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SHORT COMMUNICATION

Co-incidental *C9orf72* expansion mutation-related frontotemporal lobar degeneration pathology and sporadic Creutzfeldt–Jakob disease

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Abstract

Background: The *C9orf72* hexanucleotide expansion mutation is the most common cause of genetic frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and combined FTD-ALS. Its underlying neuropathology combines TDP-43 pathology and dipeptide repeat protein (DPR) deposits and may also associate with other neurodegeneration-associated protein aggregates. Herein we present a unique combination of *C9orf72* mutation with sporadic Creutzfeldt–Jakob disease (CJD) in a 74-year-old patient with rapidly progressive dementia.

Methods: Detailed neuropathological examination including immunohistochemistry for several proteinopathies. Genetic analysis was conducted by repeat primed polymerase chain reaction (PCR). Furthermore, we analyzed additional *C9orf72* mutation carriers for prion–protein (PrP) deposits in brain tissue and screened the cerebellar cortex of other CJD cases for p62/DPR neuronal inclusions to assess the frequency of combined pathologies.

Results: Postmortem brain examination of a patient with a rapidly progressive neurological deterioration of 8 months' duration confirmed the diagnosis of CJD. She harbored valine homozygosity at *PRNP* codon 129. In addition, a frontotemporal lobar degeneration (FTLD)-pattern with TDP-43 protein aggregates and p62+/C9RANT+ positive inclusions along with a high degree of Alzheimer-related pathology (A3B3C3) were identified. The suspected *C9orf72* expansion mutation was confirmed by repeat-primed PCR. Screening of 13 *C9orf72* cases showed no pathological PrP aggregates and screening of 100 CJD cases revealed no other *C9orf72* expansion mutation carriers.

Conclusion: A combination of a *C9orf72* expansion mutation-related FTLD with sporadic CJD in the same patient is rare. While the rarity of both diseases makes this concurrence most likely to be coincidental, questions regarding a potential link between these two neurodegenerative pathologies deserve further studies.

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KEYWORDS
C9orf72, CJD, FTLD, prion, TDP-43

INTRODUCTION

The GGGGCC hexanucleotide repeat expansion mutation in the non-coding region of chromosome 9 open reading frame 72 (*C9orf72*) gene is the most common genetic cause of familial and sporadic frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and FTD-ALS [1–3]. Clinical phenotypes are relatively broad, although those associated with FTD are commonly behavioral while ALS exhibit frequently bulbar and psychiatric symptoms [4–6]. Other phenotypes include parkinsonism, [4,7,8] Huntington's disease-mimics [9,10] or Creutzfeldt–Jakob disease (CJD)-like phenotypes with rapidly progressive course [3][11].

Neuropathologically, a combination of phospho-TDP-43 and p62+/phospho-TDP-43− protein aggregates containing the aberrant *C9orf72* protein product dipeptide repeat proteins (DPRs) is observed. DPRs are formed by repeat-associated translation, can be immunohistochemically visualized by specific antibodies, [12,13] and can be easily identified in the cerebellum and hippocampus, which represent useful screening regions for identifying *C9orf72* expansion mutation carriers [14].

We describe herein a unique constellation of sporadic CJD and *C9orf72* expansion mutation. We additionally screened other CJD brains for potential *C9orf72* expansion mutation and screened *C9orf72* expansion mutation carriers for CJD pathology.

METHODS

Neuropathological examination

Hematoxylin–eosin, Luxol fast blue stains and immunohistochemistry were performed on formalin-fixed and paraffin-embedded tissue blocks applying several primary antibodies (Table 1). The DAKO EnVision© detection kit (Dako, Glostrup, Denmark) was used for visualization of antibody reactions.

Genetic analysis

C9orf72 repeat expansion mutation was analyzed by repeat-primed polymerase chain reaction (PCR) as described previously [15] and *PRNP* sequencing was performed as described.

Screening of *C9orf72* mutation and CJD cases

To assess the potential co-existence of a prion disease in *C9orf72* mutations carriers we screened 13 additional, unrelated, postmortem cases for pathological prion–protein deposits by immunohistochemistry (anti-PrP/12F10 antibody) in selected areas (frontal cortex, hippocampus, thalamus, cerebellum).

Furthermore, to identify further potential *C9orf72* mutation carriers among prion diseases, we immunohistochemically screened 100 definite CJD cases with different histotypes (MM, MV, VV) for typical p62+/TDP-43− inclusions in the cerebellar cortex.

Ethical standards

The study was performed within OERPE in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the Medical University of Vienna (EK 396-2011).

RESULTS

Clinical summary

A 74-year-old woman was admitted to the Neurology department due to confusion, ataxia and dizziness of a few weeks' duration. An interview with her closest relatives did not indicate previous neurological

TABLE 1 Primary antibodies used for immunohistochemical characterization.

Antibody name	Clone	Company	Dilution
Anti-α-synuclein	Clone 5G4	Roboscreen, Leipzig, Germany	1:4000
Anti-βA4-amyloid	Clone 6F/3D	DAKO, Glostrup, Denmark	1:100
Anti-C9RANT	Polyclonal	Novus Biologicals, Centennial, CO, USA	1:1000
Anti-p62	Clone 3/p62 lck ligand	BD Transduction Laboratories, Franklin Lakes, NJ, USA	1:500
Anti-phosphorylated tau	Clone AT8, pS202/pT205	Thermo Scientific, Rockford, IL, USA	1:200
Anti-phosphorylated TDP-43	Clone 11-9, pS409/410	Cosmo Bio, Tokyo, Japan	1:20,000
Anti-PrP	Clone 12F10	Cayman Chemical, Ann Arbor, MI, USA	1:1000

symptoms. The patient's family history was unremarkable. Cranial magnetic resonance imaging (MRI), which included T2, fluid-attenuated inversion recovery (FLAIR) and T1 sequences with contrast, showed a small (3 cm in diameter) frontobasal tumor with a surrounding edema, suspicious for meningioma. Additionally, a mild temporal atrophy was noted. No obvious cortical or basal ganglia hyperintensities were reported, but images could not be reviewed. Although her symptoms could not be convincingly linked to the tumor itself, she was promptly operated. Histology revealed a classical meningothelial meningioma (WHO grade I). Postoperatively the patient did not improve but developed a rapidly progressive dementia, spasticity, bilateral Babinski sign, myoclonus and progressive stuporous state. A lumbar puncture 3 months after symptom onset showed positivity for 14-3-3 protein. On electroencephalography periodic sharp wave complexes were identified. MRI was not repeated. Due to increasing clinical suspicion of CJD, the surgical instruments were retrospectively identified and immediately discarded. The patient deteriorated further, presented several infections and fever episodes, evolved to akinetic mutism and finally died in a nursing home 8 months after disease onset with the final clinical diagnosis of “probable” CJD.

Neuropathological findings

Fixed brain weight was 948 g. Gross examination revealed a severe generalized atrophy with a frontobasal tissue defect caused by the surgical removal of the meningioma. On coronal sections, diffuse cortical and basal ganglia atrophy, enlargement of lateral ventricles and white matter rarefaction was found. The cerebellum revealed atrophy of the cerebellar peduncles, dentate nucleus and cerebellar cortex.

Histopathology and immunohistochemistry

Histopathological examination revealed severe neurodegenerative changes. The cerebral cortex and subcortical nuclei showed diffuse neuronal loss, prominent gliosis and spongiform change (Figure 1A,B). In the temporal cortex, a distinctive superficial laminar spongiosis was identified in addition to the severe cortical affection (Figure 1D). The cerebellar cortex showed severe loss of granule and Purkinje cells and Bergmann gliosis (Figure 1F). White matter showed marked rarefaction and gliosis (Figure 1G), accentuated in frontal and temporal lobes, and a degeneration of most white matter tracts including the pyramidal tract. A moderate cerebrovascular pathology with expanded Virchow–Robin spaces and perivascular pigment-laden macrophages was also observed.

Immunohistochemistry showed prominent pathological prion–protein (PrP) deposits in a diffuse-synaptic pattern throughout cortical layers, subcortical and brainstem nuclei, and the cerebellar cortex (Figure 1C,H,K). Occasionally perineuronal immunoreactivity was seen in deep layers of the parietal cortex (Figure 1C, inset). The frontal white matter, basal ganglia, thalamic and cerebellar white matter showed some plaque-like deposits and coarse deposits along axons and around vessels (Figure 1H, inset). No Kuru-type or florid plaques were identified [16,17].

There was a mild degree of concomitant phospho-TDP-43 pathology in cortical, subcortical and brainstem regions with diffuse-granular and compact neuronal cytoplasmic inclusions, occasional thin dystrophic neurites and fine dot-like neuropil immunoreactivity (Figure 1P,Q) [18–20]. Intranuclear inclusions were lacking. There were also widespread small, p62+ neuronal cytoplasmic inclusions in cortical neurons and granule cells of the cerebellum and hippocampal dentate gyrus (Figure 1E,I,M), suggestive of a *C9orf72* repeat expansion mutation. These were also immunoreactive for C9RANT (repeat-associated non-ATG translation) peptides or DPR. Their distribution pattern did not match that of phospho-TDP-43. As this was an archival case, these findings were observed in a second histopathological assessment 13 years later.

Moreover, we observed high load of Alzheimer's disease neuropathological change (ADNC) (A2B3C3) [21] with tau-positive neurofibrillary pathology in limbic and cortical regions (Figure 1K), granular fuzzy astrocytes in line with aging-related tau astrogliopathy (ARTAG) pathology in amygdala, temporal white matter and parietal cortex, [22] frequent neuritic plaques and moderate amyloid angiopathy without capillary involvement. No α-synuclein aggregates were identified.

Genetic analysis

C9orf72 genotyping revealed a typical saw-tooth pattern expanding over the currently used cut-off of 30 repeats, indicating a pathogenic hexanucleotide repeat expansion. Amplicon-length analysis was performed using flanking PCR to increase sensitivity and specificity of results, as described elsewhere [23]. Sequencing of *PRNP* showed no mutations and valine homozygosity was detected at codon 129.

Screening of *C9orf72* mutation and CJD cases

Immunohistochemical analysis of 13 additional *C9orf72* mutation carriers showed no pathological PrP aggregates or CJD-suggestive lesions. The screening of 100 definite sporadic CJD (sCJD) for p62-positive cytoplasmic inclusions in the cerebellar cortex revealed no other cases suspicious of *C9orf72* expansion mutation.

Retrospective cerebrospinal fluid analysis

Retrospective analysis of stored cerebrospinal fluid (CSF) samples (−80°C) revealed total tau levels of >2171 pg/ml (normal levels <500 pg/ml); real-time quaking-induced conversion (RT-QuIC) was negative.

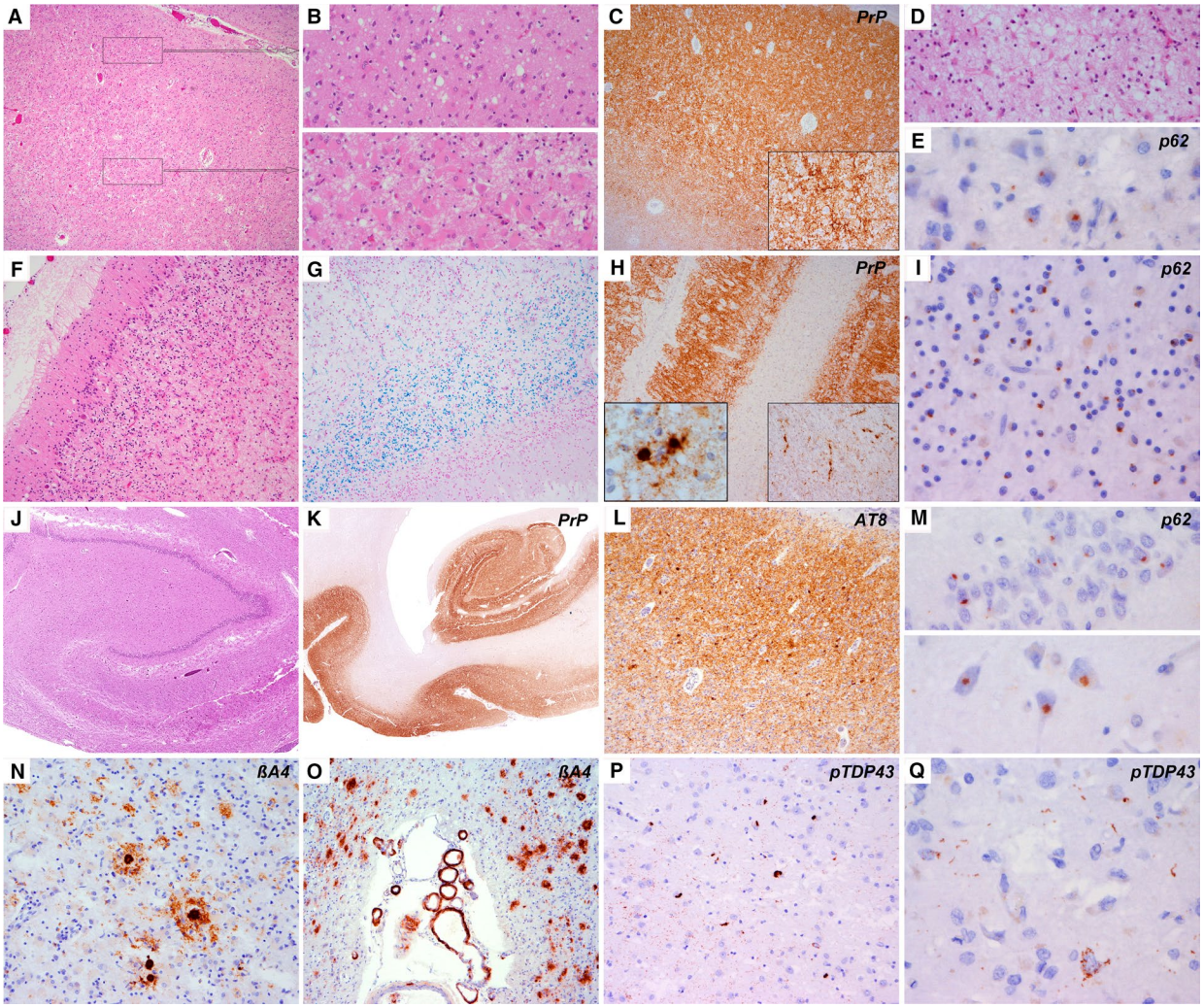

FIGURE 1 (A,B,F,G,J) Hematoxylin and eosin (H&E)-stained sections showing prominent neuronal loss, gliosis and spongiform change affecting cortical areas (A, frontal lobe; B, detail of upper (spongiform change consisting of small-to-middle-sized vacuoles in the neuropil) and middle cortical layers (with prominent gemistocytic astrocytes). (F) The cerebellum shows prominent loss of granule cells, narrowing of molecular layer, loss of Purkinje cells with Bergmann gliosis. (G) The underlying white matter shows prominent rarefaction and loss of myelin sheaths. (J) The hippocampus shows also diffuse gliosis and spongiform change in all cornu ammonis (CA) sectors. (C,H,K) Immunohistochemistry for prion–protein (PrP) (12F10 antibody) reveals intense deposits of the pathological PrP in a diffuse synaptic pattern in cortex (C), cerebellum (H) and hippocampus (K). In some areas, a perineuronal pattern (C, lower inset), and in the white matter – including the cerebellar region – focal plaque-like deposits, around vessels and along axons can be identified (H, lower insets). (L,N,O) In the hippocampus there is also abundant phospho-tau pathology in the form of neurofibrillary tangles and neuropil threads (L; AT8 antibody). (N,O) There are additional ßA4 amyloid plaques with dense central core (N) and amyloid deposits in the walls of the leptomeningeal vessels – amyloid angiopathy (O). (D,E,I,M) In addition to the Creutzfeldt–Jakob disease (CJD)-triad, there was also a superficial spongiosis (D; H&E) and abundant small cytoplasmic p62 immunoreactive inclusions in cortical neurons (E), granule cells of the cerebellar cortex (I), dentate gyrus of the hippocampus (M, upper panel) and CA4 sector of the hippocampus (M, lower panel), typical of the *C9orf72* expansion mutation. (P,Q) This pathology was associated with pTDP43 pathology in the parahippocampal region (P,Q) in the form of fine threads, cytoplasmic compact and diffuse dash-like inclusions (Q). Original magnification: A,J ×40; C,F,G,H,L,O ×100; B,D,N,P ×200; M upper ×400; E,I,M lower,Q ×600

DISCUSSION

We present a patient with a unique constellation of definite sporadic CJD carrying a *C9orf72* expansion mutation with FTLD neuropathological features, two neurodegenerative diseases which by themselves represent rare diseases. The patient presented typical symptoms of CJD and had no family history of a neurological disorder. While 14-3-3 protein and total tau levels were increased in the CSF, a retrospectively performed RT-QuIC assay for the pathological PrP was negative. Although the long storage time of 13 years might have influenced the results, some studies have shown very stable RT-QuIC results after short- and long-term (8–9 years) storage and after repetitive thawing/freezing cycles [24].

For the relatively short clinical course of 8 months, the brain was severely affected and involved also the frontotemporal regions. This exceeds what would be expected in a CJD VV subtype patient with such a short clinical history, suggesting that this severe neuropathological phenotype most likely represents superimposed CJD pathology on FTLD-TDP pathology. There was a degeneration of white matter tracts including the corticospinal tract, which while occurring in CJD, [25,26] including its panencephalopathic forms, [27] is also frequently observed in FTLD-ALS.

The distribution of CJD pathology was very severe and a mixed VV2+1 histotype was plausible due to cortical and subcortical involvement, prominent cerebellar degeneration, focal perineuronal and plaque-like deposits, and prominent synaptic PrP pathology, [16,17] and probably overlapped with FTLD pathology. Indeed, genetic analysis revealed valine homozygosity at *PRNP*-codon 129 with no mutations. Similarly, the distribution of TDP-43 pathology was consistent with that described in *C9orf72*-FTLD. This might be indistinguishable from sporadic FTLD-TDP cases, [1,2,6] and may follow a type A, type B or a type A/B pattern, as in our case [1,2,19]. Typically, DPR and phospho-TDP-43 pathologies do not follow the same distribution pattern [1,2,6]. In our case, the co-existence of CJD-PrP and *C9orf72*-FTLD-TDP-43 did not seem to influence the distribution of each other's pathology, but exacerbated the overall degenerative pathology, which was very severe.

We found no hints suggestive of prion disease in 13 additional *C9orf72* mutation carriers and no hints for *C9orf72* expansion in 100 additional sCJD. However, whether PrP, DPRs and TDP-43 influence each other and trigger their mutual misfolding and deposition, a mechanism that has been described for other neurodegenerative proteinopathies, remains unclear and merits further investigation [28,29]. Particularly, it would be of interest to know whether DPR pathology alters the cellular secretion of PrP, inducing a multilaminar synaptic damage and leading to diffuse-synaptic PrP deposits instead of laminar and plaque-like deposits as expected for the VV2 subtype.

In any case, mixed neurodegenerative pathologies are increasingly recognized [30,31]. Concomitant pathologies have been described in *C9orf72* mutation carriers, and in CJD [5,14,32–36]. In CJD, their overall frequency or extent, especially of ADNC, do not seem to exceed that of normal aging, [34] but may show an atypical tau distribution in the hippocampus [35–37]. The relationship of prion diseases with tau pathology varies between etiological forms and merits further studies [36,38]. Recently, the interaction between the cellular prion–protein and amyloid–beta oligomers has arisen interest due to the potential mediation of synaptic toxicity, making PrP^c a potential therapeutic target of Aβ pathology [39,40]. In contrast to other neurodegenerative conditions, [41–46] the relationship with TDP-43 protein is less clear, as postmortem studies have found only single CJD cases with limbic TDP-43 [33,47,48]. To our knowledge no cases of co-incidental CJD in *C9orf72* expansion mutation carriers have been described to date.

In conclusion, this case broadens the clinicopathological spectrum of *C9orf72* mutation and CJD, reinforces the value of thorough neuropathological examination in neurodegenerative diseases, and stresses the usefulness of systematic screening of concomitant proteinopathies including the *C9orf72* expansion mutation independently of other neuropathological diagnoses [14]. Finally, it also poses the question of a potential link between these two rare neurodegenerative disorders.

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DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Hsiung G-YR, DeJesus-Hernandez M, Feldman HH, et al. Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. *Brain*. 2012;135(3):709-722. https://doi.org/10.1093/brain/awr354
2. Mackenzie IRA, Frick P, Neumann M. The neuropathology associated with repeat expansions in the C9ORF72 gene. *Acta Neuropathol*. 2014;127(3):347-357. https://doi.org/10.1007/s00401-013-1232-4
3. Beck J, Poulter M, Hensman D, et al. Large C9orf72 hexanucleotide repeat expansions are seen in multiple neurodegenerative syndromes and are more frequent than expected in the UK population. *Am J Hum Genet*. 2013;92(3):345-353. https://doi.org/10.1016/j.ajhg.2013.01.011
4. Lindquist SG, Duno M, Batbayli M, et al. Corticobasal and ataxia syndromes widen the spectrum of C9ORF72 hexanucleotide expansion disease. *Clin Genet*. 2013;83(3):279-283. https://doi.org/10.1111/j.1399-0004.2012.01903.x
5. Snowden JS, Rollinson S, Thompson JC, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. *Brain*. 2012;135(3):693-708. https://doi.org/10.1093/brain/awr355
6. Stewart H, Rutherford NJ, Briemberg H, et al. Clinical and pathological features of amyotrophic lateral sclerosis caused by mutation in the C9ORF72 gene on chromosome 9p. *Acta Neuropathol*. 2012;123(3):409-417. https://doi.org/10.1007/s00401-011-0937-5
7. Wilke C, Pomper JK, Biskup S, Puskás C, Berg D, Synofzik M. Atypical parkinsonism in C9orf72 expansions: a case report and systematic review of 45 cases from the literature. *J Neurol*. 2016;263(3):558-574. https://doi.org/10.1007/s00415-016-8021-7

8. Cooper-Knock J, Frolov A, Highley JR, et al. C9ORF72 expansions, Parkinsonism, and Parkinson disease a clinicopathologic study. *Neurology*. 2013;81(9):808-811. https://doi.org/10.1212/WNL.0b013e3182a2cc38
9. Liu Y, Yu JT, Zong Y, Zhou J, Tan L. C9ORF72 mutations in neurodegenerative diseases. *Mol Neurobiol*. 2014;49(1):386-398. https://doi.org/10.1007/s12035-013-8528-1
10. Cooper-Knock J, Shaw PJ, Kirby J. The widening spectrum of C9ORF72-related disease; genotype/phenotype correlations and potential modifiers of clinical phenotype. *Acta Neuropathol*. 2014;127(3):333-345. https://doi.org/10.1007/s00401-014-1251-9
11. Grau-Rivera O, Gelpi E, Carballido-López E, Sánchez-Valle R, López-Villegas MD. Rapidly progressive dementia with psychotic onset in a patient with the C9ORF72 mutation. *Clin Neuropathol*. 2015; 34(5): 294–197. https://doi.org/10.5414/NP300853.
12. Ash PEA, Bieniek KF, Gendron TF, et al. Unconventional translation of C9ORF72 GGGGCC expansion generates insoluble polypeptides specific to c9FTD/ALS. *Neuron*. 2013;77(4):639-646. https://doi.org/10.1016/j.neuron.2013.02.004
13. Mori K, Weng S-M, Arzberger T, et al. The C9orf72 GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTLD/ALS. *Science (80-)*. 2013;339(6125):1335-1338. https://doi.org/10.1126/science.1232927
14. Ramos-Campoy O, Ávila-Polo R, Grau-Rivera O, et al. Systematic screening of ubiquitin/p62 aggregates in cerebellar cortex expands the neuropathological phenotype of the C9orf72 expansion mutation. *J Neuropathol Exp Neurol*. 2018;77(8):703-709. https://doi.org/10.1093/jnen/nly047
15. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011;72(2):257-268. https://doi.org/10.1016/j.neuron.2011.09.010
16. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. *Ann Neurol*. 1999;46(2):224-233. https://doi.org/10.1002/1531-8249(199908)46:2<224:AID-ANA12>3.0.CO;2-W
17. Parchi P, Strammiello R, Notari S, et al. Incidence and spectrum of sporadic Creutzfeldt-Jakob disease variants with mixed phenotype and co-occurrence of PrPSc types: an updated classification. *Acta Neuropathol*. 2009;118(5):659-671. https://doi.org/10.1007/s00401-009-0585-1
18. Mackenzie IRA, Neumann M, Baborie A, et al. A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol*. 2011;122(1):111-113. https://doi.org/10.1007/s00401-011-0845-8
19. Mackenzie IR, Neumann M. Reappraisal of TDP-43 pathology in FTLD-U subtypes. *Acta Neuropathol*. 2017;134(1):79-96. https://doi.org/10.1007/s00401-017-1716-8
20. Mackenzie IR, Neumann M. Subcortical TDP-43 pathology patterns validate cortical FTLD-TDP subtypes and demonstrate unique aspects of C9orf72 mutation cases. *Acta Neuropathol*. 2020;139(1):83-98. https://doi.org/10.1007/s00401-019-02070-4
21. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012;123(1):1-11. https://doi.org/10.1007/s00401-011-0910-3
22. Kovacs GG, Ferrer I, Grinberg LT, et al. Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy. *Acta Neuropathol*. 2016;131(1):87-102. https://doi.org/10.1007/s00401-015-1509-x
23. Akimoto C, Volk AE, van Blitterswijk M, et al. A blinded international study on the reliability of genetic testing for GGGGCC-repeat expansions in C9orf72 reveals marked differences in results among 14 laboratories. *J Med Genet*. 2014;51(6):419-424. https://doi.org/10.1136/jmedgenet-2014-102360
24. Cramm M, Schmitz M, Karch A, et al. Stability and reproducibility underscore utility of RT-QuIC for diagnosis of Creutzfeldt-Jakob disease. *Mol Neurobiol*. 2016;53(3):1896-1904. https://doi.org/10.1007/s12035-015-9133-2
25. Worrall BB, Rowland LP, Chin SSM, Mastrianni JA. Amyotrophy in prion diseases. *Arch Neurol*. 2000;57(1):33. https://doi.org/10.1001/archneur.57.1.33
26. Yaguchi H, Takeuchi A, Horiuchi K, et al. Amyotrophic lateral sclerosis with frontotemporal dementia (ALS-FTD) syndrome as a phenotype of Creutzfeldt-Jakob disease (CJD)? A case report. *J Neurol Sci*. 2017;372:444-446. https://doi.org/10.1016/j.jns.2016.10.038
27. Jansen C, Head MW, Rozemuller AJM, Ironside JW. Panencephalopathic Creutzfeldt-Jakob disease in the Netherlands and the UK: clinical and pathological characteristics of nine patients. *Neuropathol Appl Neurobiol*. 2009;35(3):272-282. https://doi.org/10.1111/j.1365-2990.2008.01004a.x
28. Moussaud S, Jones DR, Moussaud-Lamodière EL, Delenclos M, Ross OA, McLean PJ. Alpha-synuclein and tau: teammates in neurodegeneration? *Mol Neurodegener*. 2014;9(1):43. https://doi.org/10.1186/1750-1326-9-43
29. Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM. Synergistic interactions between Aβ, tau, and α-synuclein: acceleration of neuropathology and cognitive decline. *J Neurosci*. 2010;30(21):7281-7289. https://doi.org/10.1523/JNEUROSCI.0490-10.2010
30. Kovacs GG, Alafuzoff I, Al-Sarraj S, et al. Mixed brain pathologies in dementia: the BrainNet Europe consortium experience. *Dement Geriatr Cogn Disord*. 2008;26:343-350. https://doi.org/10.1159/000161560
31. Rahimi J, Kovacs GG. Prevalence of mixed pathologies in the aging brain. *Alzheimers Res Ther*. 2014;6(9):82. https://doi.org/10.1186/s13195-014-0082-1
32. Bieniek KF, Murray ME, Rutherford NJ, et al. Tau pathology in frontotemporal lobar degeneration with C9ORF72 hexanucleotide repeat expansion. *Acta Neuropathol*. 2013;125(2):289-302. https://doi.org/10.1007/s00401-012-1048-7
33. Grau-Rivera O, Gelpi E, Nos C, et al. Clinicopathological correlations and concomitant pathologies in rapidly progressive dementia: a brain bank series. *Neurodegener Dis*. 2015;15(6):350-360. https://doi.org/10.1159/000439251
34. Hainfellner JA, Wanschitz J, Jellinger K, Liberski PP, Gullotta F, Budka H. Coexistence of Alzheimer-type neuropathology in Creutzfeldt-Jakob disease. *Acta Neuropathol*. 1998;96(2):116-122. https://doi.org/10.1007/s004010050870
35. Rossi M, Kai H, Baiardi S, et al. The characterization of AD/PART co-pathology in CJD suggests independent pathogenic mechanisms and no cross-seeding between misfolded Aβ and prion proteins. *Acta Neuropathol Commun*. 2019;7(1):53. https://doi.org/10.1186/s40478-019-0706-6
36. Kovacs GG, Rahimi J, Ströbel T, et al. Tau pathology in Creutzfeldt-Jakob disease revisited. *Brain Pathol*. 2017;27(3):332-344. https://doi.org/10.1111/bpa.12411
37. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging*. 1995;16(3):271-278. https://doi.org/10.1016/0197-4580(95)00021-6
38. Reiniger L, Lukic A, Linehan J, et al. Tau, prions and Aβ: the triad of neurodegeneration. *Acta Neuropathol*. 2011;121(1):5-20. https://doi.org/10.1007/s00401-010-0691-0
39. Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-B oligomers. *Nature*. 2009;457(7233):1128-1132. https://doi.org/10.1038/nature07761

40. Cox TO, Gunther EC, Brody AH, et al. Anti-PrPC antibody rescues cognition and synapses in transgenic Alzheimer mice. *Ann Clin Transl Neurol*. 2019;6(3):554-574. https://doi.org/10.1002/acn3.730
41. Amador-Ortiz C, Lin WL, Ahmed Z, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. *Ann Neurol*. 2007;61(5):435-445. https://doi.org/10.1002/ana.21154
42. Josephs KA, Murray ME, Whitwell JL, et al. Updated TDP-43 in Alzheimer's disease staging scheme. *Acta Neuropathol*. 2016;131(4):571-585. https://doi.org/10.1007/s00401-016-1537-1
43. Nakashima-Yasuda H, Uryu K, Robinson J, et al. Co-morbidity of TDP-43 proteinopathy in Lewy body related diseases. *Acta Neuropathol*. 2007;114(3):221-229. https://doi.org/10.1007/s00401-007-0261-2
44. Arai T, Mackenzie IRA, Hasegawa M, et al. Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies. *Acta Neuropathol*. 2009;117(2):125-136. https://doi.org/10.1007/s00401-008-0480-1
45. Colom-Cadena M, Grau-Rivera O, Planellas L, et al. Regional overlap of pathologies in Lewy body disorders. *J Neuropathol Exp Neurol*. 2017;76(3):216-224. https://doi.org/10.1093/jnen/nlx002
46. Koga S, Lin WL, Walton RL, Ross OA, Dickson DW. TDP-43 pathology in multiple system atrophy: colocalization of TDP-43 and α-synuclein in glial cytoplasmic inclusions. *Neuropathol Appl Neurobiol*. 2018;44(7):707-721. https://doi.org/10.1111/nan.12485
47. Miguelez-Rodriguez A, Santos-Juanes J, Vicente-Etxenausia I, et al. Brains with sporadic Creutzfeldt-Jakob disease and copathology showed a prolonged end-stage of disease. *J Clin Pathol*. 2018;71(5):446-450. https://doi.org/10.1136/jclinpath-2017-204794
48. Isaacs AM, Powell C, Webb TE, Linehan JM, Collinge J, Brandner S. Lack of TAR-DNA binding protein-43 (TDP-43) pathology in human prion diseases. *Neuropathol Appl Neurobiol*. 2008;34(4):446-456. https://doi.org/10.1111/j.1365-2990.2008.00963.x

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