members for the seven patients. CSSEDs were observed in two patients, and no LPDs were observed.【Conclusions】The concomitance ratio for GPD observance on EEG by the primary physician and the committee members was 78%, indicating that diagnosing probable sCJD is quite challenging. Repeated EEG recording is important for correct diagnosis of patients showing equivocal EEG findings. Since prodromal EEG changes can convert to GPDs within 11 days at the earliest, we recommend repeating EEG recordings approximately every 2 weeks in patients with prodromal EEG changes.

References:
1) Matsubayashi, T., Akaza, M., Hayashi, Y et al. Specific electroencephalogram features in the very early phases of sporadic Creutzfeldt-Jakob disease. *Journal of the neurological sciences*, *437*, 120265.

P11

APPS2025 Abstract

Title: Electroencephalogram features in the very early phases of sporadic Creutzfeldt–Jakob disease (Interim Analyses by Japanese Prion Disease Surveillance Committee members)

Authors: ◎Ryoko Muramatsu[1)], Hirokazu Natsui[1)], Taiki Matsubayashi[2)], Ryusuke Ae[3)], Koki Kosami[3)], Katsuya Sato[4)], Sonoko Misawa[1)], Nobuo Sanjo[1)]

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Abstract (300 words):

【**Background**】In sporadic Creutzfeldt–Jakob disease (sCJD), it can be challenging to establish 'probable' diagnosis based on WHO criteria, because some patients do not display generalized periodic discharges (GPDs) on electroencephalography (EEG) in the early phases. We assess the periods of emerging prodromal EEG changes, including central sagittal sporadic epileptiform discharges (CSSEDs) and lateralized periodic discharges (LPDs), and GPDs from onset.

【**Methods**】In Japanese Prion Disease Surveillance registry records from inception through 2025, 645 patients were diagnosed as 'possible'. Among them, the committee continuously follow 382. Fifteen of these patients were re-diagnosed from 'possible' to 'probable' sCJD based on the emergence of GPDs. We reviewed EEG data from 9 of the 15 patients.

【**Results**】Among the nine reviewed patients whose EEG records were submitted to the committee, single EEGs were recorded in two patients. One patient showed GPDs, and another showed slow waves without GPDs. Among the remaining seven patients, GPDs were identified at the first recorded EEG in one patient, and no GPDs were identified even at the second recorded EEG in one patient. Conversion from prodromal EEG changes to GPDs was identified in five patients, with the median period of emergence between these discharges being 30 days (range, 11–164 days). Secondary diagnoses made by the primary physicians were concordant with those made by the committee members for the seven patients. CSSEDs were observed in two patients, and no LPDs were observed.

【**Conclusions**】The concomitance ratio for GPD observance on EEG by the primary physician and the committee members was 78%. Repeated EEG recording is important for correct diagnosis of patients showing equivocal EEG findings. Since prodromal EEG changes can convert within 11 days at the earliest, we recommend repeating EEG recordings every 2 weeks in suspicious patients.

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1. Taiki Matsubayashi, Miho Akaza, Yuichi Hayashi, Tsuyoshi Hamaguchi, Katsuya Satoh, Koki Kosami, Ryusuke Ae, Tetsuyuki Kitamoto, Masahito Yamada, Takayoshi Shimohata, Takanori Yokota, Nobuo Sanjo. Specific electroencephalogram features in the very early phases of sporadic Creutzfeldt–Jakob disease. Journal of the Neurological Sciences 437, 120265, 2022
2. Taiki Matsubayashi, Hirokazu Natsui, Katsuya Satoh, Tetsuyuki Kitamoto, Takanori Yokota, Nobuo Sanjo. Specific early electroencephalogram for the diagnosis of sporadic Creutzfeldt-Jakob disease. Prion 19, 17-24, 2025

P12

APPS2025 Abstract

Title:

Neurofilament Light Chain Levels in Serum and Cerebrospinal Fluid Do Not Correlate with Survival Times in Patients with Prion Disease

Authors:

Shimamura M, Weijie K, Nonaka T, Kosami K, Ae R, Fujita K, Matsubayashi T, Tsukamoto T, Sanjo N, Satoh K.

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Abstract (300 words):

Prion diseases, including Creutzfeldt–Jakob disease (CJD), are deadly neurodegenerative disorders characterized by the buildup of abnormal prion proteins in the brain. This accumulation disrupts neuronal functions, leading to the rapid onset of psychiatric symptoms, ataxia, and cognitive decline. The urgency of timely diagnosis for effective treatment necessitates the identification of strongly correlated biomarkers in bodily fluids, which makes our research crucial. In this study, we employed a fully automated multiplex ELISA (Ella®) to measure the concentrations of 14-3-3 protein, total tau protein, and neurofilament light chain (NF-L) in cerebrospinal fluid (CSF) and serum samples from patients with prion disease and analyzed their link to disease prognosis. However, in North American and European cases, we did not confirm a correlation between NF-L levels and survival time. This discrepancy is believed to stem from differences in treatment policies and measurement methods between Japan and the United States. Nonetheless, our findings suggest that NF-L concentrations could be an early diagnostic marker for CJD patients with further enhancements. The potential impact of our findings on the early diagnosis of CJD patients is significant. Future research should focus on increasing the number of sCJD cases studied in Japan and gathering additional evidence using next-generation measurement techniques.

References:

P13

APPS2025 Abstract

Title:
Ophthalmological abnormalities observed in two patients with Gerstmann-Sträussler-Scheinker disease

Authors: Shinsuke Fujioka[1], Ryota Ko[2], Jane YH Huang[3], Eiichi Uchio[3], Yoshio Tsuboi[4]

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Abstract (300 words):
Creutzfeldt-Jakob disease (CJD) is a rare, fatal prion disorder, while Gerstmann-Sträussler-Scheinker (GSS) disease, usually linked to the PRNP p.P102L mutation, represents a slower autosomal dominant variant[1]. Visual symptoms are well documented in sporadic CJD, but ophthalmological features in GSS remain poorly defined[2,3].

We describe two genetically confirmed GSS patients (PRNP p.P102L, codon 129 MM, 219 EE) who exhibited distinct ocular abnormalities. Patient 1, a 35-year-old man, developed gait disturbance and dysarthria, later reporting visual difficulties despite preserved cognition. Ophthalmological evaluation revealed bilateral myopic progression, superior visual field depression, and localized retinal nerve fiber layer thinning on OCT, suggesting subclinical optic neuropathy. Patient 2, a 41-year-old man, presented with gait disturbance and dysarthria but no visual complaints. Routine assessment showed bilateral Grade 2 cataracts and subsequent myopic progression during follow-up. Both patients exhibited >1.00 D/year myopic shift, unexplained by environmental or systemic factors.

These findings expand the spectrum of ocular involvement in GSS, including retinal thinning, early cataract formation, and progressive myopia. Possible mechanisms involve prion-related retinal pathology and aberrant α-crystallin accumulation, as reported in prion disease[4]. The phenotypic variability between patients with the same genetic profile suggests individual susceptibility, similar to other hereditary neurodegenerative diseases.

This is, to our knowledge, the first report of cataract and progressive myopia in GSS. Subtle ocular manifestations may be underrecognized due to overshadowing neurological symptoms. Greater awareness and further pathological studies are needed to clarify the mechanisms linking prion pathology to ocular changes.

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P14

APPS2025 Abstract

Title: Mechanism of prion propagation in primary astrocytes

Authors: Temuulen Erdenebat[1,3], Akio Suzuki[1,3], Toyotaka Sato[1,3], Motohiro Horiuchi[1,3]

Affiliation:
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Background

Astrocytes are a type of glial cell that can be infected by prions, and prion-infected astrocytes can transmit infection to neurons (1). To clarify how astrocytes contribute to prion propagation, this study analyzed the generation and localization of abnormal prion protein (PrP^{Sc}) in primary cultured astrocytes.

Materials and Methods

Primary astrocyte cultures were prepared from the brains of postnatal day 6 mice and infected with prions using microsomal fractions from 22L strain–infected mouse brains. PrP^{Sc} localization was examined by immunofluorescence staining using anti-PrP monoclonal antibodies (mAbs) 8D5 and 132. Intracellular localization was further analyzed with antibodies against organelle markers Rab5, EEA1, Rab7, Rab11, Tgn48, and Cathepsin D.

Results

Unlike primary neurons infected with prions, astrocytes showed only a few string-like PrP^{Sc} stains on the cell surface. Granular PrP^{Sc}, mainly composed of N-terminal–truncated forms, was predominantly detected in the perinuclear region. Treatment with anti-PrP mAb 31C6 from 4 days post-inoculation (dpi) reduced PrP^{Sc} levels to 23.5% of those in control antibody–treated astrocytes at 21 dpi. When 31C6 treatment began at 11 dpi, when both string-like and granular PrP^{Sc} were evident, granular staining markedly decreased, and surface string-like PrP^{Sc} disappeared, leaving only small dot-like signals. Granular PrP^{Sc} colocalized with early endosomes (7.5%), late endosomes (8.1%), and lysosomes (35.3%).

Discussion

These results suggest that prion propagation in astrocytes occurs on both the cell surface and within intracellular compartments associated with the endo-lysosomal pathway. The predominant localization of PrP^{Sc} in lysosomes differed from that observed in prion-infected neuroblastoma cells or primary neurons, indicating cell type–dependent PrP^{Sc} metabolism.

References:

Victoria, G., Arkhipenko, A., Zhu, S. et al. Astrocyte-to-neuron intercellular prion transfer is mediated by cell-cell contact. Sci Rep 6, 20762 (2016). https://doi.org/10.1038/srep20762

P15

APPS2025 Abstract

Title: A case of early-onset Alzheimer's disease with the *PRNP* V180I mutation and a family history of dementia.

Authors: Tsuyoshi Hamaguchi,[1,2] Tadanori Hamano,[2,3] Yasuhiro Kawasaki,[2,4] Takashi Uehara,[2,4] Katsuya Satoh,[5] Norikazu Hara,[6] Akinori Miyashita,[6] Takeshi Ikeuchi,[6] Tetsuyuki Kitamoto,[7] Masato Asahina[1]

Affiliation: [1]Department of Neurology, Kanazawa Medical University, [2]Center for Comprehensive Care on Memory Disorders, Kanazawa Medical University, [3]Department of Geriatric Medicine, Kanazawa Medical University, [4]Department of Neuropsychiatry, Kanazawa Medical University, [5]Department of Health Sciences, Unit of Medical and Dental Sciences, Nagasaki University Graduate School of Biomedical Sciences, [6]Department of Molecular Genetics, Brain Research Institute, Niigata University, [7]Department of Neurological Science, Tohoku University Graduate School of Medicine.

Abstract (300 words):

Objective: To investigate the potential influence of the prion protein gene (*PRNP*) V180I mutation on the onset of Alzheimer's disease (AD).

Methods: We examined a case of early-onset AD with a family history of dementia that carried the *PRNP* V180I mutation.

Case report: The patient began making frequent mistakes at work, such as forgetting appointments at age 47. He presented to our hospital 8 months after symptom onset. Family history revealed that his older brother, his mother, and her maternal grandmother had histories of dementia. Examination revealed cognitive impairment with a MMSE score of 20/30 without other neurological abnormalities. Brain MRI revealed mild atrophy in both hippocampi, but diffusion-weighted imaging (DWI) showed no abnormal signals. Cerebrospinal fluid (CSF) analysis showed the Aβ42/Aβ40 ratio was decreased at 0.036 (normal: ≥0.067), and phosphorylated tau was elevated at 175 pg/mL (normal: 21.5-59.0 pg/mL). Based on these findings, a diagnosis of early-onset AD was made. Given the family history of dementia, whole-exome sequencing was performed. No mutations were found in the amyloid precursor protein (*APP*), presenilin (*PSEN*)*1*, or *PSEN2* genes. The apolipoprotein E (*ApoE*) genotype was ε4/ε4. Additionally, a *PRNP* V180I mutation was present.

Discussion: Head MRI of the present patient showed no cortical hyperintensity on DWI, a feature characteristic of hereditary prion diseases with the *PRNP* V180I mutation, leading to the conclusion that prion disease has not developed at this time. We considered the *ApoE* gene to be involved in the early-onset dementia and family history in this case. Although the impact of the *PRNP* V180I mutation on AD onset remains unclear, one case of early-onset AD with the *PRNP* V180I mutation has been reported previously.[1]

Conclusion: We report a case of early-onset AD with a family history of dementia and the *PRNP* V180I mutation.

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Bagyinszky E, Kang MJ, Pyun J, Giau VV, An SSA, Kim S. Early-onset Alzheimer’s disease patient with prion (*PRNP*) p.Val180Ile mutation. Neuropsychiatr Dis Treat 2019; 15: 2003-2013.

P16

APPS2025 Abstract

Title: Serine Protease–Mediated Spontaneous Amyloid Formation Revealed by the RT-QuIC Assay

Authors: Tsuyoshi Mori, Morikazu Imamura, Hanae Takatsuki, Kazuki Kanemaru, Minako Ohno and Ryuichiro Atarashi.

Affiliation: Division of Immunology, Department of Infectious Diseases, Faculty of Medicine, University of Miyazaki

Abstract (300 words):

Prion diseases and Parkinson's disease are neurodegenerative disorders caused by the abnormal aggregation of specific pathogenic proteins—prion protein and α-synuclein, respectively—into amyloid-like fibrillar assemblies that accumulate within the nervous system. Although sporadic cases account for the majority of both diseases, the precise mechanisms underlying their onset remain largely unknown.

We previously developed the Real-time Quaking-Induced Conversion (RT-QuIC) assay, a highly sensitive in vitro amplification technique capable of detecting trace amounts of misfolded aggregates. In addition to its established utility for prion disease diagnosis using cerebrospinal fluid (CSF) samples, RT-QuIC has become a widely used international tool for studying the molecular mechanisms of amyloidogenic protein misfolding and propagation.

In our recent analyses employing RT-QuIC, we discovered that the presence of physiological serine proteases in the reaction buffer promotes amyloid fibril formation even in the absence of exogenous seeds. Furthermore, amyloid fibrils generated under these seed-free conditions exhibited seeding activity toward the full-length substrate protein, thereby facilitating further aggregation.

These findings suggest that endogenous serine proteases could cleave substrate proteins in vivo, thereby inducing structural transitions that trigger spontaneous formation of misfolded amyloid aggregates. We are currently conducting further investigations to elucidate the detailed molecular basis of this protease-mediated aggregation process.

P17

APPS2025 Abstract

Title:

Regional Variations in Seeding Activity, Phosphorylation, and Protein Levels of Tau in Alzheimer's Disease Brain

Authors:

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Department of Neurology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong Province, China.

Abstract (300 words):

In Alzheimer’s disease (AD), hyperphosphorylated tau propagates across brain regions through its seeding activity, much like prions. We assessed regional tau seeding activity and phosphorylation by RT-QuIC, western blotting (WB), and mass spectrometry in entorhinal cortex (ENT), inferior/middle/superior temporal gyri (ITG/MTG/STG), and cerebellum (CER). Tau-seeding was highest in ENT among the brain regions examined and correlated positively with Braak staging. AD-derived RT-QuIC products formed tau fibrils, propagating intracellularly in cell models. WB showed significantly higher pTau217/pTau396 in ITG vs. STG/CER. Seeding-activity correlated with WB levels of pTau217/pTau262/pTau396 ($p = 0.004$, $p = 0.0028$, $p = 0.003$) and Braak/Thal staging in temporal regions. Anti-tau antibodies varied in immunodepleting seeding (pTau217 > TAU5 > pTau181 > pTau396). Mass spectrometry identified 11 phospho-sites in ITG tau, while pTau231/pTau262/pTau263/pTau396 were AD-specific. Regional tau-seeding correlates with local phospho-tau levels and pathology, supporting plasma pTau217 for diagnosis and seeding activity as a potential biomarker.

[Supported by the startup package and developmental funds of the First Affiliated Hospital of Nanchang University (#500021001, #500021002), and National Natural Science Foundation (NSFC) (82471499) to WQZ, the NSFC (82160252 & 82271439) to DH, Jiangxi Key Laboratory of Neurological Diseases (2024SSY06072) to WQZ & DH, Beijing Municipal Natural Science Foundation (IS23103) to YH, Ministry of Science and Technology of the People's Republic of China, Science Innovation 2030-Brain Science and Brain-Inspired Intelligence Technology Major Project “Network Platform for Human Brain/Tissue Banking and Cooperative Research” Task 3 (2021ZD0201103) to XXY, and Scientific Research Foundation program in China (9167/28170086) & the Foreign Expert Program (9202/0210227525) to AP.]

P18

APPS2025 Abstract

Title: Monitoring Prion-like Tau Seeding Activity in an Alzheimer's Disease Mouse Model

Authors:
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Abstract (300 words):
Alzheimer’s disease (AD) is neuropathologically defined by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau. The triple-transgenic AD mouse (3xTg-AD), which carries mutations in APP, PS1, and tau, recapitulates both hallmark pathologies and has been widely studied using behavioral tests, western blotting, and immunohistochemistry (IHC). Here, we applied the highly sensitive real-time quaking-induced conversion (RT-QuIC) assay to longitudinally quantify pathological tau seeding activity in 3xTg-AD brains at 3, 6, 9, and 12 months of age. Remarkably, tau seeding was already detectable at 3 months—preceding the onset of cognitive impairment in the Water-maze and Y-maze test and the appearance of Aβ and phosphorylated tau by IHC. Seeding activity increased progressively with age and was significantly higher in 3xTg-AD mice than in wild-type controls at all time points ($p < 0.01$). To our knowledge, this represents the first systematic mapping of tau seeding dynamics in the 3xTg-AD model using RT-QuIC. These findings establish RT-QuIC as a sensitive and specific approach for detecting early pathological tau seeds, far in advance of conventional readouts. This work not only strengthens the validity of the 3xTg-AD model for tauopathy research but also underscores the translational potential of RT-QuIC in monitoring disease progression and evaluating tau-targeted therapies.

Supported by the Startup Package and Developmental Funds of the First Affiliated Hospital of Nanchang University (#500021001 and #500021002), and by the National Natural Science Foundation of China (NSFC 82471499).

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Stevens LM, Brown RE. Reference and working memory deficits in the 3xTg-AD mouse between 2 and 15-months of age: a cross-sectional study. Behav Brain Res. 2015 Feb 1;278:496-505.

P19

APPS2025 Abstract

Title:
YWHAG is associated with Alzheimer's pathology via astrocytic proteins and improves prediction accuracy

Authors:
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Abstract (300 words):
Among more than 6,000 cerebrospinal fluid (CSF) proteins, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma (YWHAG) exhibits the strongest predictive value for Alzheimer's disease (AD). However, its relationship with astrocytes remains unclear. A total of 530 participants were included. Multiple linear regression was used to examine the associations of YWHAG with nine astrocyte-related proteins, AD pathology, and cognitive function. Mediation analysis was conducted to assess whether astrocytic proteins mediated the relationship between YWHAG and AD pathology. Path analysis was performed to explore the potential pathways from YWHAG through astrocytic proteins to AD pathology and cognition. We evaluated whether combining YWHAG with astrocyte-related proteins improves its predictive performance, by comparing the area under the curve (AUC) of the combined model with that of YWHAG alone. YWHAG was positively associated with glial fibrillary acidic protein (GFAP, $\beta = 0.558$, $p < 0.001$), vimentin ($\beta = 0.329$, $p < 0.001$), aquaporin-4 (AQP4, $\beta = 0.097$, $p = 0.044$, $p < 0.05$), thrombospondin (THBS) -1 ($\beta = 0.470$, $p < 0.001$), and THBS2 ($\beta = 0.285$, $p < 0.001$), while showing negative associations with gap junction alpha-1 protein (GJα1, $\beta = -0.161$, $p < 0.001$) and serpin family A member 3 (SERPINA3, $\beta = -0.350$, $p < 0.001$). Mediation analysis indicated that certain astrocyte-related proteins may be involved in the association between YWHAG and AD pathology. Additionally, path analysis suggested a potential pathway involving YWHAG, GJα1, Aβ42, and cognitive function. The combination of YWHAG with SERPINA3 and THBS1 achieved an AUC of 0.981, outperforming YWHAG alone (AUC = 0.885). YWHAG is associated with astrocyte-related proteins, and combining them enhances its predictive accuracy for AD, highlighting its potential utility in early clinical screening.

Supported by the startup package and developmental funds of the First Affiliated Hospital of Nanchang University (#500021001, #500021002) and National Natural Science Foundation (NSFC) (82471499) to WQZ, and Jiangxi Key Laboratory of Neurological Diseases (2024SSY06072) to DH and WQZ.