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Mouse Models of Frontotemporal Dementia

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Abstract

The pace of discovery in frontotemporal dementia (FTD) has accelerated dramatically with the discovery of new genetic causes and pathological substrates of the disease. *MAPT*/Tau, *GRN*/progranulin, and *C9ORF72* have emerged as common FTD genes, and *TARDBP*/TDP-43, *VCP*, *FUS*, and *CHMP2B* have been identified as less common genetic causes. TDP-43 and FUS have joined Tau as common neuropathological substrates of the disease. Mouse models provide an important tool for understanding the role of these molecules in FTD pathogenesis. Here, we review recent progress with mouse models based on Tau, TDP-43, progranulin, VCP, and CHMP2B. We also consider future prospects for FTD models, including developing new models to address unanswered questions. There are also opportunities for capitalizing on conservation of the salience network, which is selectively vulnerable in FTD, and the availability of FTD-related behavioral paradigms to analyze mouse models of the disease.

Historically, progress in understanding neurodegenerative diseases has surged following the discovery of molecules that accumulate neuropathologically or cause disease in familial cases, in large part because such discoveries enable mechanistic studies in model systems. Frontotemporal dementia (FTD) is likely the next disorder to follow this trajectory. FTD is a devastating disease that typically strikes individuals in their mid-50s and is as common as Alzheimer disease in this presenile group, but progresses more rapidly to death.^{1,2} Until 2004, tau was the only molecule known to accumulate in FTD patients' brains, and mutations in the tau gene, *MAPT*, were the only known genetic cause of FTD. Since then, the logjam has broken and two new neuropathological substrates (TDP-43 and FUS) and six new FTD genes (*GRN*, *C9ORF72*, *VCP*, *FUS*, *CHMP2B*, and *TARDBP*, the gene for TDP-43) have been identified.

These advances have created exciting new opportunities to study FTD using mice. Mouse models are important tools for studying neurodegenerative disorders because they meet the need for an experimentally manipulable system that maintains sufficient genetic and neural conservation with humans. Mice and humans have a similar number of genes and a high degree of chromosomal synteny,³ plus conserved patterns of gene expression across brain regions.⁴ The seven "FTD proteins" in particular are highly conserved between humans and mice (Table 1). Furthermore, because neurodegenerative diseases target networks of connected brain regions,⁵ the fact that mice have brain architecture and network connections that are similar to humans, as detailed below, is an important advantage over non-mammalian models. Here, we review recent progress and future opportunities for using mouse models to understand FTD.

The FTD Spectrum

Several related conditions are grouped under the umbrella of FTD, so it is important to clarify what we are modeling. The FTD spectrum includes six clinical diagnoses: behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (PPA), nonfluent/agrammatic variant PPA, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and FTD with amyotrophic lateral sclerosis (FTD-ALS). In this review, we focus on bvFTD, the most common of the six clinical FTD-spectrum diagnoses,⁶ the symptoms of which, along with FTD-ALS, are the most amenable of the FTD-spectrum disorders to modeling in mice.

FTD-spectrum disorders are not only clinically, but also pathologically, heterogeneous, and this is particularly true for bvFTD (Fig. 1).⁷ The most common substrate is frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP), which can be further divided into four subtypes based on the subcellular location of TDP-43 aggregates.⁸ Almost as common in bvFTD is FTLD with tau pathology (FTLD-tau), including subtypes in which tau aggregates are present in different cell types or forms. A smaller fraction of bvFTD patients have FTLD with FUS pathology (FTLD-FUS), and a very few have ubiquitinated inclusions that are not immunoreactive for tau, TDP-43, or FUS, termed FTLD-UPS, for ubiquitin proteasome system.

Each FTD gene produces a certain type of pathology: *MAPT* mutations cause FTLD-Tau; *C9ORF72*, *GRN*, *TARDBP*, and *VCP* mutations all cause FTLD-TDP; *FUS* mutations cause FTLD-FUS; and *CHMP2B* mutations cause FTD-UPS (Fig. 1). Large cohort studies have made clear that *C9ORF72*, *MAPT*, and *GRN* mutations are common genetic causes of FTD.⁹ While *TARDBP*, *VCP*, *FUS*, and *CHMP2B* are rarer, the overlap between clinical and pathological syndromes makes them interesting to dissect mechanistically. And because all of these molecules cause not only bvFTD but also the other clinical syndromes, knowledge gained from studying mouse models of bvFTD may be even more broadly applicable. That is, while it is most straightforward to think of a TDP-43 mouse modeling bvFTD, the molecular pathogenesis is likely to be similar in semantic variant PPA or other cases with FTLD-TDP pathology.

Recent Progress in FTD Models

Many new FTD models have been developed in the last few years. We begin by reviewing new models based on *TARDBP*/TDP-43, *GRN*, *VCP*, and *CHMP2B*, and then consider the latest, next-generation models based on *MAPT*/tau. For each molecule, we first consider its association with FTD, which impacts the applicability of the models, and then its molecular genetics, which informs what type of models are appropriate. We then review the data generated from these models, what they are teaching us about FTD, and what important questions remain.

TDP-43

TDP-43–related FTD—TDP-43 is connected to FTD both by neuropathology and genetics, but the neuropathologic link is much stronger. In terms of neuropathology, FTD with TDP-43–positive inclusions (FTLD-TDP) is the most common substrate for FTD.¹⁰ Relative to FTLD-Tau, FTLD-TDP is more likely to include cases of FTD-ALS and semantic variant PPA and less likely to include nonfluent/agrammatic PPA. In terms of genetics, mutations in *TARDBP*, the TDP-43 gene, account for about 5% of familial ALS and about 1% of all ALS,¹¹ but only a few families with FTD.^{12–14} As one would expect, most FTD due to *TARDBP* mutations manifests as FTD-ALS, although a few cases of

“pure” FTD have been described. Thus, both wild-type and mutant TDP-43 models are potentially relevant to FTD.

Molecular Genetics—TDP-43 is a multifunctional, nuclear protein that binds both DNA and RNA.¹⁵ Its name derives from its ability to bind the HIV trans-activating region (TAR) and repress transcription of nearby genes.¹⁶ In addition, TDP-43 is a member of the heterogeneous nuclear ribonuclear protein (hnRNP) family and regulates several aspects of RNA processing, including alternative splicing, miRNA production, and mRNA trafficking and stabilization.

TDP-43 has two conserved RNA recognition motifs and a carboxy-terminal glycine-rich domain that mediates interactions with other hnRNP family members. Essentially all ALS- and FTD-associated *TARDBP* mutations are missense changes in the glycine-rich domain. Whether mutations exert their effects due to gain- or loss-of-function remains unclear, but a shift in TDP-43 from the nucleus to the cytoplasm occurs in FTLTDP, so both loss of nuclear function and gain of cytoplasmic function have been hypothesized.

Mouse Models—Knockout mice provide a tool for assessing loss-of-function effects. Complete TDP-43 deficiency (*Tardbp*^{−/−}) is embryonic lethal.^{17–19} Heterozygous *Tardbp*^{+/-} mice have normal TDP-43 protein levels and no obvious neuropathology,^{17–19} limiting their utility, although one report found subtle motor weakness with aging.¹⁹ *Tardbp* deletion at 4–6 weeks in a conditional knockout line led to death within 9 days due to increased fat oxidation and resulting weight loss.²⁰ Thus, a brain-specific conditional knockout is required to clearly determine the effect of TDP-43 loss-of-function in neurons.

Numerous transgenic TDP-43 mouse models have been described in recent years (Table 2). The first models used heterologous promoters to drive human TDP-43 expression throughout the nervous system and developed a dramatic phenotype, with severe motor impairment leading to death in weeks to months.^{21–25} This occurred with both wild-type and mutant TDP-43 and seemed to relate primarily to the level of expression in spinal cord. While perhaps relevant to ALS, the profound impairments in these lines for the most part preclude their evaluation as FTD models. Interestingly, though, in each of these pan-neuronal TDP-43 lines in which brain pathology was examined, layer V of frontal cortex was selectively vulnerable to development of ubiquitinated neuronal inclusions, astrogliosis, and neuron loss.^{21–23} Layer V contains large pyramidal neurons that serve as the primary efferents from the cortex, and layer V neurons are particularly vulnerable in FTD and FTD-ALS.^{26,27}

Subsequent models were engineered with more restricted promoters to better isolate the forebrain effects of TDP-43 from the motor phenotypes seen in pan-neuronal lines. Forebrain expression (driven by the CaMKII promoter) of even wild-type TDP-43 was sufficient to cause neurodegeneration and behavioral deficits.^{28,29} Again, certain neuronal populations were more vulnerable than others. In a line expressing wild-type human TDP-43 at only 0.8-fold endogenous levels, more than 75% of dentate granule neurons were lost while CA1 pyramidal neurons were resistant, and deep cortical layers were more affected than superficial layers.²⁹ Expression of wild-type murine TDP-43 at twice endogenous levels impaired learning and memory and synaptic plasticity.²⁸

More recently, the entire human TDP-43 gene has been expressed in mice. Driven by its own promoter, human TDP-43 is expressed in all tissues examined, with brain levels about three times endogenous.³⁰ Whether wild-type or mutant TDP-43 was expressed, astrogliosis developed before five months of age, and learning/memory and motor deficits developed

around seven months. By at least ten months, the mice had several pathological features seen in patients with FTLTDP, such as neuronal inclusions of ubiquitinated TDP-43.

The presence of FTD-related phenotypes in TDP-43 mouse models should enable using them to determine mechanisms by which TDP-43 contributes to the disease. One of the first questions is which of the pathological features best correlates with degeneration or behavioral deficits. However, while many lines exhibit pathological features seen in FTLTDP, such as neuronal intranuclear or cytoplasmic inclusions, carboxy-terminal fragments of TDP-43, and nuclear clearing of TDP-43, none of these features correlates well with the presence of functional deficits across different lines (Table 2), suggesting that other mechanisms may be more pertinent. Because of the tight control of TDP-43 levels by autoregulation, it has been suggested that suppression of endogenous mouse TDP-43 by transgenic human TDP-43 produces a loss-of function effect,²⁹ although it is not clear why human TDP-43, which is 96% identical to mouse TDP-43 (Table 1), would be unable to replace the lost function of the endogenous protein.

Progranulin

Progranulin-related FTD—Mutations in the progranulin gene, *GRN*, account for about 5% of all FTD cases and along with *C9ORF72* are a common genetic cause of FTLTDP.³¹ FTD due to *GRN* mutations is similar to sporadic cases with FTLTDP, except it begins a few years earlier and ALS is a less likely accompaniment.³² Pathologically, *GRN* mutations cause type A FTLTDP, the most common form of FTLTDP.^{8,10} Thus, progranulin-based mouse models are potentially relevant to a large swath of FTD.

Molecular Genetics—Around 70 different *GRN* mutations have been identified in FTD³³ and all reduce progranulin levels or result in loss of progranulin function. The majority, including the most common R493X mutation, result in an unstable mRNA that is degraded by nonsense-mediated decay, causing progranulin haploinsufficiency.^{34,35} Others cause loss of the entire *GRN* gene³⁶ or production of mutant progranulin that cannot be secreted^{37,38} or properly cleaved.³⁹ Because progranulin mutations appear to act through a loss-of-function mechanism, progranulin-deficient mice are a suitable disease model.

Mouse models—Three different lines of progranulin knockout (*Grn*^{−/−}) mice have been published, and preliminary findings from others have been described in abstract form. All lines had early abnormalities in social behavior without impairment in overall health or motor function.^{40–42} Hippocampus-dependent learning and memory, assessed by the Morris water maze, was preserved until late.⁴¹ Thus, the behavioral phenotype of *Grn*^{−/−} mice bears similarities to FTD and these mice may be good models for studying the mechanisms of neuronal dysfunction induced by progranulin deficiency.

Early work on the neuropathology of *Grn*^{−/−} mice highlights potential roles for protein mishandling and neuroinflammation. Evidence for protein mishandling in *Grn*^{−/−} mice includes accumulation of ubiquitinated protein and, in one study, phosphorylated TDP-43.^{43,44} The evidence for neuroinflammation is even stronger, with all published lines showing high degrees of astrogliosis and microgliosis.^{42–44} In addition, macrophages derived from *Grn*^{−/−} mice exhibit increased activity when stimulated,^{43,45} and *Grn*^{−/−} mice are more susceptible to inflammatory arthritis mediated by TNFα.⁴⁶

Important questions remain for progranulin-related models of FTD. The foremost task is to establish the mechanistic basis of the FTD-related behavioral deficits in *Grn*^{−/−} mice, including testing whether the observed protein mishandling or neuroinflammation phenotypes are causally related to neuronal dysfunction, and/or whether other mechanisms are in play. Given the striking gliosis and neuroinflammation, attention has largely focused

on roles for microglia-derived progranulin, but progranulin is also highly expressed in neurons,⁴⁷ where its roles are not yet well understood.

VCP

VCP-related FTD—Mutations in *VCP*, which encodes valosin-containing protein (VCP in humans or p97 in mouse), can cause pure FTD but more commonly cause a syndrome of FTD with muscle and bone disease.⁴⁸ This rare disorder, called inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD), has been reported in about forty families. The penetrance of FTD is reportedly less than 50%,⁴⁹ but this may reflect under-diagnosis because the myopathy tends to develop first. The clinical presentation of FTD in IBMPFD includes both bvFTD and semantic variant PPA presentations, with mean onset in the mid- to late fifties.^{50,51} Neuropathologically, FTD caused by VCP mutations is associated with FTLT-DTP type D, a distinct subtype that is not seen in sporadic FTD or with other mutations. Type D FTLT-DTP is distinguished by the combination of TDP-43-positive neuronal intranuclear inclusions and dystrophic neurites with few neuronal cytoplasmic inclusions.⁵² Thus, FTD due to *VCP* mutations is rare and has a few notable differences from more common forms.

Molecular Genetics—VCP/p97 is a ubiquitously expressed member of the *ATPase* associated with diverse cellular activities (AAA⁺) family. Like other AAA⁺ proteins, VCP/p97 has numerous functions, including regulating protein degradation through the ubiquitin-proteasome system, endoplasmic reticulum-associated degradation, and autophagy. Complete loss of VCP/p97 is embryonic lethal.⁵³ *VCP* mutations in ~80% of families with IBMPFD are in the amino-terminal CDC48 domain of the protein, most at a single site, R155. The CDC48 domain mediates VCP/p97 substrate recognition and cofactor binding. Because all FTD-associated *VCP* mutations are at sites positioned near R155 in the tertiary structure of VCP/p97,^{54,55} *VCP* mutations are likely to cause disease by disrupting a specific function mediated through this domain of the protein and it is probably important that mouse models include a mutation in this region.

Mouse models—Two transgenic and one knock-in line are available as models of *VCP*-related FTD (plus others using muscle-specific promoters to examine the myopathy of IBMPFD). The transgenic models express human *VCP* with either the R155H or A232E mutation from a ubiquitous promoter at levels 2–3-fold higher than the endogenous gene.⁵⁶ The knock-in model expresses the R155H mutation in the endogenous mouse gene and capitalizes on the conservation between mouse and human VCP/p97 (Table 1).⁵⁷ Like other knock-in models, it avoids potentially spurious effects of heterologous promoters.

All three models exhibit a range of age-dependent muscle, bone, and brain disease related to human IBMPFD. Neuronal dysfunction in the transgenic lines includes increased anxiety-related behavior and impaired novel object recognition.⁵⁶ The knock-in mice were not impaired on novel object recognition to at least 15 months, but did have seizures.⁵⁷ On postmortem examination, all three models had age-dependent loss of nuclear TDP-43 with accumulation of ubiquitinated TDP-43 in the cytoplasm and gliosis.^{56,57} Thus, these lines should serve as useful models for studying how mutant VCP/p97 affects TDP-43 and causes neuronal dysfunction.

CHMP2B

CHMP2B-related FTD—Mutations in *CHMP2B* are the rarest cause of FTD considered here, with four proven pathogenic mutations identified in five families to date.³³ In the original Danish kindred, the clinical syndrome is similar to sporadic bvFTD, with a mean age of 58 at onset.⁵⁸ However, the atrophy on neuroimaging is more diffuse than seen in

typical bvFTD.⁵⁹ In addition, the neuropathology is unique, representing the small cluster of FTD cases with ubiquitinated neuronal cytoplasmic inclusions that do not contain tau, TDP-43, or FUS (FTLD-UPS; Fig. 1).^{60,61} More recently, missense mutations have been identified that cause FTD and/or motor neuron disease, and these cases do appear to have TDP-43 pathology.⁶²

Molecular Genetics—*CHMP2B* encodes charged multivesicular protein 2B (CHMP2B), a component of the endosomal sorting complex required for transport III (ESCRT-III), which is involved in trafficking endosomes to degradation in lysosomes. The original Danish mutation is at the splice acceptor site for the last exon of CHMP2B, producing two novel products termed CHMP2B^{Intron5} and CHMP2B^{Δ10} that differ from wild-type CHMP2B in their carboxy-terminal sequences.⁶³ CHMP2B^{Intron5} fails to dissociate normally from the ESCRT-III complex, impairing its function and leading to accumulation of autophagosomes.⁶⁴

Mouse models—Mice expressing CHMP2B^{Intron5} from the prion promoter develop inclusions of ubiquitinated proteins that are negative for TDP-43 and FUS, as in the FTLD-UPS pathology in patients with *CHMP2B* mutations.⁶⁵ The mice also develop axonal swellings and have reduced survival. None of these abnormalities was seen in mice expressing wild-type CHMP2B at even higher levels or in *Chmp2b* knockout mice, consistent with a gain-of-function effect unique to CHMP2B^{Intron5} (ref. ⁶⁵).

Tau

Tau-related FTD—Tau was the first molecule linked to FTD, both by neuropathology and by genetics. The neuropathological term for cases with tau pathology is FTLD-tau and the clinical term for cases with *MAPT* mutations is frontotemporal dementia and parkinsonism linked to chromosome 17, tau gene (FTDP-17T). Both are common. FTLD-tau is the substrate for about half of all bvFTD cases (Fig. 1) and an even larger proportion of PSP, CBS, and nonfluent/agrammatic PPA cases.⁶⁶ *MAPT* mutations are one of the major genetic causes of FTD, along with *GRN* and *C9ORF72* mutations.^{31,67} Patients with *MAPT* mutations have FTLD-tau pathology are likely to have the same clinical syndromes associated with sporadic FTLD-tau.⁶⁸ Given these strong and diverse associations, tau models have broad applicability to FTD.

Molecular Genetics—More than 40 different FTD-associated mutations have been found in *MAPT*.³³ Although they are concentrated in certain regions, no single unifying mechanism appears to explain the effect of tau mutations. Most are missense mutations in the microtubule-binding region, some of which are in exon 10 (the alternatively spliced microtubule-binding domain) and thus occur only in four-repeat tau isoforms, while others occur in all six isoforms. A few mutations occur outside the microtubule-binding region at the amino or carboxy termini of tau, although because these regions tend to fold back toward the repeat region⁶⁹ they may be structurally and functionally related to mutations in the microtubule-binding domains. Finally, some tau mutations are silent (changing the mRNA, but not the protein, sequence) or intronic and shift the ratio of isoforms with three vs. four microtubule-binding domains (3R vs. 4R tau). Tau mutations have both loss-of-function (reduced microtubule stabilization) and gain-of-function (increased aggregation and phosphorylation) effects.^{70,71}

Mouse Models—Since tau is the elder statesman of FTD molecules, there is a much longer history of tau mouse models. The first decade of this history has previously been reviewed⁷² so we focus here on the most recent advances and newer tau models. Details on the types and levels of tau expressed in these lines are presented in Table 3.

Early models had shown that expressing mutant tau was sufficient to cause both aggregated tau pathology and neuronal death. One of the more interesting recent findings has been the dissociation of these two processes. In both the rTg4510 and hTau lines, neuronal tau aggregates form but neurons without aggregates are susceptible to death.^{73,74} Furthermore, *in vivo* imaging in rTg4510 mice suggests that tangle formation *reduces* the likelihood of cell death.⁷⁵ On the other hand, adding experimental mutations that prevent tau aggregation (in Anti-Aggr mice; see Table 3) prevents the neuronal death seen in Pro-Aggr mice in which tau does aggregate.⁷⁶ The most parsimonious explanation of these data is that soluble tau aggregates (oligomers), but not the larger tangle-like aggregates visible by light microscopy, are responsible for neuronal death.

Even more interestingly, both aggregated tau pathology and neuronal death have been dissociated from the functional deficits in tau mouse models. In PS19 mice, synaptic loss and behavioral deficits precede tangle formation by several months.⁷⁷ And in two different regulatable tau lines, rTg4510 and Pro-Aggr, turning off expression of mutant tau reverses synaptic and behavioral deficits despite persistent aggregated tau pathology and neuron loss.^{76,78,79} The anatomical correlate of functional improvement was restoration of normal synapse density.⁷⁹ Indeed, the synapse increasingly appears to be a critical site for tau pathogenesis. Mutant tau is mislocalized to synaptic fractions in rTg4510 mice, where it seems to impair synaptic transmission even before spines are lost.⁸⁰

Another interesting lesson from tau models is that the synapse is not just a target for tau, but a likely site of spreading pathology. Modeling suggests that the propensity of neurodegenerative diseases to target large-scale networks is most likely due to transneuronal spread.⁸¹ Consistent with this prediction and findings that tau aggregates can propagate to unaffected cells in culture,⁸² transneuronal spread of abnormal tau has also been shown in mouse models. Months after either injecting brain extracts from mice with tau pathology⁸³ or genetically expressing mutant tau in a restricted neuronal population,^{84,85} tau aggregates were found in other, synaptically connected regions. The mechanisms by which tau is released and then taken up could serve as therapeutic targets for slowing the progression of disease.

Tau models of FTD are already being used to evaluate other potential therapeutic strategies. The JNPL3 line has been the workhorse for many of these studies, although PS19, pR5, and rTg4510 have also been used. Kinase inhibitors,^{86,87} microtubule stabilizers,⁸⁸ immunization with a phospho-tau peptide,⁸⁹ passive immunotherapy with tau antibodies,⁹⁰ and the immunosuppressant FK506 (ref. ⁷⁷) prevented tau pathology and functional deficits in various lines. Certain therapies, including passive immunization and microtubule stabilizers, were able to reverse existing deficits.⁹¹ Underscoring the findings with genetic approaches, methylene blue also reversed existing behavioral deficits without clearing tau aggregates or restoring lost neurons.⁹² The field now awaits clinical trials of these approaches in FTD patients.

Future Opportunities with FTD Models

As much as we've already learned from mouse FTD models, recent progress shows no signs of slowing and there are many opportunities for further advances.

New Mouse Models

One opportunity is for continued development of new models to address unanswered questions. Models of the newer genes will likely follow a course like the tau models, with the initial models that express at high levels from heterologous promoters giving way to models that express at closer to physiological levels and from the gene's own promoter,

which are thus less susceptible to spurious results. Regulatable models to address questions of reversibility have yet to be developed for many of these genes. And in some cases, tissue- or cell type-specific models will be important, for example to compare the effects of progranulin insufficiency in neurons and microglia or to determine the effects of brain-specific loss of TDP-43. For progranulin, models with one allele intact, e.g. *Grn*^{+/-} mice or knock-in mice expressing an FTD-associated mutation, will have advantages over existing *Grn*^{-/-} models by more closely modeling the haploinsufficient state of progranulin mutation carriers and enabling study of therapies to increase expression from the intact allele, which may be a fruitful avenue for treating the disease in patients with progranulin mutations.

Models of FUS- and *C9ORF72*-related FTD are also on the horizon. FUS models will come first, but apply to a relatively small fraction of FTD; while FUS is an important cause of ALS, FUS pathology is found in <10% of FTD (Fig. 1). Although it will take some time, models based on mutations in *C9ORF72*, which were recently found to be an important cause of sporadic and familial FTD,^{67,93} will be highly anticipated. The most common clinical presentation of *C9ORF72* mutations is bvFTD (or FTD-ALS), occasionally nonfluent/agrammatic variant PPA, and rarely semantic variant PPA.⁹⁴ The pathology is FTLTDP, type A or B.⁹⁴ Given that *C9ORF72* appears to be the most common FTD gene (Fig. 1) and mutations are present in some sporadic cases as well,^{67,93} these models will be directly relevant to a significant fraction of FTD patients.

The Salience Network

Hints at selective vulnerability in some FTD models, like the predilection of TDP-43 for layer V neurons, highlight another opportunity for studying mouse models. The anatomic conservation between rodents and humans of structures and networks relevant to neurodegenerative disease is an important advantage of mouse models. For example, rodents have a default mode network⁹⁵ and mouse models of Alzheimer's disease (AD) have been very effective for studying how A β peptides impair the function of entorhinal cortex and hippocampal circuits that are particularly involved in AD.

What about FTD, sometimes thought of as a disease of the prefrontal cortex? The prefrontal cortex is vastly expanded and uniquely specialized in humans relative to mice,⁹⁶ suggesting a potential limit to modeling FTD in mice. But the relevance of this difference dissolved with the realization that FTD does not target the prefrontal cortex *per se*, but rather a distributed network termed the salience network.^{5,97-99} Anchored in the anterior insula, the salience network includes anterior cingulate cortex, ventral striatum, amygdala, dorsomedial thalamus, hypothalamus, and brainstem nuclei including periaqueductal gray, substantia nigra, and ventral tegmental area.¹⁰⁰

These salience network nodes and their connectivity are phylogenetically well conserved between mice and men (Fig. 2). The salience network is one of the brain's "resting state" or intrinsic connectivity networks and its name derives from its role processing multimodal information and identifying the most relevant (salient) stimuli.^{100,101} Salience network nodes control a number of "primitive" functions. The insula is activated in response to interoceptive stimuli such as pain, hunger, taste, thirst, and autonomic feedback.¹⁰² The ventral striatum is involved in reward and motivation.¹⁰³ The amygdala controls fear responses.¹⁰⁴ Given the nature of these functions and their connection to basic homeostatic mechanisms, it is not surprising that the salience network is well conserved from mice to humans. Thus, the mouse brain does contain the anatomic substrate of FTD, and it would be interesting to determine the extent to which salience network regions are selectively vulnerable to FTD proteins.

A related issue of comparative anatomy for mouse models of FTD is the role of von Economo neurons (VENs). VENs are large, spindle-shaped neurons that are found only in anterior cingulate and anterior insular cortex (the main cortical nodes of the salience network).¹⁰⁵ In FTD, VENs are more vulnerable to neurodegeneration than surrounding neurons in these regions.²⁷ However, VENs are found only in humans, great apes, and certain other large mammals, and not in mice. So obviously, mice cannot model VEN degeneration. However, at this point, it is unclear whether VENs themselves are selectively vulnerable to FTD, or whether the salience network regions in which VENs are found are selectively vulnerable and these huge neurons with a high metabolic demand are simply the first to succumb. Further research on susceptibility of the salience network to FTD-related insults, including in mouse models, will help address this question.

FTD-related Behavioral Tests

Another opportunity is an expanding repertoire of FTD-related behavioral paradigms for mice. The AD field has relied heavily on tests of hippocampus-dependent learning and memory, such as the Morris water maze and contextual fear conditioning. These tests provide a robust means of testing the brain networks that are most susceptible in AD and they model the memory-predominant symptoms of AD. However, in FTD, hippocampal function and episodic memory are relatively spared — their preservation (at least until late in the disease) is in fact incorporated into the diagnostic criteria.^{106,107} So these tests are probably not the most appropriate for mouse FTD models.

Although the symptomatology of FTD may at first seem too complex to model in mice, several aspects of FTD are potentially amenable to study in the mouse model. Work on autism, which bears some similarities to FTD in its social and behavioral features, has demonstrated the utility of mouse models to study a disorder with these features.¹⁰⁸ Here we highlight a few behavioral domains that have not only surface similarity with the symptoms of FTD, but also a common underlying neuroanatomy.

Social Dysfunction—Social dysfunction is one of the earliest and most prominent symptoms of FTD. The hallmarks of social dysfunction in FTD, reflected in the new diagnostic criteria, are diminished social interest and loss of empathy. Social interest can be measured in mice either in formal assays such as the sociability test¹⁰⁹ or more naturalistically by simply quantifying the time two mice interact with each other over time. Reduced social interest has been observed in mouse models of FTD.^{40–42} Recent reports have also described methods for measuring empathy in mice.^{110,111} Other aspects of the social phenotype in FTD might also be accessible in mouse models. Social dominance is lost in FTD¹¹² and can be studied in mice through assays like the tube test.¹¹³

Intriguing parallels in the neuroanatomy of social deficits between FTD patients and mouse models make social testing of FTD mice all the more interesting. Social abnormalities in FTD map to medial prefrontal cortex.¹¹⁴ Interestingly, mutant mice with selective developmental defects in dorsomedial prefrontal cortex showed reduced social interactions, suggesting that social interest in mice is regulated by brain regions affected by FTD.¹¹⁵ Similarly, mouse empathy depends on anterior cingulate cortex,¹¹¹ also a vulnerable node in FTD. These anatomic parallels suggest that social phenotypes in mouse models may bear more than superficial similarity to the human disease.

Repetitive Behavior—Initially considered a supportive feature for the diagnosis of FTD,¹⁰⁶ repetitive behavior is now recognized as a core feature in the new diagnostic criteria.¹⁰⁷ Most FTD patients develop some form of repetitive behavior,¹¹⁶ which can evolve into self-injurious pathological grooming as patients rub or pick at areas even after

the skin is broken.¹¹⁷ Repetitive behavior in mice most commonly takes the form of repetitive grooming. While not yet described in FTD models, repetitive grooming has been described in several knockout mouse lines.^{118–120} Again, there are interesting neuroanatomic parallels, as the striatum seems to be highly involved in both FTD-associated repetitive behavior^{121,122} and repetitive grooming in mutant mice.^{119,120}

Emotional Behavior—FTD typically impairs emotion, particularly negative emotions such as fear, anger, and disgust.¹²³ Fear is easy to study in mouse models, usually in response to an aversive stimulus such as a mild foot shock. Fear conditioning paradigms have also been designed for human subjects, commonly using loud noises instead of electrical shock, and these tests show impaired fear responses in FTD patients.¹²⁴ Perhaps not surprisingly, voxel-based morphometry indicates that fear impairment in FTD correlates with atrophy in the amygdala.¹²⁴ Similarly, abnormal fear conditioning responses in mice relate to the amygdala.¹²⁵

Conclusions

This is an exciting time in FTD research. Several of the new FTD molecules were almost completely unstudied in the brain before they were linked to the disease, so the prospects for discovery are tremendous. Mouse models will play an important role in understanding how the new players contribute to FTD, as these questions play to their strengths: close genetic conservation (see Table 2) and neuroanatomic homology (see Fig. 2) to humans, combined with relative ease of molecular/genetic manipulations and a wide variety of relevant functional and pathological outcome measures to study.

Of course, the limited track record of mouse models in fostering the development of effective treatments for other neurodegenerative diseases cannot be ignored. Among the drawbacks of mouse models is their relatively short lifespan (about two years), which may not allow for modeling events that occur over decades in humans. And the much more rapid metabolism of mice creates pharmacokinetic issues for preclinical drug studies in mouse models.¹²⁶ However, it is worth noting that FTD may have certain advantages over AD in terms of mouse models. First, FTD has a stronger genetic component than AD, which mollifies the criticism of AD models that they are based on exceedingly rare genetic causes of the disease. Second, mouse models of FTD, in general, seem to produce a fuller representation of the pathology of the human disease, including neuron loss, which is a limitation of many AD mouse models.

Given the rapid progress already being made and the additional opportunities reviewed here, there is ample reason for optimism about the power of FTD mouse models to advance treatment of this horrible disease.

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Figure 1. Neuropathology and Genetics of Behavioral Variant FTD

The spectrum of bvFTD, divided by neuropathological subtype (color) and genetic causes (black outlines), in proportion to frequency. About half of FTD patients have TDP-43 pathology (FTLD-TDP, purple), while tau pathology (FTLD-tau, blue) is seen in ~40% and the remainder have either Fus pathology (FTLD-FUS, red) or other ubiquitinated inclusions that are negative for tau, TDP-43, and FUS (FTLD-UPS, green). *MAPT*, *C9ORF72*, and *GRN* mutations are the most common genetic causes of FTD. *MAPT* mutations lead to tau pathology and *C9ORF72* and *GRN* mutations lead to TDP-43 pathology. *TARDBP* and *VCP* mutations are uncommon causes of TDP-43 pathology, *FUS* mutations cause FUS pathology, and *CHMP2B* mutations cause FTD-UPS.

Figure 2. Saliency Network in Humans and Mice

Left, Regions of reduced intrinsic connectivity in FTD identified by functional MRI imaging. These areas are nodes in the saliency network. InsC, insular cortex; CgC, cingulate cortex; VStr, ventral striatum; Amy, amygdala; SN, substantia nigra; VTA, ventral tegmental area; PAG, periaqueductal grey. Images kindly provided by Dr. W.W. Seeley, originally published in ref. ¹³² and adapted with permission from Oxford University Press. *Right*, Schematic coronal sections through the mouse brain, with homologous regions of the saliency network highlighted in the left hemibrain. Each of the major nodes in the human saliency network is represented in the mouse brain. Images reproduced from *The Mouse Brain in Stereotaxic Coordinates, 3rd Edition* by Keith B.J. Franklin and George Paxinos, with permission of the publisher, Elsevier.

Table 1
Close conservation between human and murine FTD proteins

The seven FTD-related proteins are highly conserved in mice. Numbers in parenthesis indicate number of amino acids. Of the two proteins that are not at least 96% conserved overall, tau is 99% conserved (273/275 amino acids) in the carboxy-terminal $\frac{2}{3}$ of the protein containing the proline-rich and microtubule domains and almost all disease-related phosphorylation sites, and progranulin is 92% conserved in the granulin domains.

Protein	% Identity	% Conservation
C9ORF72	98% (472/481)	99% (480/481)
CHMP2B	99% (212/213)	100% (213/213)
FUS	95% (500/528)	96% (508/528)
Progranulin	75% (446/593)	85% (503/593)
Tau	89% (393/441)	93% (409/441)
TDP-43	96% (398/414)	99% (409/414)
VCP	100% (806/806)	100% (806/806)

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TDP-43 mouse models

Table 2

Pertinent details about the construction of each line, including the promoter and transgene (m and h denote mouse and human), level of TDP-43 overexpression (expressed as fold over endogenous), age at which functional deficits or death occurs, and the presence or absence of pathological features such as neuronal intranuclear inclusions (NII), noting whether they are immunoreactive for TDP-43 [TDP+] or not), neuronal cytoplasmic inclusions (NCI), carboxy-terminal fragments (CTFs), and nuclear clearing. n/d, not determined.

Model Design			Functional Deficits			Pathology		
Promoter	Transgene	Mutation	Line	TDP-43 Level	Motor	Cognitive	Death	Ref
mPrP	cDNA (h)	WT	Homozygous	2.5	21d	n/d	1–2m	23
mThy1	cDNA (h)	WT	TAR4/4	2.0	14d	n/d	24d	22
mThy1	cDNA (h)	WT	W3	4.6 [†]	14–18d	n/d	n/d	25
hTDP	Genomic (h)	WT	TDP-43 WT	2.8	42w	9m	n/d	30
mCaMKIIα	cDNA (m)	WT	n/a	2.0	6m	2m	495d	28
mCaMKIIα Tet-off	cDNA (h)	WT	WT12	0.8	1–3m	n/d	>6m	29
mPrP	cDNA (h)	A315T	Prp- TDP43 ^{A315T}	3.0	3–4m	n/d	153d	21
mPrP	cDNA (h)	A315T	Line 23	4.0	5w	n/d	75d	24
hTDP	Genomic (h)	A315T	TDP-43 A315T	2.8	38w	9m	n/d	30
hTDP	Genomic (h)	G348C	TDP-43 G348C	3.0	36w	7m	n/d	30
mCaMKIIα Tet-off	cDNA (h)	ΔNLS	ΔNLS4	7.9	1w	n/d	>6m	29

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*In spinal cord only, not brain
†In males; levels in females were 50% lower
‡Rare, but those present were TDP+
§Rare, but those present were TDP+
**Rare, but those present were TDP+

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Commonly used tau models

This list is not comprehensive, but provides pertinent details on the models mentioned in the text. Isoform refers to the number of microtubule binding (R) and amino-terminal (N) repeats.

Table 3

Line	Isoform	Mutation	Promoter	Fold Expr.	Source	Ref.
JNPL3	4R0N	P301L	MoPrP	1x	Taconic 002508-M	127
rTg4510	4R0N	P301L	CaMKIIa, Tet-off	13x	JAX 015815	128
PS19	4R1N	P301S	MoPrP	5x	JAX 008169	77
Pro-Aggr	Tau ¹ _{RD}	ΔK280	CaMKIIa, Tet-off	0.7x	Mandelkow Lab	76
Anti-Aggr	Tau ¹ _{RD}	ΔK280, I277P, I308P	CaMKIIa, Tet-off	0.7x	Mandelkow Lab	76
pR5	4R2N	P301L	MoThy1.2	0.7x	Götz lab	129
hTau ²	all six	Wild-type	Human Tau	3.7x	JAX 005491	130,131

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¹Tau repeat domain, aa 244–372, including only the four microtubule-binding domains

¹Tau repeat domain, aa 244–372, including only the four microtubule-binding domains

²hTau mice are a cross between the 8c genomic tau transgenic line and mouse tau knockout mice