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RESEARCH ARTICLE

Neuropathology of trisomy 21 mosaicism in a case with early-onset dementia

Phong T. Ngo[1] | **Jesse R. Pascual**[1] | **Sierra Wright**[1] | **Christopher K. Williams**[2] | **Shino Magaki**[2] | **William H. Yong**[3] | **Harry V. Vinters**[2,4] | **John M. Ringman**[5] | **Elizabeth Head**[1]

[1]Department of Pathology and Laboratory Medicine, University of California, Irvine, Irvine, California, USA

[2]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[3]Department of Pathology and Laboratory Medicine, University of California Medical Center, Irvine, Orange, California, USA

[4]Department of Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[5]Department of Neurology, Keck School of Medicine at University of Southern California, Los Angeles, California, USA

Correspondence
Elizabeth Head, Department of Pathology and Laboratory Medicine, University of California, Irvine, 1111 Gillespie Neuroscience Research Facility, Irvine, CA 92697, USA.
Email: heade@uci.edu

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Abstract

INTRODUCTION: This study investigated the impact of trisomy 21 mosaicism (mT21) on Alzheimer's disease (AD) neuropathology in a well-characterized clinical case described by Ringman et al.

METHODS: We describe AD neuropathology in mT21 including amyloid beta, phosphorylated tau, astrogliosis, microgliosis, α-synuclein, and TAR DNA-binding protein 43 (TDP-43) in cerebral cortex, hippocampal subregions, and amygdala using immunohistochemistry.

RESULTS: We observed high AD neuropathologic change with a score of A3B3C3. In addition, there was widespread astrogliosis, cerebral amyloid angiopathy, and perivascular space widening throughout the brain. Lewy bodies and neurites were noted in the amygdala only and no TDP-43 was observed.

DISCUSSION: The findings in this case report highlight that mT21 is sufficient to induce AD neuropathology and early-onset dementia.

KEYWORDS
Alzheimer's disease, amyloid beta, Down syndrome, neurofibrillary tangles, perivascular space widening

HIGHLIGHTS

- Trisomy 21 mosaicism (mT21) occurs when three copies of chromosome 21 are present in some but not all somatic cells in an individual. mT21 accounts for ≈ 2% of people diagnosed with Down syndrome (DS).
- Immunohistochemical identification of amyloid beta, tau, astrocytes, microglia, α-synuclein, and TAR DNA-binding protein 43 show that Alzheimer's disease (AD) pathology in mT21 is similar to full trisomy 21.
- The findings in this case report highlight that mT21 is sufficient to induce AD neuropathology and early-onset dementia.

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1 | BACKGROUND

First described in 1866 by the British physician Dr. John Langdon Down, Down syndrome (DS) is recognized as the most commonly occurring chromosomal disorder. In the United States, a diagnosis of DS occurs in 1 out of every 700 children born.[1,2] Among people living with DS, ≈ 95% have full trisomy 21 (fT21) where three copies of chromosome 21 are present throughout all the somatic cells. Of the remaining 5%, translocation affects ≈ 3% of the population while trisomy 21 mosaicism (mT21) accounts for ≈ 2% of people living with DS.[3] mT21 is the result of an unequal distribution of the triplicated chromosome 21 in the cells and organs of an individual. Therefore, individuals living with mT21 have a mixture of both trisomic and euploid cells throughout their bodies. This presents a unique opportunity to investigate whether these differences in gene expression may underlie biology unique to fT21 through masking factors shared regardless of trisomic or euploid cells.[4]

In fT21 individuals, overexpression of the amyloid precursor protein (APP) gene is thought to lead to an accelerated accumulation of amyloid beta (Aβ) protein, a neuropathological hallmark of Alzheimer's disease (AD).[5–8] The link between AD and DS was identified by G.A. Jervis in 1948 through extensive neuropathological examination.[9] Subsequently, other pathological similarities between AD in DS and late-onset AD have been observed in *post mortem* studies such as the comparable accumulation of Aβ plaques and neurofibrillary tangles (NFTs) along with a similar pattern of cortical atrophy.[10] As a result of this genetic predisposition, individuals with fT21 experience an early onset and accelerated progression of AD with extracellular Aβ deposits first observed consistently after the age of 30 years, formation of intraneuronal NFTs in their 40s, and the manifestation of clinical symptoms in the following decade.[11]

Despite well-documented studies of AD neuropathology in people with fT21, comparatively less is known about AD neuropathology in people who are mosaic for trisomy 21. Since its initial description in 1961 by Clarke et al.,[12] there has been a small number of case reports documenting the occurrence of mT21 in the clinic.[13–16] In one study,[13] mild cortical atrophy was noted by computed tomography scan, cortical blood flow by single-photon emission computed tomography was reduced in another[14] and a more recent paper shows that tau positron emission tomography (PET; Braak V/VI) and cortical amyloid by PET reveal tangles and plaques, respectively.[16] Glucose hypometabolism consistent with AD occurred in the parietotemporal region along with small white matter magnetic resonance imaging (MRI) hyperintensities.[16] Many of these same features were noted clinically in the current case.[15]

To our knowledge, there are few neuropathology studies reported in the brains of clinically well-characterized individuals with mT21. To address this gap, the purpose of our current study is to describe the *post mortem* neuropathology of a 64-year-old adult male with DS caused by mT21 who was diagnosed with early-onset dementia.[15] The aim of our investigation is to characterize AD neuropathology in the brain of this patient.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched PubMed and Google Scholar for literature on Alzheimer's disease (AD), mosaicism, trisomy 21, and Down syndrome (DS) in AD.
2. **Interpretation**: Mosaicism of trisomy 21 often goes undiagnosed in the general population due to minimal clinical and physical manifestations often seen in infants and children with DS. Previous clinical case reports by Ringman et al. and Nuebling et al. show that mosaic patients may present to the clinic with early signs of dementia and a medical history of mildly delayed intellectual development. *Ante mortem* studies consist of neuroimaging, neuropsychological testing, and plasma levels consistent with an AD diagnosis. Our study provides *post mortem* evidence that mosaicism for trisomy 21 is sufficient to drive AD and associated neuropathology.
3. **Future directions**: We suggest screening early-onset people with dementia with a history of intellectual disability for mosaicism in trisomy 21. We also suggest comparing larger cohorts of people with trisomy 21 mosaicism to full trisomy 21 to understand the age of onset of cognitive decline, rate of progression, and impact on AD pathology (neuroimaging, fluid biomarkers, neuropathology).

2 | METHODS

2.1 | Case presentation

An adult male had developed early signs of dementia at 55 years of age as described in a case report by Ringman et al.[15] An initial standard karyotype analysis of peripheral lymphocytes revealed that 1 in 60 metaphase cells studied were trisomic for chromosome 21. Subsequent metaphase and interphase fluorescent in situ hybridization (FISH) indicated he was 10% mosaic for chromosome 21. He died at 64 years of age of progressive neurological decline and underwent brain donation at the Alzheimer's Disease Research Center (ADRC) at the University of California Los Angeles (UCLA).

2.2 | Clinical presentation

The patient's clinical presentation has been previously described.[15] Briefly, he had a history of mild learning disability and hearing loss but had never been diagnosed with DS. He began to have a progressive decline in memory and executive function at the age of 52 years. At age 55 years, he met the criteria for mild dementia, and his work-up for reversible causes was unremarkable. He underwent a lumbar puncture, which showed a diminished Aβ level and an elevated total tau level consistent with the diagnosis of AD. Despite the absence of many features

of DS (low-set ears, broad space between the first and second toes, single palmar crease, brachycephaly, oblique eye fissures) in the presence of subtle dysmorphic features (micrognathia and clinodactyly), standard karyotyping from 60 peripheral white cells was performed, which demonstrated one cell with trisomy 21. This was followed up with FISH testing on both metaphase and interphase cells with DNA probes specific for chromosome 21, which identified trisomy 21 in 20 of 200 cells studied. Though specifics of his subsequent decline are lacking, he suffered progressive neurological decline and died at the age of 64 years.

2.3 | Brain tissue samples

The individual with mT21 had a brain weight of 1380 grams at the time of autopsy. The brain was fixed in formalin, sampled according to the UCLA dementia protocol and submitted for examination on formalin-fixed paraffin-embedded (FFPE) tissue sectioned at 6 µm. The sections of tissue were placed in a 42°C water bath and transferred to positively charged superfrost slides. The FFPE sections from the following left-hemisphere brain regions were provided by the UCLA ADRC: hippocampus (B4), superior temporal lobe (B5), parietal lobe (B8), entorhinal cortex (B10), dorsolateral prefrontal region (B12), amygdala (B18), occipital lobe (B22), and cerebellum (B16).

2.4 | Immunohistochemical procedures

The mT21 FFPE sections were deparaffinized and rehydrated using a dewaxing agent and a series of ethanol washes. Post-hydration, the sections were subjected to heat-mediated antigen retrieval using sodium citrate buffer (pH 6.0) at 95°C. In addition, sections designated for Aβ staining with 6E10 (an anti-β-Amyloid, 1-16 antibody) were incubated in 90% formic acid for 5 minutes. Endogenous peroxidase activity was blocked using a 3% hydrogen peroxide and 10% methanol in Tris-buffered saline (TBS) solution. Sections were incubated in blocking solution with primary antibodies for single-staining of A$\beta_{1\text{-}16}$, phosphorylated tau (Ser202, Thr205), ionized calcium-binding adapter molecule 1 (Iba1), glial fibrillary acidic protein (GFAP), TAR DNA-binding protein 43 (TDP-43), and α-synuclein overnight at 4°C (Table 1). The next day, sections were incubated in the corresponding biotinylated secondary antibodies (Table 1). Amplification and visualization of positive staining were done with avidin–biotin complex peroxidase kit and 3,3′ diaminobenzidine substrate kit. Immunostained FFPE sections were dehydrated in a series of ethanol washes, cleared in Histoclear, and cover slipped with Depex mounting media.

2.5 | Image acquisition and analysis

FFPE sections were imaged in brightfield using the Keyence BZ-X800 all-in-one microscope system. Sections stained with 6E10, AT8, Iba1, TDP-43, and α-synuclein were taken at a single *z* plane that provided the most focused picture. To assist in the visualization of the astrocytes and their respective processes, *z* stack images of sections stained with GFAP were captured at 0.4 µm step intervals after the upper and lower boundaries were established. The *z* stack images were then compressed into one standard image using the Keyence Microscopy software. Furthermore, the distribution of Aβ plaques, NFTs, and neuritic plaques (NPs) in the brain was characterized by comparing to established progression patterns and ABC scoring criteria.[17–22]

3 | RESULTS

3.1 | Aβ

Immunostaining for A$\beta_{1\text{-}16}$ using 6E10 revealed significant Aβ pathology throughout the patient's brain. With the brain regions provided, we observed Aβ deposition consistent with a Thal phase 5 and an ABC score for Aβ of A3. Within the hippocampus proper, there were mature plaques in the dentate gyrus and both mature and diffuse plaques throughout the cornu ammonis (Figure 1A). Mature Aβ plaques were also observed in the entorhinal (Figure 1B) and subicular cortices. We noted the presence of lake-like, diffuse Aβ deposits in the presubiculum. Subcortically, many diffuse, mature, and dense-cored plaques were observed in the amygdala (Figure 1C). Last, we observed diffuse and dense-cored Aβ plaques throughout the cortex of the dorsolateral prefrontal region, superior temporal lobe, parietal lobe, and occipital lobe (Figure 1D–G).

3.2 | Tau

AT8 immunostaining revealed that the distribution of NFTs was consistent with a Braak stage V/VI and an ABC stage for NFTs of B3 in the individual with mT21. We observed the presence of neuropil threads (NTs), pretangles, mature NFTs, and ghost tangles throughout the hippocampal formation (Figure 2A–B). AT8-associated NPs were observed with the most prominent NPs seen in the dentate gyrus and only sparsely visualized in the cornu ammonis (Figure 2A). In the amygdala, we observed NTs, pretangles, mature NFTs, ghost tangles, and NPs (Figure 2C). However, NPs were visually smaller and occurred less frequently than that observed in the hippocampal formation and transentorhinal region. In the cerebral cortex, we observed the presence of NTs, pretangles, mature NFTs, ghost tangles, and NPs in the superior temporal lobe, parietal lobe, occipital lobe, and dorsolateral prefrontal region (Figure 2D–G). The presence of NPs observed was consistent with a C3 score on the ABC staging criteria.

3.3 | Cerebrovascular pathology

In the cerebral cortex of mT21, we observed significant cerebral amyloid angiopathy (CAA) within the dorsolateral prefrontal and occipital lobes. There were abundant Aβ deposits lining both the cortical blood

TABLE 1 Antibody information.

Antibody	Clone	Manufacturer	Catalog no.	Lot no.	Host, antibody clonal type
Anti-Aβ, 1-16	6E10	BioLegend	803003	B353947	Mouse, monoclonal
Anti-phospho-tau (Ser202, Thr205)	AT8	Invitrogen	MN1020	XD3545842	Mouse, monoclonal
Anti-iba1 (for immunocytochemistry)	–	Fujifilm Wako	019-19741	SKN4887	Rabbit, polyclonal
Anti-GFAP	2A5	AbCam	ab4648	GR3224042-15	Mouse, monoclonal
α-synuclein	–	Millipore Conc.	AB5038	–	Rabbit, polyclonal
TDP-43 (N-terminal)	–	Proteintech	10782-2-AP	–	Rabbit, polyclonal

Abbreviations: Aβ, amyloid beta; GFAP, glial fibrillary acidic protein; iba1, ionized calcium-binding adapter molecule 1TDP-43, TAR DNA-binding protein 43.

vessels of the gray matter and the leptomeningeal vessels in both regions (Figure 3A). CAA was also observed—to a lesser extent—within the parietal and superior temporal lobe. In the parietal lobe, Aβ deposits were only observed within the leptomeningeal vessels within the sulci and the areas immediately surrounding it. In the superior temporal lobe, some Aβ deposits were observed within the cortical vessels in the gray matter; however, unlike the CAA pathology observed in the dorsolateral prefrontal region and occipital lobe, the cortical vessels in the superior temporal lobe were intermittently lined with Aβ deposits when viewed along a cross-sectional or longitudinal plane. There was no CAA pathology observed in the hippocampal formation. Subcortically, we observed rare occurrences of Aβ deposits in vessels in the amygdala. In addition to CAA, we also noted enlargement of the perivascular space (PVS) around vessels in the gray and white matter throughout all brain regions (Figure 3B).

3.4 | Glial pathology

Using an anti-Iba1 monoclonal antibody, we observed the distribution and morphology of microglia in the mT21 brain. In the prefrontal dorsolateral region, we observed a few Iba1-positive microglia in the gray matter and an abundance within the white matter. The microglial population in the gray matter was composed of primarily ramified, homeostatic microglia (Figure 3C) with sparse hypertrophic and dystrophic microglia. Within the white matter, we observed a range of microglial phenotypes that included many ramified and dystrophic microglia. This trend persisted throughout other regions in the cerebral cortex, including the occipital lobe, parietal lobe, and superior temporal lobe. In the hippocampus, we observed many rod-shaped microglia in the third sector of the cornu ammonis (Figure 3D). Microglia in the subiculum and presubiculum cortices of the hippocampal formation were dystrophic or ramified. Subcortically, we observed many ramified or dystrophic microglia and a lower occurrence of hypertrophic microglia.

Additionally, we examined the extent of astrogliosis using an anti-GFAP antibody. In the hippocampal formation, we observed an abundance of GFAP-positive, hypertrophic astrocytes in the gray matter of the entorhinal, presubiculum, and subiculum cortices, which can be identified by their enlarged somas and processes. Within the hippocampus proper, most of the GFAP-positive astrocytes were in the hippocampal stratum radiatum and lacunosum-moleculare of CA1 through CA3. Initially, the stratum pyramidale layer of CA1 had limited staining for GFAP-positive astrocytes—many of which were in clusters that are likely associated with Aβ plaques or cortical vessels with enlarged PVSs (Figure 3E). However, as we transitioned from areas CA2 to CA4 in the hippocampus, we observed an increasing number of GFAP-positive astrocytes. In the white matter of the hippocampal formation, we saw an abundance of both hypertrophic and homeostatic astrocytes. In the cerebral cortex, we observed GFAP-positive, hypertrophic astrocytes in the gray matter and a mixture of hypertrophic and homeostatic astrocytes in the white matter—albeit at a qualitatively lower load compared to the hippocampus. We also noticed hypertrophic astrocytes in clusters surrounding Aβ plaques, which was most common in the occipital lobe (Figure 3F). Similarly, there were many hypertrophic astrocytes in the amygdala.

3.5 | TDP-43 and Lewy bodies

To ascertain whether these cognitive changes before death may have been due to other related neuropathology, additional stains for TDP-43 and Lewy body pathology were performed using TDP-43 (N-terminal) and α-synuclein antibodies, respectively. Sections of the amygdala (B18) and dorsolateral prefrontal cortex (B12) were negative for TDP43-immunopositive inclusions or neurites. A-synuclein immunostaining showed scattered Lewy bodies and neurites in the amygdala but none in the cerebral cortex of the dorsolateral prefrontal region.

4 | DISCUSSION

The aim of this case report was to investigate the neuropathological features of AD in the brain of a person with DS caused by mT21. In trisomy 21, typically dementia occurs between 53 and 56 years of age, and the average age at death of a person with fT21 is ≈ 58

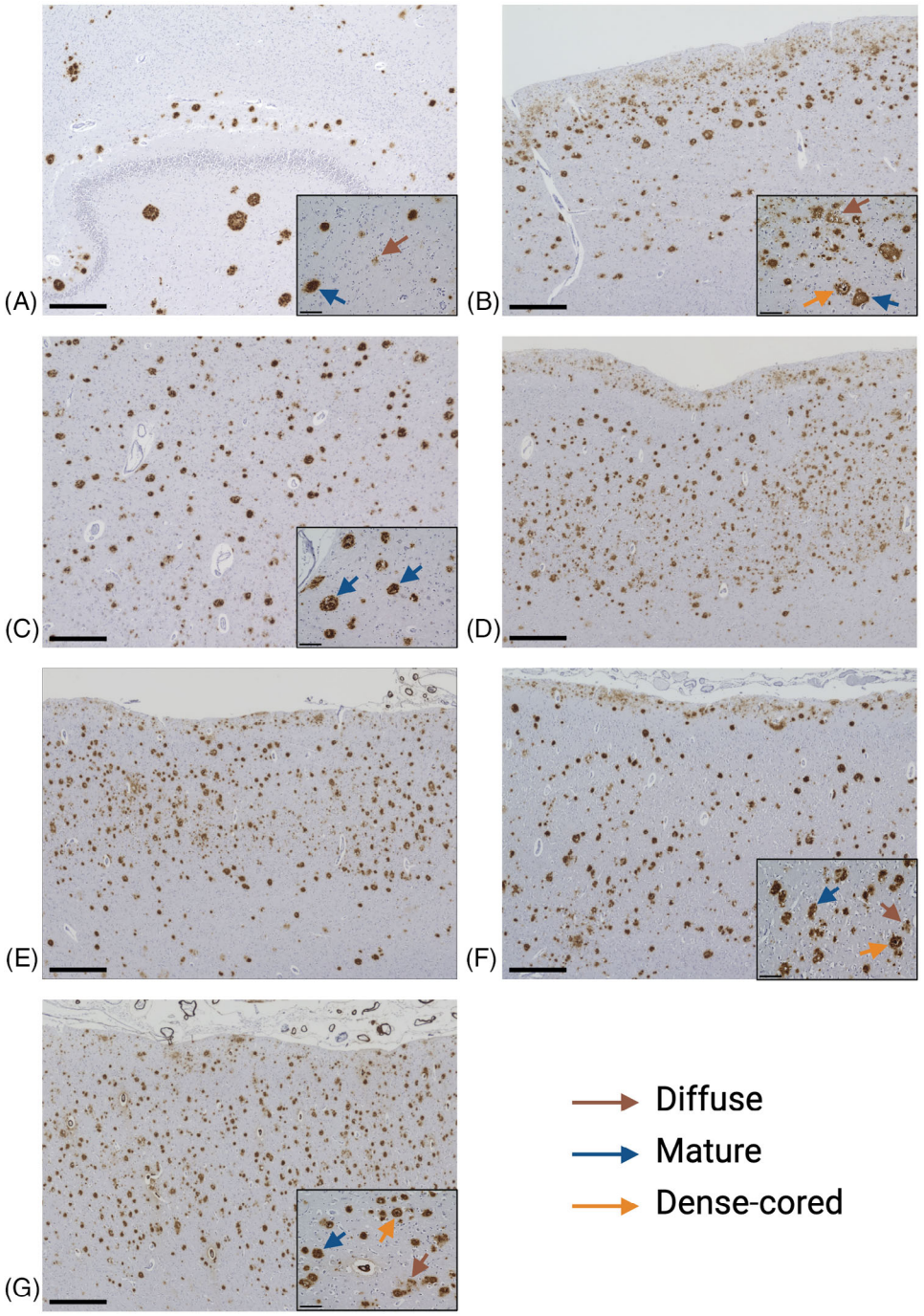

FIGURE 1 Amyloid beta (Aβ) plaques were observed throughout the individual with trisomy 21 mosaicism's brain. Low-power images were taken with a 4 × objective lens with 500 µm scale bars. All inset images were taken using a 20 × objective lens with 100 µm scale bars. (A) Plaques in the hippocampus with an inset image of mature and diffuse plaques observed in the CA1. (B) The entorhinal cortex presented with dense-cored, mature, and fibrillar plaques with neurons captured inside as seen in the inset image. Plaques in the (C) amygdala and (D)superior temporal lobe (E) parietal lobe are shown. (F) The occipital lobe contained small compact and cored plaques as well as dense fibrillar Aβ deposits. (G) In the dorsolateral prefrontal region, we observed many cored and compact plaques of smaller sizes.

years of age.[23] Thus, in many respects, the current mT21 individual shared many features in common with fT21 with the exception of a longer duration of dementia. The spread and progression of AD-related Aβ and tau pathology have been well characterized in the brains of people with and without DS caused by fT21.[17–19,24] In this case report, we observed widespread deposition of Aβ and accumulation of tau that was consistent with a Thal phase 5 and Braak tangle stage V/VI.[17,18] In combination with Consortium to Establish a Registry for Alzheimer's Disease scoring for NPs,[21] we made conservative estimates that this mT21 individual had high AD neuropathologic change

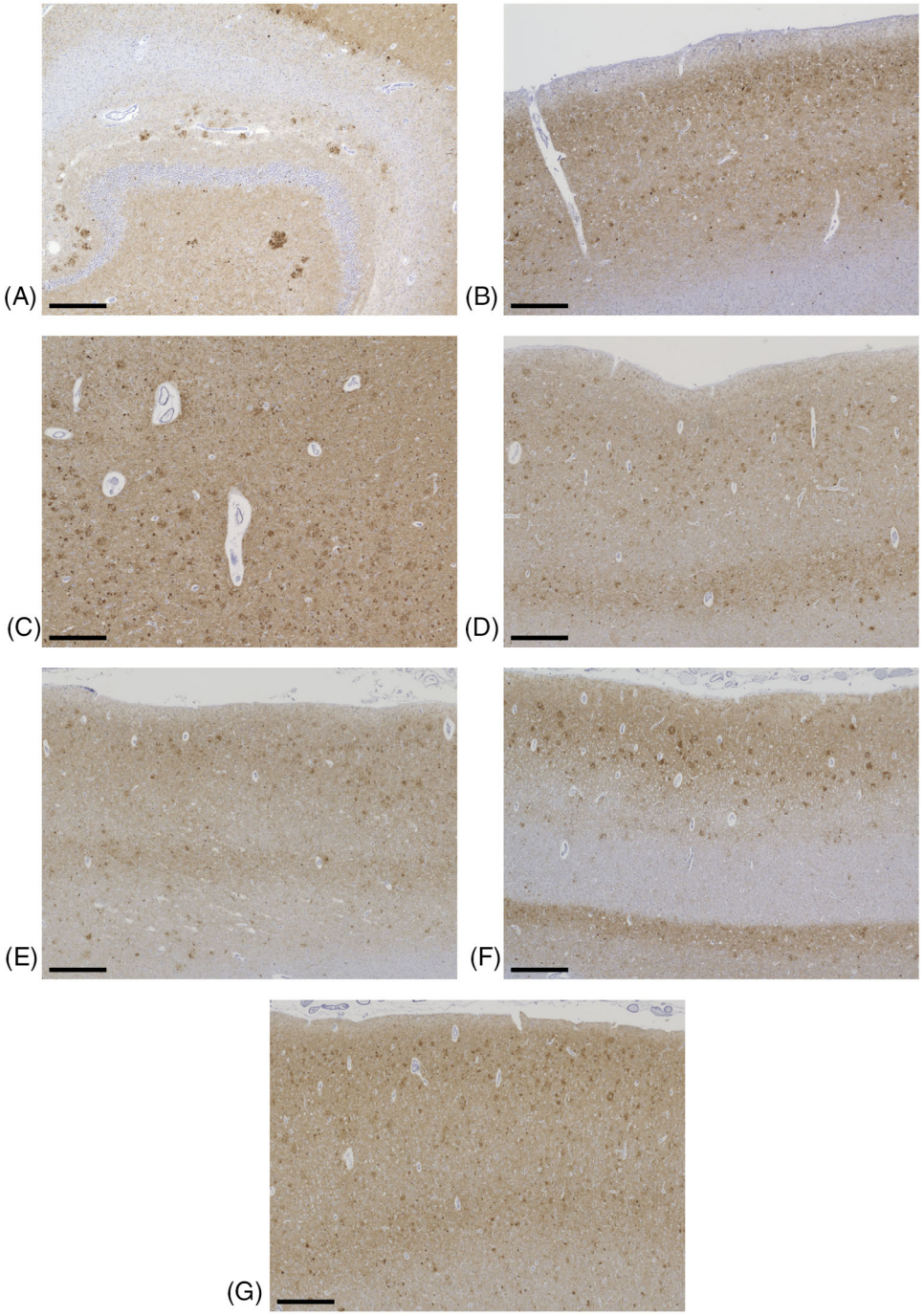

FIGURE 2 AT8 immunohistochemical staining for hyperphosphorylated tau proteins in the brain of the individual with trisomy 21 mosaicism. All images were taken using a 4 × objective lens with 500 μm scale bars. (A) In the hippocampus proper, large NPs were observed in the dentate gyrus region. NFTs and NTs were observed throughout the cornu ammonis sectors. Many NFTs and NTs were seen in the entorhinal cortex (B), amygdala (C), superior temporal lobe (D), and parietal lobe (E). Large, noticeable NPs were observed in the occipital lobe (F) and dorsolateral prefrontal region (G). NFTs, neurofibrillary tangles; NPs, neuritic plaques; NTs, neuropil threads.

(ADNC): A3B3C3.[20] Our findings suggest that AD was a significant contributor to the early onset of dementia in this case.

Interestingly, despite the individual's mosaic status, he presented with significant Aβ, NFT, and CAA neuropathology that is comparable in distribution to individuals with fT21 of similar age.[11,24,25] Our findings suggest that the expression of APP—from the mosaic standpoint—plays a significant role in driving Aβ pathology.[5,26–28] Previously reported by Bushman et al., neurons in people with sporadic AD have on average, an 8% increase in *APP* gene dose compared to neurons in people without sporadic AD.[29] Therefore, a low-degree increase in chromosome 21 in this individual with mT21—and the resulting increase in the number of *APP* genes—may be sufficient to induce Aβ

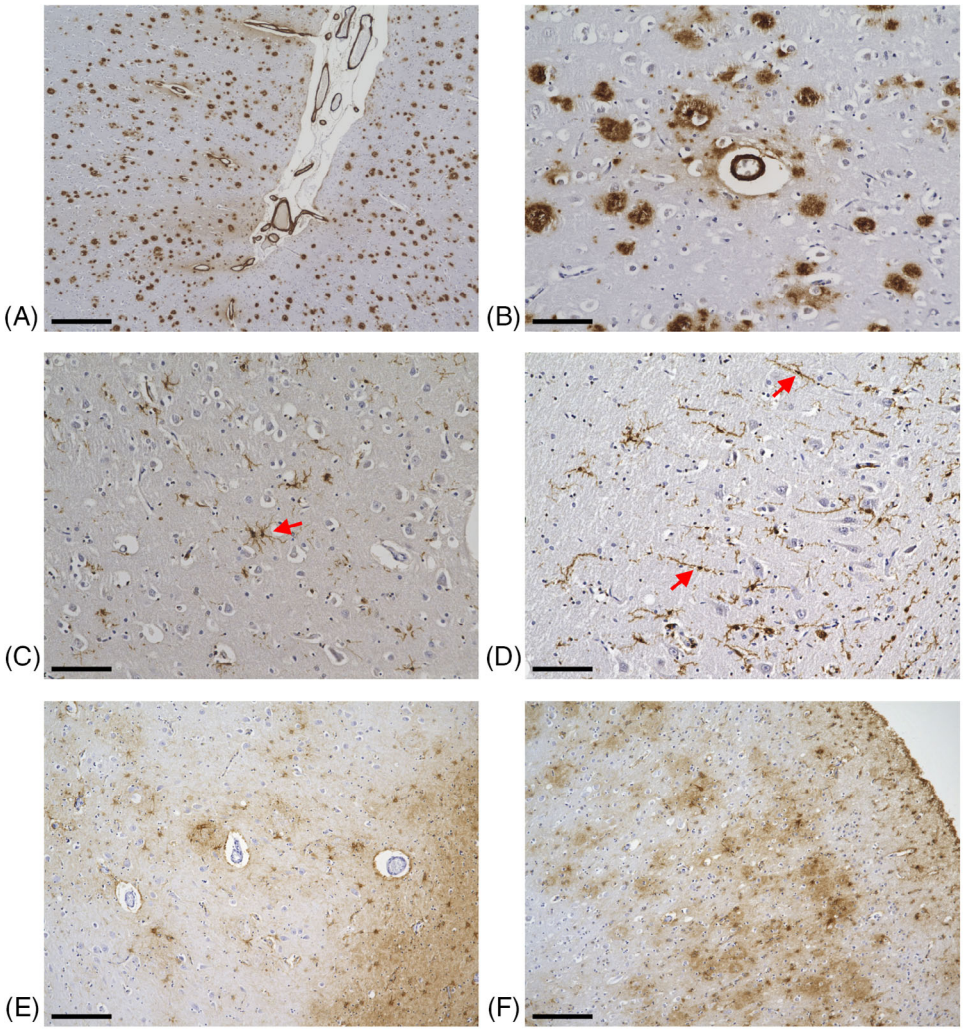

FIGURE 3 Cerebral amyloid angiopathy and glial pathology in the individual with trisomy 21 mosaicism. (A) A 4 × image depicting the extensive presence of cerebral amyloid angiopathy within the dorsolateral prefrontal region in the form of amyloid beta (Aβ) deposits in both leptomeningeal and cortical vessels in the brain. (B) A 20 × image capturing Aβ deposits lining the entire cross-sectional view of a cortical vessel in the gray matter of the dorsolateral prefrontal region. Additionally, the enlarged perivascular space can be seen surrounding the cortical vessel. (C) Ramified, ionized calcium-binding adapter molecule 1–positive microglia in the gray matter of the dorsolateral prefrontal region. Image was captured using a 20 × objective lens. (D) As indicated by the red arrows, we observed rod-shaped microglia in the cornu ammonis sector 3 (20 × image). (E) Hypertrophic, glial fibrillary acidic protein–positive astrocytes were seen interacting with blood vessels with enlarged perivascular spaces surrounding cortical vessels in the cornu ammonis sector 1 region of the hippocampus proper. The image was captured using a 10 × objective lens. (F)22 A 10 × image of hypertrophic astrocytes in the gray matter of the occipital lobe. The astrocytes can be seen in clusters with their processes surrounding spherical objects—presumably plaques. Scale bar = 500 µm (A), 200 µm (E–F), and 100 µm (B–D).

and, subsequently, NFT pathology we observed in the brain, and potentially contribute to the early onset of dementia. With respect to the relationship between Aβ and cerebrovascular pathology, the presence of CAA in people with DS is associated with cerebral microbleeds, which may contribute to the development of dementia.[30,31]

The presence of advanced AD neuropathology in this case raises the interesting hypothesis that peripherally established mosaicism may translate to the brain. Standard karyotype analysis of peripheral white blood cells and FISH testing confirmed trisomy 21 in 1.67% and 10% of the cells, respectively.[15] However, the percentage of mosaicism fluctuates depending on the diagnostic method and tissue sample tested.[16,32–34] Indeed, it has been reported by Yokoyama et al. that elevated tissue-specific mT21 level in the heart and lung of a patient could be the cause of their congenital heart abnormalities—a complication often seen in people with fT21.[33] Therefore, this leaves open the possibility that the occurrence of mosaicism in the mT21 brain could potentially be elevated relative to that measured in his peripheral white blood cells. The abundance and distribution of cells trisomic for chromosome 21 in the brain may be possible using single-cell quantitative polymerase chain reaction.[29]

In response to the deposition of Aβ and accumulation of NFT in AD, astrocytes and microglia may become activated as they undergo molecular and phenotypic changes.[35,36] In this adult male with mT21, we observed a widespread presence of hypertrophic astrocytes

throughout all examined regions of the brain. This was expected given the advanced AD pathology that was observed, and the role hypertrophic astrocytes play in the compaction and clearance of Aβ in and from the brain.[37,38] Additionally, a previous report suggests that individuals with DS also experience early astrocytic activation.[39]

Early and chronic activation of microglia occurs in people with DS. Flores-Aguilar et al. previously reported elevated inflammatory cytokine levels in children and young adults with DS before the presentation of advanced AD pathology, which indicates an early state of neuroinflammation in these individuals.[40] Further, with the presence of AD pathology, there are increasing numbers of dystrophic microglia in DS to a greater extent than that observed in late-onset AD.[41] Chronic microglial activation is exacerbated during adulthood with the pathological changes associated with AD in DS.[41,42] As a result, our observations of abundant ramified and dystrophic microglia in the brain of the individual with mT21 was consistent with the literature. However, we observed fewer hypertrophic microglia than expected given the extent of AD pathology. The activation of microglia—like astrocytes—also plays a critical role in the compaction of Aβ plaques.[43,44] Therefore, the widespread distribution of visually less compact Aβ plaques throughout the brain of the individual with mT21 could serve as a reflection of a weak presence of hypertrophic microglia. We also observed rod cells in the hippocampus of the mT21 case, which has also been reported in fT21.[45,46] Low numbers of microglia in the gray matter of this case may reflect technical issues but assuming this result can be replicated in other mT21 case studies, appears atypical for the more common fT21.[40,41] Further, the distribution of astrocytes responding to NFTs and Aβ plaques reported here may suggest that the neuroinflammatory response is suppressed in this person, potentially as a consequence of a lower gene dose effect for immune genes on chromosome 21.[47]

Another distinguishing feature in the brain of the individual with mT21 was the presence of enlarged PVSs (ePVSs) around cortical vessels in both grey and white matter. ePVSs have been documented in *post mortem* neuropathological studies and are associated with Aβ load, tau burden, CAA, and prevalence of both AD and/or vascular dementia in people without DS.[48,49] Similarly, cross-sectional neuroimaging analyses have highlighted the association between ePVS burden and AD status in the general population.[50,51] Interestingly, there is a range of ePVSs observed by MRI in individuals with DS that is associated with white matter hyperintensities suggesting that this case falls well within the range of ages when ePVSs occur in fT21.[52] Given the PVS's function as a route for the clearance of solute from the brain,[48,53] the development of ePVS at an earlier age in people with DS could be a result of early and chronic exposure to Aβ or a reflection of underlying astrocytic dysfunction or reaction to the disease. Moreover, due to the extensive nature of ePVSs, astrogliosis, and CAA in the mT21 individual's brain, there is likely a cerebrovascular component contributing to his cognitive decline and early onset of dementia. However, the possibility that the extensive ePVSs in this case is related to the *post mortem* interval or may reflect a fixation artifact cannot be entirely ruled out. We also observed Lewy bodies and neurites in the amygdala but not cortex and TDP-43 pathology was absent.

The results of this case report are consistent with a recent epidemiology study by Rubenstein et al. suggesting that mosaicism is associated with a higher prevalence of AD compared to fT21.[54] Using Medicaid data, the authors identified 94,533 people with DS using International Classification of Diseases codes. Of these individuals, 1966 (2.08%) were mosaic for DS. The authors noted that 438 or 22.3% of those with mosaicism had claims for AD dementia compared to 21.5% (n = 19,901) who were fT21.[54] Interestingly, the results from the unadjusted Cox proportional hazard model suggest that the mosaic group has 1.15 the hazard of dementia compared to fT21 individuals (95% confidence interval [CI]: 1.0, 1.3) and an adjusted hazard ratio of 1.19 (95% CI: 1.04, 1.31).[54] It will be important to follow up with a larger case series comparing tissue from people who are mosaic for DS to those with fT21 to determine the neurobiological underpinnings of potential differences in AD pathogenesis.

In summary, our *post mortem* neuropathological investigation highlights the extensive accumulation of Aβ plaques and NFTs throughout the brain of an individual with mT21, which reflected a high ADNC with a score of A3, B3, and C3. We observed widespread astrogliosis, CAA, and ePVSs, but little microgliosis throughout the subcortical and cortical regions. Future studies suggest the need to identify the relationship between peripheral mosaicism for chromosome 21 between organ systems and blood[33] and the number of cells in the brain that have trisomy 21. Additionally, identifying the percent mosaicism in the brain will allow us to investigate any possible associations with AD neuropathological burden.

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CONFLICT OF INTEREST STATEMENT

The authors declare there are no competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

This neuropathology case report was considered exempt from human subject research by the University of California Irvine Institutional Review Board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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