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A Comprehensive Resource for Induced Pluripotent Stem Cells from Patients with Primary Tauopathies

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SUMMARY

Primary tauopathies are characterized neuropathologically by inclusions containing abnormal forms of the microtubule-associated protein tau (MAPT) and clinically by diverse neuropsychiatric, cognitive, and motor impairments. Autosomal dominant mutations in the MAPT gene cause heterogeneous forms of frontotemporal lobar degeneration with tauopathy (FTLD-Tau). Common and rare variants in the MAPT gene increase the risk for sporadic FTLD-Tau, including progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). We generated a collection of fibroblasts from 140 MAPT mutation/risk variant carriers, PSP, CBD, and cognitively normal controls; 31 induced pluripotent stem cell (iPSC) lines from MAPT mutation carriers, non-carrier family members, and autopsy-confirmed PSP patients; 33 genome engineered iPSCs that were corrected or mutagenized; and forebrain neural progenitor cells (NPCs). Here, we present a resource of fibroblasts, iPSCs, and NPCs with comprehensive clinical histories that can be accessed by the scientific community for disease modeling and development of novel therapeutics for tauopathies.

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) with inclusions containing the microtubule-associated protein tau (FTLD-Tau) account for half of all cases of FTLD. This heterogeneous group of diseases includes progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick disease, and other rare forms of tauopathy. Patients with FTLD-Tau exhibit a broad range of neurological deficits including movement and motor neuron disease (e.g., gait and balance disturbances, impaired speech and swallowing, visual impairment), psychiatric impairment (e.g., mood and behavior), and cognitive impairment (e.g., memory, executive dysfunction, language and attention) (Perry et al., 2017). Due to significant overlap in the clinical syndromes, a definitive diagnosis can only be obtained by postmortem examination of brain tissue obtained at autopsy or more rarely by biopsy (Perry et al., 2017). Thus, to understand disease etiology, it is particularly valuable to generate a collection of induced pluripotent stem cells (iPSCs) from patients who have been followed clinically and from whom detailed neurological, neuroimaging, and neuropathological data and tissues are available. This requires a coordinated multidisciplinary effort and is the central impetus for the development of the resource described here.
| Mutation   | Clinical                                      | Neuropathology | Microscopy | Tauopathy                                                                 | Tau Isoforms | Referencesa | iPSCs Reported |
|------------|----------------------------------------------|----------------|------------|---------------------------------------------------------------------------|--------------|--------------|----------------|
| P301L      | bvFTD, personality change, language         | atrophy of     | neuronal    | neurons: tau-immunoreactive perinuclear, ring-like and dot-like cytoplasmic  | 4R           | Mirra et al., 1999 | Iovino et al., 2015; Paonessa et al., 2019; Silva et al., 2019 |
|            | abnormalities                                | frontal and     | loss,       | inclusion, fibrillary neuronal inclusions, and neuropil threads             |              |              |                 |
|            |                                              | temporal lobes, | ballooned   | astrocytes: thorn-shaped inclusions                                         |              |              |                 |
|            |                                              | basal ganglia,  | neurons,    | oligodendrocytes: coiled bodies                                            |              |              |                 |
|            |                                              | hippocampus,    | and gliosis |                                                                           |              |              |                 |
|            |                                              | and depigmentation of substantia nigra | and gliosis |                                                                           |              |              |                 |
| S305I      | bvFTD, personality change, language         | atrophy of     | neuronal    | neurons: tau-immunoreactive fibrillary inclusions and diffuse cytoplasmic    | 4R           | Kovacs et al., 2008 | N/A |
|            | abnormalities                                | medial temporal | loss,       | staining                                                                      |              |              |                 |
|            |                                              | lobe, temporal  | gliosis,    |                                                                           |              |              |                 |
|            |                                              | pole, and       | and ballooned |                                                                           |              |              |                 |
| S305N      | bvFTD, personality change, memory loss      | atrophy of     | neuronal     | neurons: tau-immunoreactive Pick body-like and ring-like inclusions         | 4R           | Boeve et al., 2005; Iijima et al., 1999 | N/A |
|            |                                              | frontal and     | loss and    |                                                                           |              |              |                 |
|            |                                              | temporal lobes  | gliosis     |                                                                           |              |              |                 |
| S305S      | bvFTD, memory loss                          | atrophy of     | neuronal     | neurons: tau-immunoreactive neurofibrillary tangles and pretangles          | 4R           | Skoqlund et al., 2008; Stanford et al., 2000 | N/A |
|            |                                              | frontal and     | loss,       |                                                                           |              |              |                 |
|            |                                              | temporal lobes  | gliosis,    |                                                                           |              |              |                 |
| IVS10+16   | bvFTD, personality change, executive        | atrophy of     | neuronal     | neurons: tau-immunoreactive fibrillary inclusions and diffuse cytoplasmic   | 4R           | Janssen et al., 2002; Lantos et al., 2002 | Espuny-Camacho et al., 2017; Esteras et al., 2017; Paonessa et al., 2019; Sposito et al., 2015 |
|            | dysfunction, memory loss, parkinsonism,     | frontal and     | loss,       | inclusion, and neuropil threads                                            |              |              |                 |
|            | non-fluent aphasia                           | temporal lobes, | gliosis,    |                                                                           |              |              |                 |
|            |                                              | cingulate and   | and ballooned |                                                                           |              |              |                 |
|            |                                              | insular cortex, | neurons,    |                                                                           |              |              |                 |
|            |                                              | hippocampus,    | and gliosis |                                                                           |              |              |                 |
|            |                                              | striatum,       | and ballooned|                                                                           |              |              |                 |
|            |                                              | amygdala and    | neurons,    |                                                                           |              |              |                 |
|            |                                              | brainstem      | and gliosis |                                                                           |              |              |                 |
|            |                                              |                | and gliosis |                                                                           |              |              |                 |

(Continued on next page)
While the majority of patients with primary tauopathy are sporadic, autosomal dominant FTLD-Tau families have been reported to carry mutations in the microtubule-associated protein tau (MAPT) gene. More than 50 MAPT mutations are reported to cause FTLD-Tau (Table 1; http://www.molgen.ua.ac.be/ADMutations/) (Cruts et al., 2012). The MAPT gene is alternatively spliced in the central nervous system (CNS) to produce six tau isoforms that differ based on the presence of the N-terminal insertion (0N, 1N, 2N) and the number of microtubule-binding repeats (3R, 4R; Figure 1). In normal adult human brains, the ratio of 3R/4R tau is 1:1 (Trabzuni et al., 2012). MAPT mutation carriers may bear 3-repeat (3R), 4-repeat (4R), or mixed 3R/4R tau inclusions (Table 1) (Cairns et al., 2007).

Several mechanisms have been proposed to explain how MAPT mutations cause disease: abnormal MAPT splicing, altered microtubule-binding kinetics, impaired degradation, or tau accumulation and aggregation, among others (van Swieten and Spillantini, 2007). We have focused our collection on mutations that represent these proposed mechanisms. A subset of MAPT mutations occur at sites that alter MAPT splicing, resulting in increased levels of exon 10-containing (4R) mRNA (e.g., IVS10+16, S305I, S305N, S305S) (Liu and Gong, 2008). In the case of intronic mutations such as IVS10+16, no mutant protein is produced. Instead, there is a shift in the levels of 4R tau, skewing the normally balanced 3R/4R tau ratio in human adult brain. Another set of mutations occurs in exon 10, which is exclusively present in 4R tau isoforms (e.g., P301L, P301S) (Hutton et al., 1998). Many of the mutations located in and around exon 10 have been implicated in disrupting microtubule-binding kinetics (Dayanandan et al., 1999; Fischer

### Table 1. Continued

| Mutation | Clinical | Macroscopy | Microscopy | Tauopathy | Tau Isoforms | References | iPSCs Reported |
|----------|----------|------------|------------|------------|-------------|------------|----------------|
| V337M    | antisocial behavior, paranoia, executive dysfunction | atrophy of frontal and temporal lobes and hippocampus | neuronal loss and gliosis | neurons: tau-immunoreactive neurofibrillary tangles, pretangles, and neuropil threads | 3R & 4R | Spillantini et al., 1996; Spina et al., 2017 | Ehrlich et al., 2015; Sohn et al., 2019 |
| G389R    | progressive aphasia, apathy, rigidity | atrophy of frontal and temporal lobes, hippocampus, and amygdala | neuronal loss and gliosis | neurons: tau-immunoreactive Pick body-like and filamentous inclusions | 3R & 4R | Murrell et al., 1999 | N/A |
| R406W    | memory loss | severe atrophy of frontal and temporal lobes and hippocampus | neuronal loss, gliosis, and ballooned neurons | neurons: tau-immunoreactive neurofibrillary tangles, Pick body-like inclusions | 3R & 4R | Miyasaka et al., 2001; Reed et al., 1997 | Imamura et al., 2016; Jiang et al., 2018 |
| R406W/R406W | bvFTD | N/A | N/A | N/A | 3R & 4R | Behnam et al., 2015; Ng et al., 2015 | N/A |

N/A, not available.
*See additional references at the AD/FTD Mutation Database (Cruts et al., 2012).
et al., 2007). Other MAPT mutations are located some distance from exon 10 and are expressed by all MAPT transcripts (e.g., R5H, V337M, G389R, R406W); thus, their mode of action may be linked to aspects of tau biology beyond microtubule binding, such as membrane association (Gauthier-Kemper et al., 2011). Additionally, all MAPT mutations increase the propensity for the tau protein to aggregate. Despite the clear association of MAPT mutations with FTLD-Tau, we have little understanding of the mechanisms by which these mutations lead to disease.

Rare and common variants in MAPT have been associated with increased risk for PSP, CBD, and frontotemporal dementia (FTD) (Coppola et al., 2012; Höglinger et al., 2011). MAPT A152T decreases binding of tau to microtubules and increases tau oligomer formation in vitro (Coppola et al., 2012). When expressed in Caenorhabditis elegans, MAPT A152T induces neuronal dysfunction,

Figure 1. MAPT Mutations Cause Primary Tauopathy
(A) Schematic of the location of MAPT mutations reported in this collection. MAPT A152T, V337M, G389R, and R406W occur in all tau isoforms expressed in the brain. MAPT P301L, P301S, and S305I/N/S occur exclusively in transcripts containing exon 10 (2N4R, 1N4R, and 0N4R). MAPT P301L/S, S305I/N/S and IVS10+16 alter splicing of tau such that more 4R-containing transcripts are expressed.
(B–I) Neuropathology in human brains with primary tauopathies. (B–E) MAPT R406W carrier. (B) Atrophy of the frontal lobe with dilatation of the lateral ventricle and prominent shrinkage of the medial temporal lobe. Scale bar, 0.5 cm. (C) Neuronal loss, gliosis, and microvacuolation of superficial laminae of the superior temporal gyrus. H&E. (D) Neuronal cytoplasmic PHF1-immunoreactive inclusions are seen in the hippocampal CA1 subfield. (E) Pick body-like, PHF1-immunoreactive inclusion bodies in the dentate fascia. Scale bar in (C), (D), and (E), 50 μm. (F and G) Anterior cingulate gyrus of a MAPT V337M carrier. (F) RD4-immunoreactive cytoplasmic inclusions in spindle, also called von Economo, neurons and surrounding layer V neurons. (G) R3 (RD3) tau-immunoreactive cytoplasmic inclusions in spindle and surrounding layer V neurons, and in the neuropil. (H) Dentate gyrus of MAPT P301L case showing typical pTAU (CP13) ring-like perinuclear deposit and Pick body-like inclusions. (I) PSP associated with a MAPT A152T variant. Tufted astrocyte (left; white arrow), neurofibrillary tangle (center; open arrow), and oligodendroglial coiled bodies (right; black arrow), stained with a phospho-tau antibody (CP13). Scale bar, 25 μm.
mislocalization of pre-synaptic proteins, and distorted mitochondrial distribution and trafficking, and reduces life span independently of protein aggregation (Butler et al., 2019; Pir et al., 2016). Mouse models expressing A152T demonstrate age-dependent neuronal loss and seizures, which occur both in the presence (Decker et al., 2016) or absence of tau aggregates (Maeda et al., 2016). iPSC-derived neurons from MAPT A152T carriers exhibit increased total tau levels and phosphorylation, detergent-insoluble tau, dysregulation of proteostasis pathways involving autophagy and lysosomal activity, and vulnerability to specific cellular stressors (Biswas et al., 2016; Fong et al., 2013; Silva et al., 2016). Our fibroblast and stem cell resource containing MAPT variants that are predicted to modify PSP and CBD risk will allow for the cellular and molecular dissection of disease phenotypes.

Patient-derived iPSCs have emerged as a powerful resource to study the molecular mechanisms underlying neurodegenerative diseases. These iPSCs can be differentiated into the neuronal and glial subtypes that are affected in primary tauopathies, giving us a tool toward understanding the biology of tau in a human cell model that may more faithfully reflect the endogenous condition. To date, iPSCs carrying the MAPT mutations N279K, P301L, V337M, R406W, and IVS10+16 and the risk variant A152T have been described, and their neural derivatives show phenotypes such as tau accumulation, tau hyperphosphorylation, tau insolubility, vulnerability to specific cellular stressors, and other phenotypes that begin to reveal possible disease mechanisms (Ehrlich et al., 2015; Hallmann et al., 2017; Imamura et al., 2016; Iovino et al., 2015; Jiang et al., 2018; Seo et al., 2017; Silva et al., 2016; Sposito et al., 2015; Wren et al., 2015). Most prior studies, however, have not included genome-edited isogenic controls, which increase the power to detect variant-specific phenotypes by decreasing inter-individual variability. These promising findings warrant the investment in a comprehensive, isogenically controlled collection of MAPT iPSC lines.

Here, we present a resource of fibroblast and iPSC lines that includes known disease-associated MAPT mutations and paired isogenic iPSCs, MAPT risk variant carriers, and PSP-syndrome (PSP-S) and corticobasal syndrome (CBS) lines from individuals where a MAPT mutation has not been detected. Most of the cell lines presented in this study were obtained from participants who underwent detailed clinical phenotyping, and for whom fluid biomarkers, imaging biomarkers, and genetic and neuropathological information are available that can be used for correlative analyses with cellular phenotypes. Together, this represents a comprehensive resource that can be accessed for tauopathy modeling and the discovery of novel therapeutics.

**RESULTS**

**Selection of Fibroblast Lines**

Dermal fibroblasts were collected from: (1) families with pathogenic MAPT mutations; (2) individuals carrying MAPT missense variants that increase risk for PSP, CBD, and FTD; (3) sporadic PSP-S and CBS cases; and (4) cognitively normal (non-mutant) controls at the Memory and Aging Center at the University of California San Francisco, the Knight Alzheimer Disease Research Center at Washington University, and the National Institute of Neurological Disease and Stroke (NINDS) Cell Repository. A total of 36 fibroblast lines were generated from individuals with pathogenic MAPT mutations (P301L, S305I, IVS10+16, V337M, G389R, R406W; Figure 1 and Table 2). These mutations are representative of some of the most common MAPT mutations and capture the range of clinical and neuropathological phenotypes associated with FTLD-Tau (Tables 1 and 2). The collection also includes fibroblasts from eight MAPT A152T risk variant carriers, which has been reported to increase the risk for PSP, CBD, and FTD (Coppola et al., 2012). Additionally, we have banked fibroblast lines from research participants clinically diagnosed with PSP-S, CBS, or mixed dementias (Alzheimer's disease and Lewy body disease) and from cognitively normal controls (Table 2). These fibroblasts were obtained from subjects who are part of larger clinical programs that obtain a detailed clinical history, including physical and neurological examinations, cognitive testing, and neuroimaging (magnetic resonance imaging [MRI], β-amyloid positron emission tomography [PET], and tau PET). Many fibroblast lines also have corresponding plasma and cerebrospinal fluid (CSF) samples. Additional covariates for the fibroblast lines including age at biopsy, sex, and genotypic data are available upon request from http://neuralscil.org/tau.

The patient-specific fibroblasts in this collection capture classical aspects of clinical and neuropathology associated with primary tauopathies (Table 1). A MAPT R406W carrier presented with progressive memory loss and later developed the behavioral variant of FTD (bvFTD). Macroscopically, there was pronounced atrophy of the temporal lobe (cell line F1362; Figures 1B–1E). Microscopically, there was severe neuronal loss and gliosis and cortical neurofibrillary tangles similar to those seen in Alzheimer's disease. Frequent Pick body-like, tau-immunoreactive inclusions were seen in affected areas including the hippocampus and dentate gyrus. Tau-immunoreactive glial inclusions were also present. A MAPT V337M carrier included in the collection exhibited bvFTD; neuropathological examination revealed inclusions containing both 3R and 4R tau (cell line GIH6; Figures 1F and 1G). MAPT P301L cases more commonly present clinically with bvFTD, and
A152T  PSP, CBD, FTLD-Tau  bvFTD  4R  57.5  N/A  8  N/A
P301L  FTLD-Tau  bvFTD  4R  52.6  6.7  13  3
S301I  FTLD-Tau/AGD  bvFTD  4R  39  2  2  1
IVS10+16  FTLD-Tau  bvFTD/AD  4R  49.1  10.3  4  1
V337M  FTLD-Tau  bvFTD  3R & 4R  51.5  15.4  4  2
G389R  FTLD-Tau  bvFTD  3R & 4R  39.8  2.5  3  1
R406W  FTLD-Tau  AD  3R & 4R  56.3  11.5  9  2
R406W/R406W  FTLD-Tau  bvFTD  3R & 4R  34  7  1  1
WT  PSP  PSP-S  4R  N/A  N/A  12  N/A
WT  CBD  CBS  4R  N/A  N/A  5  N/A
WT  PSP/CBD mixed  PSP-S/CBS/mixed  4R  N/A  N/A  10  N/A
WT  normal  N/A  N/A  N/A  N/A  69  N/A

AAO, age at onset; bvFTD, behavioral variant frontotemporal dementia; AGD, argyrophilic grain disease; AD, Alzheimer’s disease; PSP, progressive supranuclear palsy; CBD, cortical basal degeneration; N/A, not available.

aData from the AD/FTD Mutation Database presented in years (Cruts et al., 2012).

Pathologically display neuronal cytoplasmic inclusions with perinuclear ring-like concentration and the presence of mini Pick body-like inclusions (Figure 1H). A MAPT A152T carrier (cell line FTD19; Figure 1I) included in the collection presented with symptoms characteristic of PSP-S, including motor slowing, falls, and cervical dystonia that progressed to dysarthria as well as supranuclear gaze palsy, and neuropathological examination revealed classical PSP neuropathology featuring 4R tau-immunoreactive tufted astrocytes (white arrow in Figure 1I), neurofibrillary tangles (open arrow in Figure 1I), and oligodendroglial coiled bodies (black arrow in Figure 1I).

**Generation and Characterization of iPSCs**

To establish cellular models that can inform on the pathophysiological mechanisms of MAPT mutations, MAPT risk variants, and sporadic PSP, including cell types affected by disease, we reprogrammed a subset of fibroblasts described in Table 2 into iPSCs. All iPSCs were generated using non-integrating Sendai virus carrying SOX2, OCT4, KLF4, and cMYC (Table 3, Figure 2A). Multiple clones are available for each line. iPSCs were grown in feeder-free conditions using Matrigel and maintained in mTeSR1. Resulting iPSCs have been characterized for pluripotency based on morphology and gene expression markers (Figures 2B and 2C). We confirmed the silencing of exogenous Sendai virus-driven pluripotent markers by qPCR (Figure 2C). Correct mutation propagation was verified by Sanger sequencing (Figure 2D), chromosomal stability was assessed by karyotyping (Figure 2E), and the capacity to form cell types from the three germ layers was also confirmed (Figures 2F and 2G). All iPSC lines reported in this study meet these quality-control criteria (Table S1 and Figure S1, are included in the cell bank, and are available upon request from http://neuralsci.org/tau.

**Genome Editing and Characterization of iPSCs**

Genetic background of individual donors is a large contributor to phenotypic variability in iPSCs (Kilpinen et al., 2017). To define phenotypes driven specifically by a mutant or risk allele, we used CRISPR/Cas9 genome editing to establish isogenic controls of donor iPSC lines (Figure 2A). For each set of edited lines, additional iPSC clones were selected that underwent the CRISPR/Cas9 editing pipeline but remained unmodified. These unmodified iPSC clones serve as important controls, in addition to the parental donor line, to account for selective pressures that may occur during the editing process (Budde et al., 2017). Donor iPSC lines carrying the MAPT mutations IVS10+16, P301L, S301I, R406W, and V337M have been corrected to wild type (WT; Tables 4 and S2).

The most commonly used mouse model of tauopathy overexpresses MAPT P301S (Yoshiyama et al., 2007). Clinically, MAPT P301S carriers present with a more aggressive form of FTD than MAPT P301L carriers and have an earlier age at onset (P301S: mean age at onset 33.7 years and mean disease duration 4.2 years; P301L: mean age at onset 52.6 years and mean disease duration 6.7 years) (Cruts et al.,
**Table 3. Human iPSCs for Modeling Primary Tauopathies**

| Donor ID | Alternative Donor ID | Mutation | Clinical Status<sup>a</sup> | Autopsy | Corrected Line | Fibroblast Source | Neural Induction |
|----------|----------------------|----------|-----------------------------|---------|----------------|------------------|-----------------|
| FTD30 (FTD-FF) | 151209SBA1 | A152T/WT | S pending | no | UCSF | yes |
| FTD19 (FTD-T) | 151209SBA2 | A152T/WT | S PSP | no | UCSF | yes |
| GIH2 | 151209SBA3 | A152T/WT | A N/A | no | UCSF | yes |
| FTD38 | 151209SBA4 | A152T/WT | A N/A | no | UCSF | yes |
| GIH169 | 160311SBA5 | A152T/WT | S N/A | no | UCSF | yes |
| GIH56 | 160311SBA6 | A152T/WT | S N/A | no | UCSF | yes |
| TAU6 (Tau225-7) | 160311SBA7 | A152T/WT | S CBD | no | UCSF | yes |
| F0510 | F0510 | P301L/WT | A N/A | yes | NINDS repository | yes |
| F13535 | F13535 | P301L/WT | A N/A | no | WUSM | N/A |
| F14537 | F14537 | P301L/WT | S FTLD-Tau | no | WUSM | N/A |
| F14536 | F14536 | WT/WT<sup>b</sup> | A N/A | no | WUSM | N/A |
| MHF110 | 17524NCE1 | S305I/WT | S N/A | no | UCSF | N/A |
| 75.11 | AG255075 | S305I/WT | N/A N/A | yes | ARTFL/LEFFTDS | N/A |
| 300.12 | AG251300 | S305N/WT | N/A N/A | no | ARTFL/LEFFTDS | N/A |
| GP1.1 | GP-1i | S305S/WT | N/A FTLD-Tau | yes | NSWBB | N/A |
| GIH36 | 160311SBC1 | IVS10+16/WT | A N/A | yes | UCSF | yes |
| GIH161 | I18XXYNCG1 | WT/WT<sup>b</sup> | A N/A | no | UCSF | N/A |
| GIH178 | I18XXYNCC1 | IVS10+16/WT | N/A N/A | no | UCSF | N/A |
| GIH6 | 160311SBB1 | V337M/WT | S FTLD-Tau | yes | UCSF | yes |
| GIH7 | 160311SBB2 | V337M/WT | A N/A | yes | UCSF | yes |
| GIH155 | 160311SBB3 | V337M/WT | S N/A | no | UCSF | N/A |
| ND32951A | ND32951A | V337M/WT | A N/A | yes | NINDS repository | yes |
| MHF100 | 171018NC1 | G389R/WT | A N/A | no | UCSF | N/A |
| MHF101 | 171018NC2 | G389R/WT | A N/A | no | UCSF | N/A |
| MHF102 | 171018NC3 | G389R/WT | S N/A | no | UCSF | N/A |
| F11374 | F11374 | R406W/WT | A N/A | no | WUSM | N/A |
| F11362 | F11362 | R406W/WT | S FTLD-Tau | yes | WUSM | yes |
| F11421 | F11421 | R406W/WT | A N/A | yes | WUSM | yes |
| GIH143 | UCSF1 | R406W/R406W | S N/A | no | UCSF | N/A |
| GIH131 | 170524NC1 | WT/WT | S PSP | no | UCSF | N/A |
| GIH92 | 170103NCF3 | WT/WT | S PSP | no | UCSF | N/A |

UCSF, University of California San Francisco Memory and Aging Center; WUSM, Washington University, Knight Alzheimer’s Disease Research Center; NINDS repository, National Institute of Neurologic Disorders and Stroke; ARTFL/LEFFTDS, Advancing Resource and Treatment for Frontotemporal Dementia/Longitudinal Evaluations of Familial Frontotemporal Dementia Subjects; NSWBB, New South Wales Brain Bank; N/A, not available.

<sup>a</sup>At biopsy: A, asymptomatic; S, symptomatic.

<sup>b</sup>Non-carrier, related to MAPT family.
However, fibroblast lines from MAPT P301S carriers, which would be useful to validate mouse studies, were not available for reprogramming at the time of this study. Thus, we used CRISPR/Cas9 to mutate the MAPT P301L donor iPSC line to MAPT P301S (Tables 4 and S2). For this series, we performed whole-genome sequencing and analysis of the mutational burden induced by genome editing and observed no modifications at computationally predicted off-target sites from CRISPR/Cas9 (Budde et al., 2017). The mutational burden that was observed in the edited iPSC lines was largely driven by selective pressures of culture (Bhutani et al., 2016; Budde et al., 2017; Merkle et al., 2017).

To understand the specific contribution of MAPT mutations and risk variants to disease phenotypes, we introduced MAPT mutations into an unaffected control line. In a control donor iPSC line (F11350) from a male individual carrying APOE 3/3 and MAPT H1/H1, we introduced MAPT R5H, P301L, or G389R (Tables 4 and S2). In a second control iPSC line (F13505) from a female individual carrying APOE 3/3 and MAPT H1/H1, we introduced MAPT S305I or S305S (Tables 4 and S2). All resulting edited or

Figure 2. Generation and Characterization of iPSC Models of Tauopathy
Representative images of control (MAPT WT/WT), mutant (MAPT P301L/WT), and CRISPR/Cas9-edited, isogenic control (MAPT WT/WT-iso) iPSCs.
(A) Diagram of reprogramming and CRISPR/Cas9 editing.
(B and C) Immunostaining (B) and qPCR (C) for pluripotency markers. Graph represents mean ± SEM.
(D) Sanger sequencing.
(E) Karyotyping.
(F and G) Spontaneous differentiation into cells within the three germ layers evaluated by RT-PCR (F) and immunostaining (G). MAPT WT/WT (iPSC line: F11350); MAPT P301L/WT (iPSC line: F0510); MAPT WT-iso (iPSC line: F0510.2Δ2'H1). Scale bars, 50 μm. See also Table S1.
unmodified clones were characterized for pluripotency and chromosomal stability as described above (Table S2). We are continuing to build this collection on the same genetic background with additional MAPT mutations.

Differentiation of iPSCs into Neural Progenitor Cells and Differentiated Neural Cells

iPSCs have the capacity to form the diverse neural cell types affected by primary tauopathies. By exploiting our understanding of CNS development, several groups have established protocols to generate neuroectodermal neural progenitor cells (NPCs) that can be further patterned into specific neuronal subtypes (Doi et al., 2014; Elkabetz et al., 2008; Muratore et al., 2014). We adapted a neural aggregate-based method that allows for the efficient generation of a scalable pool of NPCs, which have the capacity to be patterned into cultures enriched for different types of neurons or glia (Figure 3). Production of cryopreserved

Table 4. CRISPR/Cas9-Edited iPSC Lines

| Donor ID | Donor Genotype | Isogenic Genotype | Ngn2 Integration | Engineering Methoda | Line Name | Neural Induction |
|---------|---------------|------------------|-----------------|---------------------|-----------|-----------------|
| F11362  | R406W/WT      | WT/WT            | no              | CRISPR             | F11362.1A1C11, F11362.1A1B6 | yes |
| F11421  | R406W/WT      | WT/WT            | no              | CRISPR             | F11421.12A2A07 | yes |
| F11374  | R406W/WT      | N/A              | yes             | TALENs             | NF11374.65 | yes |
| 160311SB1 | V337M/WT     | WT/WT            | no              | CRISPR             | G1H6C1A1E11 | yes |
| 160311SB2 | V337M/WT     | WT/WT            | no              | CRISPR             | G1H7C2A2B12, G1H7C2A2F02 | yes |
| ND32951A | V337M/WT     | WT/WT            | no              | CRISPR             | ND32951A.1A1B06, ND32951A.1A1C12 | yes |
| G1H36   | IVS10+16/WT   | WT/WT            | no              | CRISPR             | G1H36C2A1D01 | yes |
| F0510   | P301L/WT      | WT/WT            | no              | CRISPR             | F0510.2A2E7, F0510.2A2H1 | yes |
| F0510   | P301L/WT      | WT/WT            | no              | CRISPR             | F0510.2A3A11, F0510.2A3A9 | yes |
| F0510   | P301L/WT      | WT/P301S         | no              | CRISPR             | F0510.2A3E10, F0510.2A4B3, F0510.2A4B4 | yes |
| F0510   | P301L/WT      | P301S/P301S      | no              | CRISPR             | F0510.2A3B5 | yes |
| F0510   | P301L/WT      | N/A              | yes             | TALENs             | NF0510.23, NF0510.12 | yes |
| 75.11   | S305I/WT      | WT/WT            | no              | CRISPR             | 75.11-IW1A12 | N/A |
| 75.11   | S305I/WT      | S305I/S305I      | no              | CRISPR             | 75.11-IH1B9 | N/A |
| GP1.1   | S305S/WT      | S305S/S305S      | no              | CRISPR             | GP1.1-SH1G8 | N/A |
| F13505  | WT/WT         | S305I/WT         | no              | CRISPR             | F13505.1I1B10 | N/A |
| F13505  | WT/WT         | S305S/WT         | no              | CRISPR             | F13505.1S3H5 | N/A |
| F11350  | WT/WT         | WT/RSH           | no              | CRISPR             | F11350.1RSH2F06 | N/A |
| F11350  | WT/WT         | WT/G389R         | no              | CRISPR             | F11350.1G389R1COSΔE03 | N/A |
| F11350  | WT/WT         | P301L/P301L      | no              | CRISPR             | F11350.1.P301LΔ4A02, F11350.1.P301LΔ4A08 | N/A |
| F12468  | WT/WT         | N/A              | yes             | TALENs             | NF12468.131 | yes |
| WTC11   | WT/WT         | N/A              | yes             | TALENs             | NWTC11.G3 | yes |
| WTC11   | WT/WT         | WT/WT            | yes             | TALENs/Crispr      | NWTC11.G3.0036 | yes |
| WTC11   | WT/WT         | V337M/WT         | yes             | TALENs/Crispr      | NWTC11.G3.0212 | yes |
| WTC11   | WT/WT         | V337M/V337M      | yes             | TALENs/Crispr      | NWTC11.G3.3917 | yes |

aNgn2 was engineered by TALENs; MAPT mutations/corrections were engineered by CRISPR/Cas9.
banks of stable and expandable intermediate NPC populations will help to reduce time, effort, and variability across experiments.

We have applied this neural induction protocol to the donor lines in this collection across multiple laboratories (Figure S1; Tables S1 and S2). We have verified that the iPSC collection presented here has the capacity to form NPCs that can be expanded and cryopreserved (Figures 3A–3E). These NPCs express early neuroectodermal markers including PAX6, SOX2, and Nestin, and lack expression of SOX10, which marks the neural crest, indicating a CNS expression pattern (Figure 3F). The viability of these NPCs after thaw is high (mean 89% ± 1.2% live cells). These NPCs maintain their capacity to differentiate into neuronal subtypes when used at early passages (between passage 1 and passage 5), while astrocyte differentiation as measured by glial fibrillary acidic protein (GFAP) and S100b can be promoted using NPCs from early or later passages (beyond passage 5). By incorporating fluorescence-activated cell sorting for cell-surface markers CD133+, CD184+, and CD271−, the resulting selected pool of NPCs can be maintained with a high proportion of neuronal differentiation for at least 50 passages (Cheng et al., 2017). It is critical to culture NPCs at a high density for the successful maintenance of a stable and expandable population of progenitors (Cheng et al., 2017).

NPCs can be patterned into different neural CNS regions and differentiated into neuronal and glial subtypes to model primary tauopathies (Figures 3I and 3J) (Jiang et al., 2018; Silva et al., 2016; Tcw et al., 2017). By default, these NPCs tend to adopt anterior CNS characteristics, such as FOXG1 expression, but this fate can also be stimulated by the addition of patterning factors (Kirwan et al., 2015; Saurat et al., 2016). The resulting forebrain neurons produce tau that is physiologically similar to human CNS tau (Sato et al., 2018), with the exception of intracellular 4R tau levels. Achieving splicing of the six major tau isoforms expressed in adult brains remains a challenge in the iPSC system (Hefti et al., 2018; Sposito et al., 2015). Despite the low levels of 4R tau, iPSC-derived neural cells from MAPT mutation/risk variant carriers phenocopy aspects of primary tauopathies. This includes the accumulation of phosphorylated forms of tau (Ehrlich et al., 2015; Imamura et al., 2016; Iovino et al., 2015; Silva et al., 2016, 2019), mitochondrial defects (Esteras et al., 2017), and increased cell vulnerability (Hallmann et al., 2017; Silva et al., 2016; Wren et al., 2015). More recently, we have demonstrated that neurons expressing MAPT...
R406W (F11362) capture molecular signatures related to altered synaptic function that are also present in human brains from MAPT R406W carriers and in mouse models of primary tauopathies (Jiang et al., 2018). Cryopreserved NPCs from the iPSCs reported here (Tables 3 and 4) are available upon request from http://neuralsci.org/tau.

Generation of Integrated, Isogenic, and Inducible Neurogenin-2 iPSCs
Integrating, isogenice, and inducible neurogenin-2 (i3N) iPSCs engineered with a doxycycline-inducible mouse Neurogenin-2 (NgN2) transgene in the AAVS1 safe-harbor locus can be scalably differentiated to homogeneous excitatory neurons, which enables the use of human neurons for high-throughput drug discovery (Wang et al., 2017). We have engineered two healthy control WT (F12468 and WTC11), as well as MAPT P301L (F0510) and MAPT R406W (F11374), to i3N iPSCs (Table 4) (Wang et al., 2017). We also mutagenized a control i3N line (WTC11) to be heterozygous or homozygous for MAPT V337M (Sohn et al., 2019). All modified lines were characterized for chromosomal stability, and confirmed for NgN2 integration and neuronal differentiation (Figure S2 and Table S2), and are available upon request from http://neuralsci.org/tau.

DISCUSSION
We present a comprehensive and valuable resource that can be used to model primary tauopathies and for drug discovery. Our patient-based cohort consists of a library of 140 dermal fibroblast lines and respective iPSC lines with multiple clones that are focused on primary tauopathies: 29 iPSC lines from patients carrying pathogenic MAPT mutations or risk variants; 2 iPSC lines from autopsy-confirmed PSP patients; 28 isogenic iPSCs; and 8 NgN2-integrated iPSCs. Importantly, most of these cell lines were obtained from deeply clinically phenotyped individuals with detailed neurological and neuropsychological assessment and availability of fluid biomarkers (CSF and plasma), imaging biomarkers (MRI, β-amyloid PET, and tau PET), genetic data, and, for some, neuropathological data.

Phenotypic Diversity of MAPT Mutations
More than 50 mutations in MAPT have been reported to cause FTLD-Tau and are located primarily in exons 9–13; yet FTLD-Tau is both clinically and neuropathologically heterogeneous (Table 1). Broadly, FTLD-Tau is defined by neuronal loss, gliosis, and spongiform changes in layer II with predominant involvement of the frontal, temporal, cingulate, and insular cortices and variable involvement of subcortical nuclei. Clinically, patients with FTLD-Tau pathology can present with a broad range of phenotypes spanning behavioral, cognitive, and motor disturbances. Various different combinations of clinical symptoms may be seen in association with specific mutations and even among affected members of a single family (Spina et al., 2008). Hence, there is a need to understand the impact of specific MAPT mutations within the genetic background of individuals with known clinical and pathological manifestations. Our fibroblast and iPSC resources allow for the investigation of common and unique cellular phenotypes driven by these mutations.

The Clinical and Pathological Spectrum of the Most Common 4R Primary Tauopathies
FTLD-Tau, PSP, and CBD are neuropathologically defined as 4R tauopathies (Kovacs, 2015). PSP pathology occurs in neurons and glia (astrocytes and oligodendrocytes) and preferentially affects the tectum, tegmentum, globus pallidus, diencephalon, and superior cerebellar peduncle (Dickson et al., 2007). In CBD, neuronal and glial pathology occurs within gray and white matter regions of the cortex, basal ganglia, diencephalon, and rostral brainstem (Forman et al., 2002). While 4R-tau aggregation is characteristic of both PSP and CBD, differences in proteolytic processing of tau have been reported to distinguish the two diseases: detergent-insoluble tau occurs at a doublet around 37 kDa in CBD and as a single band at 33 kDa in PSP (Arai et al., 2001, 2004). The MAPT P301S risk variant has been associated with both clinical and pathological forms of PSP-S/PSP and CBS/CBD. Our fibroblast resources containing sporadic PSP-S and CBS will allow for the cellular and molecular dissection of disease phenotypes, providing a powerful system for understanding the cellular mechanisms that drive phenotypic differences between PSP-S/PSP and CBS/CBD.

Challenges in Modeling Primary Tauopathies in Traditional Cell and Mouse Models
Current cellular and animal models used to study primary tauopathies have several limitations. Critically, there is no natural animal model of tauopathy, as these diseases are largely restricted to Homo sapiens (Heuer et al., 2012; Holzer et al., 2004). While tau isoforms may share broad functional similarities, different isoforms likely play distinct physiological and pathological roles in the cell (Goedert and Jakes, 1990; Karch et al., 2012; Kosik et al., 1989; Panda et al., 2003). Notably, the expression of tau isoforms drastically differs between human and rodent brains. While the adult human brains have roughly equal levels of 3R and 4R tau, adult rodents express almost exclusively 4R tau, limiting the conclusions that can be drawn from mouse models (Trabzuni et al., 2012). Additionally, most cellular
and transgenic models (e.g., C. elegans, Drosophila, and mice) rely on overexpression of a mutant transgene comprising a single tau isoform, which may produce effects that are a function of excessive protein expression, specific isoform expression, and possible off-target effects, rather than a disease-relevant phenotype. Finally, neuronal and glial cells are the primary cell types affected in tauopathies; therefore, studies in immortalized cell lines may fail to capture the phenotypes specific to neurons and glia. Thus, our understanding of how tau is metabolized in the human brain has been obtained from experimental paradigms that do not fully capture physiological conditions relevant to human tauopathies. Stem cell models begin to address these gaps; however, tau generated by stem cell-derived neurons remains in the fetal state (e.g., primarily 3R0N) (Hefti et al., 2018; Iovino et al., 2015; Sposito et al., 2015). Nevertheless, cells expressing 4R-containing MAPT mutations, such as P301L, exhibit altered tau phosphorylation, tau accumulation, and cell vulnerability (Iovino et al., 2015; Silva et al., 2019). These phenotypes can be reversed with novel tau degraders (Silva et al., 2019).

Basic Science, Clinical, and Translational Applications of Human Tauopathy Models

Beyond modeling the molecular and cellular pathophysiology of primary tauopathies, the derivation of patient-specific expandable NPCs enables large-scale functional genomics, proteomics, and small-molecule-based and CRISPR-based genetic modifier screens (Boselli et al., 2017; Cheng et al., 2017; Silva et al., 2016; Tian et al., 2019; Wang et al., 2017). This includes the use of high-content imaging methodologies with subcellular level resolution of molecular and morphological changes in defined neuronal subtypes with and without glial subtypes. We envision that using the framework of phenotypes from the autosomal dominant mutations and risk factors for tauopathy described here will also assist in the interpretation of genetic variants of unknown pathological significance that are being identified by exome and whole-genome sequencing projects.

One of the challenges in modeling diseases that typically present clinically in mid to late adulthood is to accelerate aging in iPSC-derived cells. This is particularly difficult given that during reprogramming to pluripotency, the features of aging present in originating somatic cells are reset. In contrast, fibroblasts directly reprogrammed into neurons retain their aging characteristics such as DNA methylation (Huh et al., 2016; Maherali et al., 2007; Mertens et al., 2015). Efforts to induce chronological aging in iPSC-derived neurons are under way (Miller et al., 2013). In the meantime, the ability to study both reprogrammed iPSCs and their source fibroblasts directly differentiated into neurons may help the field dissect how gene mutations contribute to the neurodegenerative process at both early and late age-dependent stages.

Our intention is to extend the existing resource, particularly by adding fibroblasts and iPSCs carrying novel mutations with clear pathogenicity and unique clinical features such as those associated with extremely early age of onset or rapid disease progression. Other variants in specific domains of tau or in non-coding genomic elements (e.g., 5’/3’ UTRs, enhancer sites) would also be of interest to the collection as well as additional genome engineering in existing lines.

Conclusions

In total, the resource presented here represents an opportunity to understand the mechanisms by which pathogenic mutations or risk variants in MAPT drive tauopathy. This resource will also be of interest to the broader community working on neurodegenerative disease. The collaborative efforts through which this resource has been generated can serve as a model for other neurodegenerative disease subtypes as well as other neurological and non-neurological diseases under genetic influence. Our intention is to broadly share the collection of fibroblasts, iPSCs, and NPCs and related data and information, which are available upon request. We are continuing to build this collection with additional reprogramming and genome editing, and updates will be available at http://neuralsci.org/tau (Figure S3).

EXPERIMENTAL PROCEDURES

The Washington University and University of California San Francisco Institutional Review Boards reviewed the Neuropathology Cores (from whom the brains were obtained) operating protocols as well as this specific study and determined it was exempt from approval. Our participants provide this consent by signing the hospital’s autopsy form. If the participant does not provide future consent before death the DPOA or next of kin provide it after death. All data were analyzed anonymously.

Skin punches were performed following written informed consent from the donor. The informed consent was approved by the Washington University School of Medicine and the University of California San Francisco Institutional Review Board and Ethics Committee (IRB 201104178, 201306108 and 10-03946). The consent allows for use of tissue by all parties, commercial and academic, for the purposes of research but not for use in human therapy.

Peripheral blood mononuclear cells or dermal fibroblasts were transduced with non-integrating Sendai virus carrying OCT3/4, SOX2, KLF4, and CMYC. iPSC lines were analyzed for pluripotency markers by immunocytochemistry (ICC) and qPCR; spontaneous differentiation into the three germ layers by ICC or qPCR; and chromosomal abnormalities by karyotyping. Human iPSCs were edited using CRISPR/Cas9 as previously reported (Budde et al.,...
SUPPLEMENTAL INFORMATION

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Conceived and designed experiments: C.M.K., A.W.K., C.W., M.C.S., S.J.H., J.K.I., K.S.K., L.G., A.M.G., and S.T. Performed experiments: C.M.K., R.M., J.A.M., A.A., K.R.B., D.A.P., P.T., S.S., S.H., C.W., C.H., P.D.S., D.B., M.C.S., and N.J.C. Analyzed data: C.M.K., A.W.K., A.K., K.M., A.A., S.H., C.W., C.H., and P.D.S. Contributed reagents, materials, and analysis tools: C.M.K., A.W.K., A.K., K.R.B., K.M., Y.H., S.E.L., N.G., J.N., F.M., B.F.B., M.C.S., S.J.H., J.K.I., B.L.M., L.G., L.T.G., W.W.S., A.M.G., K.O., and S.T. Wrote the manuscript: C.M.K., A.W.K., S.S., and S.T. Edited the manuscript: C.M.K., C.W., L.T.G., M.C.S., S.J.H., J.K.I., K.S.K., L.G., A.M.G., S.T., N.G., M.K., N.J.C., and J.F.C.

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