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Precision medicine of frontotemporal dementia: from genotype to phenotype

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1. ABSTRACT

Frontotemporal dementia (FTD) is the second most common neurodegenerative cause of early-onset dementia. FTD has an important genetic component contributing to its pathogenic mechanisms. Currently, extensive research on neuroimaging biomarkers and neurochemical biomarkers in FTD is being conducted to address the clinical need for a sensitive and specific diagnostic marker. Here, we review the advances in genetics, biomarkers and treatment of FTD and how this may represent a shift towards precision medicine. To advance the clinical use of precision medicine, big data cohort for

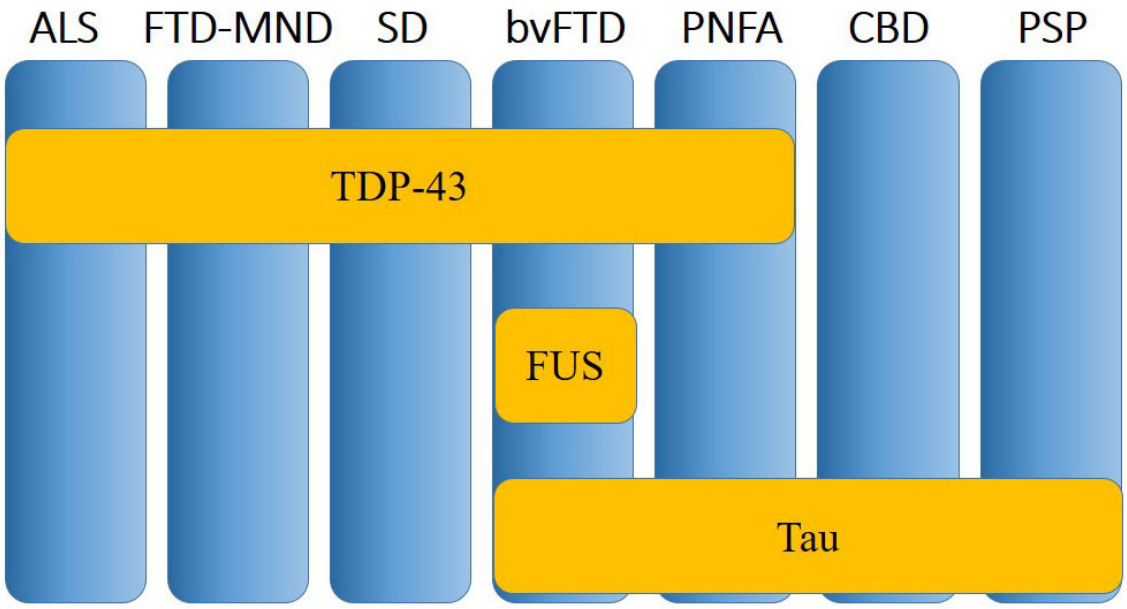

Figure 1. Classification of crosstalk between phenotype and neuropathology of FTLD.ALS – amyotrophic lateral sclerosis; FTD-MND – frontotemporal dementia – motor neuron disease; SD – semantic dementia; bvFTD – behavioural variant frontotemporal dementia; PNFA – progressive non-fluent aphasia; CBD – corticobasal degeneration; PSP – progressive supranuclear palsy.

genotype/phenotype research and multidisciplinary team approaches are necessary.

2. INTRODUCTION

Frontotemporal dementia (FTD) represents a spectrum of clinical presentations characterized by insidiously progressive deterioration in behavior, executive and language abilities. It is the second most important cause of dementia (FTD, OMIM 600274) worldwide, especially in younger onset dementia, being at least as prevalent as Alzheimer's disease (AD) in individuals under 65 years of age (1-3).

It is reported that FTD accounted for approximately 10% of all pathologically diagnosed dementias in subjects who developed disease before the age of 65 (4), and demonstrated a prevalence of 11.3.% in clinical trials (5). A recent estimate based on US and European sources, FTD occurs between 4 to 15 cases per 100,000 (6), and according to certain studies, the prevalence of FTD even exceeds the prevalence of AD in the age group between 45 to 65 years(7).

In the last two decades, FTD phenotypically divided into behavioral (bvFTD, also known as behavioral variant FTD, accounting for 50-70% cases (8)) or language syndromes. The language component consists of primary progressive aphasias (PPAs), including three major subtypes: nonfluent variant (nfvPPA, also known as progressive nonfluent aphasia), semantic variant (svPPA, also known as semantic dementia), and logopenic variant (lvPPA, also known as logopenic aphasia)(9).

In addition to the clinical classification of phenotypes, FTD can also be classified according to its histopathological substrate established after autopsy. Macroscopically, brain atrophy predominates in the frontal and temporal lobes, with distinct sparing of the posterior brain regions. Microscopically, FTD is either characterized by tau-positive inclusion bodies, or tau negative, ubiquitin positive TDP-43(TAR DNA-binding protein 43) or FUS (fused in sarcoma protein) subtypes (1). The tau-negative, TDP-43 positive variant is considered to be the most common underlying pathology for frontotemporal lobe degeneration (FTLD) (10). All pathological substrates were found to correlate with inferior medial temporal and inferior frontal lobe atrophy (11)(Figure 1-4).

Parkinsonism and ALS are the two common neurodegenerative movement disorders that may occur concurrently with FTD. Of the two, Parkinsonism is the most common symptoms in patients with bvFTD, but rarely occurs in patients with PPA(12, 13). Also, FTD patients may present with features of Richardson syndrome or cortico-basal degeneration (12). Additionally, it had been shown that ALS and FTD haveoverlapping neuropathology, as a majority of patients with ALS or FTD demonstrate neuronal cytoplasmic protein deposits consisting of TDP-43(14). In 2008, mutations in the TDP-43 coding *TARDBP*

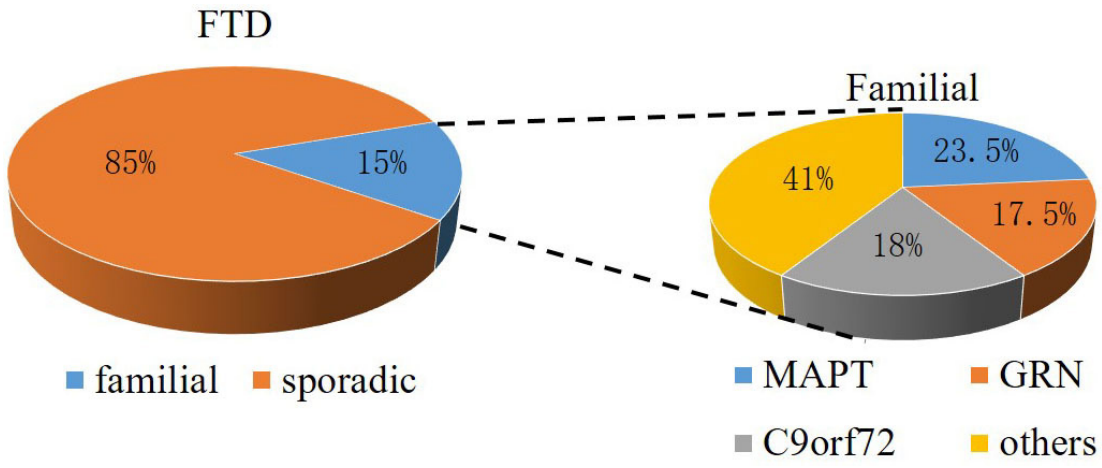

Figure 2. Classification of genotype of FTLD.

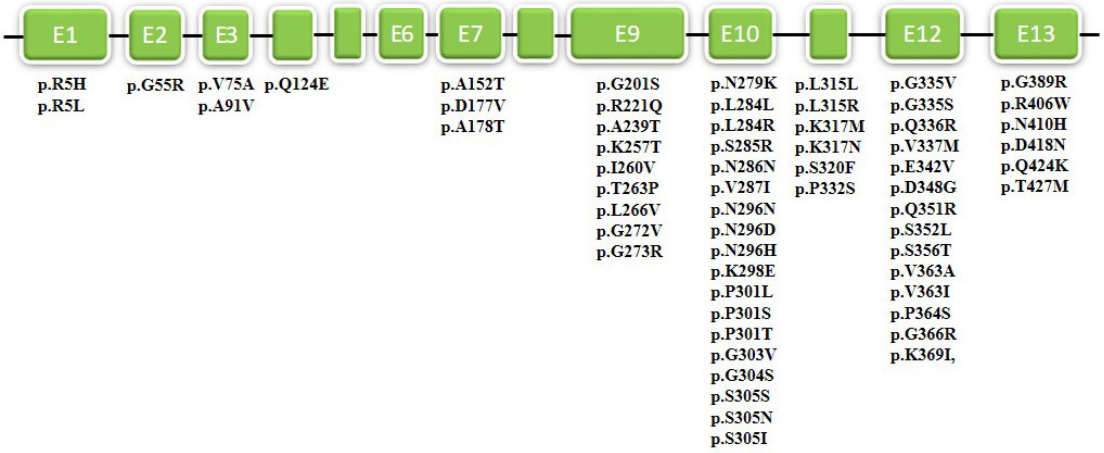

Figure 3. MAPT mutations associated with FTD.

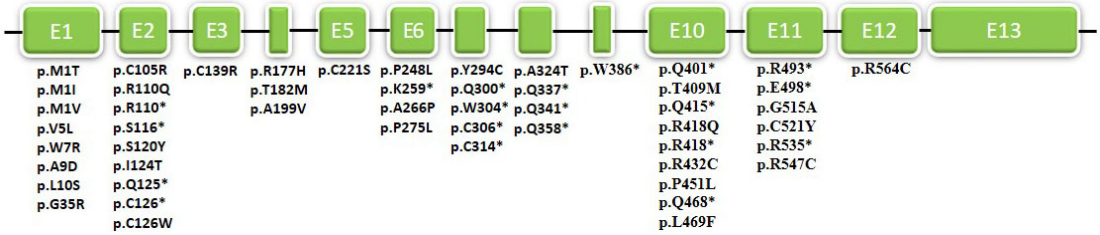

Figure 4. GRN mutations associated with FTD.

gene were identified as a cause for both ALS and FTD, which had also demonstrated possible familial inheritance (15, 16). Thus, ALS and FTD have been increasingly recognised as parts of the same spectrum of neurodegenerative diseases (17).

Under the current classification of FTD, clinicians are facing with several diagnostic challenges as it primarily affects individuals younger than 65 years of age (18), and the presenting symptoms are often mistaken for psychiatric or other neurological disorders, thus leading to a delay in the correct diagnosis being made. In addition to pathological evidences which is only available definitively via biopsy, genetic assessment, neurochemical tests in peripheral blood or cerebrospinal fluid, neuroimaging

and neuropsychiatric assessments could also help us to improve the accuracy for the diagnosis of FTD. Here, we discuss the precision medicine of FTD from genotype to phenotype, including: 1. Genetic assessment (Genotype), 2. Phenotype of neuroimaging; 3. Phenotype of neurochemical biomarkers, and 4. Phenotype of neuropsychiatric assessment, respectively.

FTD has an important genetic component since approximately 40% patients have at least one first degree relative with a disease in the FTD spectrum, and 10-15% of patients have a family history of FTD(19). Understanding the genetics of of FTD genetics would further enlighten us on the pathological processes and potentially providing guidance for future therapeutic implication.

2.1. microtubule-associated protein tau (MAPT)

The first major Mendelian gene linked to FTD was *microtubule-associated protein tau* (*MAPT*) identified in 1998 (20). *MAPT* (NM 001123066) has 15 exons from exon 0 to exon 14, and only 6 major isoforms are expressed in the brain: 2N3R, 1N3R or 0N3R isoforms, and 2N4R, 1N4R or 0N4R tau isoforms (21), ranging from 352 to 441 amino acids in length by *MAPT* alternative splicing of exons 2, 3, and 10 (22). Tau is an intrinsically disordered protein with a structure that can be subdivided into four domains: N-terminal, proline-rich, microtubule (MT) binding and C-terminal (21). The N terminal region of tau is composed of highly acidic inserts represented by expression of either exon 2 alone (1N, 29 amino acids), exons 2 and 3 (2N, a total of 58 amino acids) or neither of them (0N). The microtubule binding domain of tau consists of a tubulin-binding motif, represented by three or four repeat domains (3R or 4R, respectively) and a C-terminal tail.

Tau is a highly phosphorylated MT-related protein. There are 79 putative phosphorylation sites on the tau protein, and at least 30 of them have been shown to be phosphorylated. Phosphorylation is the major system that regulates tau binding to MT: non-phosphorylated sites lead to stronger binding and phosphorylated sites reduce binding strength, making MTs more unstable(23).

Even though mutations in *MAPT* can lead to most subtypes of FTD, but FTD-Parkinsonism and bvFTD are the main clinical phenotypes demonstrated in mutatation carriers (24). Mutations in *MAPT* can be identified as missense mutations in exons 9 to 13, affecting the normal function of tau proteins to stabilize microtubules, as well as introns and some mutations that affect exon 10 splicing at mRNA levels, resulting in a change in the ratio of 3R to 4R tau isoforms (25).

Most *MAPT* missense mutations reduce the ability of tau to interact with MT, as the ability to promote MT assembly by mutant tau is evidently decreased (26). Nevertheless, several exonic mutations are synonymous variants and do not alter the amino acid sequence of tau(12) . The MT binding domain (exon 9-12; amino acids 244-368) is essential to maintain the function of tau(27), i.e. MT binding, polymerization and dynamics regulation. Most of the missense mutations localized in the MT binding domain have been shown to confer a reduced capacity to interact with tubulin, slowing MT formation and demonstrated a reduced in -*vitro* affinity or polymerization assay of recombinant tau proteins with monomeric tubulin (26, 28). The pathogenic mechanismof such mutations is suggested by the alternative splicing of exon 10; by either affecting the last two positions in the last codon of exon 10 (c.2241 and c.2242), or affecting exonic splicing enhancer or splicing silencer sequences.

2.2. progranulin (GRN)

The second major Mendelian gene leading to FTD was *progranulin* (*GRN*, NM002087.2.) reported in 2006. The extensive sanger sequencing of a 6 Mb critical region eventually allowed the identification of loss-of-function mutations in *GRN* as the cause of autosomal dominant FTD in two independent studies in 2006 (29, 30). The *GRN* gene is located on the long arm of chromosome 17 (17q21.3.2 region) and consists of 13 exons. It encodes a 593 amino acid protein, progranulin, which can be cleaved into granulin peptides (A, B, C, D, E, F and P)(31).

Progranulin is a multifunctional growth factor expressed in various tissues, primarily in epithelial and hematopoietic cells, as well as neurons and microglia in the nervous system. The protein is involved in a variety of physiologic processes, including cell proliferation, wound healing and inflammation regulation (32, 33). Altered progranulin levels play a major role in the pathogenesis of neurodegenerative diseases, including AD, FTD and ALS, even in the absence of GRN mutations (34). Multiple studies have shown that progranulin participate in the pathogenesis of AD through a variety of pathways, including Aβ deposition and clearance, neuroendocrine deposition of phosphorylated tau, neuronal inflammation and neuronal survival (35). Null GRN mutations will alter intercellular communication (36) and in FTD, GRN mutations affects cerebral oscillatory activity (37). Furthermore, null mutations in GRN strongly reduce the number of released exosomes and alter their composition, along with a reduced level of circulating progranulin.

GRN mutations were subsequently found to account for 5–20% of FTD patients with a positive family history, and 1–5% of apparently sporadic FTD

patients (38). GRN gene mutations demonstrate an autosomal dominant pattern of inheritance, with the estimated penetrance at 60 years being 50-60%, which rises to greater than 90% at age 70 (39-41). In our unpublished clinical research, *GRN* gene mutations (1.2.%) were also identified in sporadic FTD patients in China (unpublished data). To date, more than 70 pathogenic *GRN* mutations have been identified, including frameshift, nonsense, missense and splice mutations, and also with rare partial deletions and a complete deletion of *GRN* (42). All pathogenic mutations resulted in a 50% loss of progranulin protein levels, resulting in phenotypical disease manifestation through haploid deficiency(12).

Out of all discovered FTD gene mutations, *GRN* mutation carriers have the widest variation in their clinical phenotype. The primary clinical diagnosis is bvFTD, followed by nfvPPA (43). As the disease progresses, language dysfunction seems to become more common. Parkinsonism is present in about 40% of patients and episodic memory impairment is frequently observed, which have led to a clinical diagnosis of AD in some instances (41, 44). In addition, *GRN* mutations were also identified in patients with corticobasal syndrome (45), Gaucher disease (46), complex spastic paraplegia (47), and posterior cortical atrophy (48).

2.3. the chromosome 9 open reading frame 72 (C9orf72)

The third major Mendelian gene mutation leading to FTD is located at *the chromosome 9 open reading frame 72* (*C9orf72*, NM 018325.2.) identified in 2011. Two separate studies led to the discovery of the hexonucleotide GGGGCC repeat expansion due to *C9orf72* mutation as a leading cause for familial FTD or ALS (49, 50).

In western Europe, the frequency of *C9orf72* expansion was 9.9.8% in all FTD patients, 11.7.-18.5.2% in those with familial FTD and 6.2.6% in those with sporadic disease (50, 51). Our research did not identify any case with expanded hexanucleotide (GGGGCC) repeats of *C9orf72* gene in sporadic FTD patients in China, which is comparable to previous Korean data (52). Also, *C9ORF72* repeat amplification was the most common genetic abnormality in familial ALS (23.5.%). This repeat amplification accounted for 46.0.% of familial ALS and 21.1.% of sporadic ALS in a Finnish population (50). The identification of repeat amplification in *C9orf72* adds ALS/FTD to the list of ever-increasing nucleotide repeat amplification diseases, including Huntington's disease, myotonic dystrophy, fragile X syndrome, Friedreich ataxia, and several spinocerebellar ataxia subtypes (53).

The C9orf72 protein is localized mainly in the nucleus, and is structurally similar to the differentially expressed in normal and neoplasia (DENN) proteins. Repeated expansion leads to the loss of an alternative splice of the *C9ORF72* transcript and the formation of nuclear RNA foci (49). Knockdown or knockout of *C9orf72* caused motor phenotype and axonal lesions in zebrafish or worms (54, 55), whereas knockout of *C9orf72* in mice (via intraventricular injection of antisense oligonucleotides) did not (56).

Hypermethylation was reported for the affected allele upstream of GGGGCC repeats (mutated repeat amplification) in a subset (up to 36%) of *C9orf72* cases (57). *C9orf72* hexanucleotide repeat expands itself in ALS and FTD patients (58), which is associated with silenced gene expression by inhibition of histone trimethylation (59). Although *C9orf72* methylation was similar in motor neuron disease and FTD, *C9orf72* hypermethylation was associated with a smaller hexanucleotide repeat length, older age at death, and longer disease duration in FTD, but it also correlates with a shorter disease duration in patients with motor neuron disease (57). These data strongly suggest that hypermethylation has a modulatory effect through gain-of-function mutations, which may be toxic to the nervous system.

2.4. coiled-coil-helix-coiled-coil-helix domain-containing protein 10 gene (CHCHD10)

In 2014, a large family with late-onset neurodegenerative phenotypes including motor neuron disease, cognitive decline similar to frontotemporal dementia, cerebellar ataxia, and myopathy was reported. Using the entire exon sequencing group, *coiled-coil-helix-coiled-coil-helix domain-containing protein 10 gene* (*CHCHD10*, NM 213720.2.) was identified as being associated with FTD and ALS (60, 61). The *CHCHD10* gene located on 22q11.2.3 encodes a mitochondrial protein located in the intermembrane space and is enriched at the cristae junction. *CHCHD10* is predicted to have the MTS fragment, a N-terminal presequence with a length of 15–50 residues, in mitochondrial preproteins enables to target these precursor proteins to mitochondria through TIM/TOM complexes (62).

Subsequent studies have identified *CHCHD10* mutations associated with various phenotypes, mainly ALS and FTD, but also Charcot-Marie-Tooth type 2(63), spinal muscular atrophy (64) and AD (65). Interestingly, studies from China have shown that although *CHCHD10* mutations are rare in ALS (66), there may be a more important cause of FTD (67).

However, how *CHCHD10* mutations cause FTD is unclear. Both endogenous and overexpressed *CHCHD10* S59L altered mitochondrial cristae ultrastructure and caused fragmentation of the

Table 1. Neuroimaging of FTD

Classification	Feature of MRI
Clinical phenotype	
bv-FTD	Dorsolateral, orbital and medial frontal cortices
SD	"Knife-edge" type atrophy of the anterior temporal lobes of the affected side
PNFA	Left-sided perisylvian degeneration
Genotype	
MAPT	Focal symmetrical anterior temporal lobe and orbitofrontal lobe atrophy
GRN	Asymmetric atrophy of the temporal, inferior frontal and inferior parietal lobes
C9orf72	A distributed symmetrical pattern of atrophy

mitochondrial network (68). Overexpression of a *CHCHD10* mutant allele in HeLa cells can leadto fragmentation of the mitochondrial network and ultrastructural major abnormalities including dilatation, disorganization or loss of cristae (60). Mitochondria from *CHCHD10* mutant fibroblasts also showed poor genomic repair post oxidative stress (68).

2.5. others

The FTD-MND phenotype was also reported in the following genetic mutations, including *TARDBP* (69, 70), *FUS* (71, 72), *UBQLN2* (ubiquilin) (73), charged multivesicular body protein 2B (*CHMP2B*) (74, 75), superoxide dismutase (*SOD1*) (76), dynactin 1 (*DCTN1*) (77), angiogenin (*ANG*) (78), Sigma Non-Opioid Intracellular Receptor 1 (*SIGMAR1*) (79), DJ-1 (*PARK 7*) (80), valosin containing protein (*VCP*) (81, 82), and sequestosome 1 (*SQSTM1*) (83).

Evidently, there are significant genetic mutation overlaps between FTD and other neurodegenerative disorders, including AD, ALS, Parkinson's disease (PD) and essential tremor (ET).

3. NEUROIMAGING EXAMINATION OF FTD

Over the course of the last three decades, there has been significant progress in the visualisation of the brain via imaging techniques and our understandings of the morphology of neurodegenerative diseases have greatly advanced (84). Ongoing researches are continuously being conducted to correlate the area of brain atrophy to the clinical manifestations associated with FTD, thus allowing a greater understanding of the anatomical associations of the brain to various cognitive and executive functions.

3.1. Neuroimaging according to clinical phenotypes

The development of computerised tomography (CT) in the 1980s first allowed the visualisation of brain parenchyma. However, in the setting of neurodegenerative diseases, structural imaging is largely conducted using magnetic resonance imaging (MRI) as it achieves better resolution and hence greater details of possibly underlying pathology (84). Each of the subtypes of FTD presents with distinct patterns of brain atrophy on imaging, but early MRI scans may not reveal abnormalities. As the disease progresses, focal atrophy of frontal and temporal lobes, hippocampus and amygdala will become apparent on structural MRI (1, 85). The areas most affected compared to healthy control individuals include the bilateral insula, left middle frontal gyrus, bilateral inferior frontal gyrus, bilateral orbitofrontal gyrus and left precentral gyrus, as well as left and right anterior/inferior cingulate gyrus (86).

3.1.1. bv-FTD

The clinical manifestations of bv-FTD such as personality and behavioural changes, apathy and disinhibition are associated with focal frontal atrophy involving the dorsolateral, orbital and medial frontal cortices. In early disease, the medial paralimbic region is usually first affected, involving the anterior cingulated, orbital frontal and frontoinsular cortices (87, 88). The disease often progresses to involve gray matter in the ventromedial regions, bilateral insula, dorsolateral prefrontal cortext and medial premotor regions. Comparison of frontal lobe volume to healthy controls using MRI is able to correctly identify 93% of bv-FTD patients (89), and there is significantly more atrophy of caudate and putamen compared to other subtypes of FTD (90). Patients with a normal MRI on presentation tend to follow a milder course of disease compared to those with atrophy at presentation, possibly reflecting the difference in contributing pathological substrate (91).

3.1.2. SD

In SD patients, cortical degeneration of the anterior temporal lobe usually predominates on one

side. On coronal MRI, the hallmark of SD is the "knife-edge" type atrophy of the anterior temporal lobes of the affected side. These changes may be subtle and can be easily missed by CTs and even MRIs if coronal views were not obtained (92). Left sided SD patients presents with the typical symptoms of semantic memory loss, whilst right sided SD patients mimic bv-FTD and show significant behavioural change, but tend to have more rigid routines and higher rates of constitutional symptoms when compared with true bv-FTD patients (1). Structurally, SD presents with smaller hippocampal and amygdala volumes when compared to bv-FTD, which are important differentiators diagnostically (93). The caudate nucleus and putamen are relatively preserved (90). Most patients initially present with left-sided atrophy, but the disease will progress to involve the contralateral side after approximately 3 years (94).

3.1.3. PNFA

Patients with PNFA have significant left-sided perisylvian degeneration, focusing on the frontal operculum, premotor and supplementary motor areas as well as the insula (1). On MRI, patients often demonstrate asymmetric atrophy of the left inferolateral and dorsomedial frontal cortices. Specifically, the pars opercularis and the triangularis (Broca's area) as well as the pars orbitalis located on the left inferior frontal gyrus are significantly affected, accounting for the motor component of the aphasia (95). The left precentral gyrus and sulcus are also affected along with the insula, with atrophy extending to the middle frontal gyrus. The caudate nucleus and putamen also have been found to undergo atrophy bilaterally (95), as patients with PNFA demonstrate more marked subcortical atrophy than other FTD subtypes (96).

3.1.4. Metabolic changes on functional neuro-imaging

In addition to structural changes, hypoperfusion and hypometabolism are also indicators of FTLD. Hypoperfusion is best observed in the frontal region for bv-FTD, temporal region for SD and perisylvian regions for PFNA (97, 98), concordant with structural atrophy observed on MRI. Studies such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) have proven to be useful tools to differentiate FTLD from dementias with other underlying pathologies (85), particularly in cases where there are discrepancies between clinical presentation and structural imaging (99). Functional neuroimaging has also contributed to the development of an improved clinical tool for the diagnosis of FTLD, as the FTLD modified Clinical Dementia Rating scores had been found to correlate with the degree of hypoperfusion on SPECT in the frontotemporal lobes of suspected FTLD patients(100).

3.2. Neuroimaging according to genotypes

3.2.1. *MAPT*

Patients with *MAPT* mutations have 10% lower dermal volume than controls (101), and these patients mainly present with focal symmetrical anterior temporal lobe and orbitofrontal lobe atrophy (102). Caudate, insula and anterior cingulate involvement have also been reported (103, 104). In addition, preliminary findings suggest a more lateral temporal lobe signature for *MAPT* mutations in the coding region, while those mutations affecting the splicing of exon 10 target the medial temporal lobes (105). Presymptomatic *MAPT* carriers demonstrated more widespread white matter abnormalities throughout frontotemporal tracts (106), consistent with regions implicated in symptomatic *MAPT* patients. Structural connectivity investigations with diffusion tensor imaging (DTI) found that in bv-FTD patients with a *MAPT* mutation, the cingulum and uncinate fasciculus are particularly affected (107).

Using resting-state fMRI, some studies found that in *MAPT* mutations, reduced connectivity in the lateral temporal and prefrontal regions (part of the default mode network) were demonstrated in some patients (108), while other studies have failed to find significant connectivity changes within these regions in presymptomatic carriers (106). For *MAPT* mutation carriers, differences emerged first in the hippocampus and amygdala (15 years prior to symptoms onset), followed by temporal lobe (10 years prior to symptoms onset) and insula (5 years prior to symptoms onset). Preliminary results from a 56-year-old man with the P301L mutation demonstrated robust retention in characteristic frontotemporal regions, (104) matching known tau pathology in these mutation carriers (103).

3.2.2. *GRN*

For patients with *GRN* mutations, neuroanatomical pathology typically manifest with markedly asymmetric atrophy of the temporal, inferior frontal and inferior parietal lobes (109, 110). Using resting-state fMRI, reduced functional connectivity in the anterior midcingulate cortex (part of the salience network) was found in *GRN* carriers in one study (106), but other studies have either shown increased functional connectivity in the medial prefrontal cortex (111), or no functional connectivity changes at all (112). For *GRN* mutation carriers, abnormlaities first emerged in the insula (15 years before onset), the temporal and parietal lobes (both 10 years before onset) and then striatum (5 years before onset), with

clear imaigng evidence of asymmetry emerging 5 years before expected symptoms.

3.2.3. *C9orf72*

Neuroanatomical signatures with *C9orf72* mutations show a more distributed symmetrical pattern of atrophy, predominantly involving dorsolateral and medial frontal and orbitofrontal lobes, with additional volume loss in anterior temporal, parietal and occipital lobes, as well as in the thalamus and cerebellum (113-115). The *C9orf72* carriers presented with atrophy in subcortical regions including the thalamus, the insula and posterior cortical areas, 25 years before expected symptom onset. This was followed by the frontal and temporal lobes, both 20 years prior to onset and the cerebellum 10 years before expected symptoms. In *C9orf72* mutation carriers, fractional anisotropy reductions have been shown in the superior cerebellar peduncles, consistent with previous findings of cerebellar atrophy in *C9orf72* patients(102, 113, 114).

4. NEUROCHEMICAL BIOMARKERS OF FTD

Recently, the identification of Tau and Aβ42 in CSF was included in the diagnostic criteria of AD (116). Indeed, Tau, pTau181, and Aβ42 are also the most promising biomarker candidates to help differentiating FTD from other dementia, ie. AD and DLB.

4.1. Ratio Aβ42/pTau181

Several meta-analysis that investigated Tau, pTau181, and Aβ42 in FTD and AD had found that CSF Aβ42 is reduced (117), but Tau (118) and pTau181(118, 119) are increased in AD compared to FTD. Given that up to half of FTD patients demonstrate tau pathology in the brain (8), it is unexpected that CSF Tau level is not significantly altered in FTD patients, yet a marked increase is observed in AD (120). Several other studies are in line with these observations (121, 122). For CSF Tau and pTau181, there were little difference reported between FTD and DLB patients, which is also in agreement with previous studies. Aβ42 was shown in previous studies to be slightly decreased in DLB compared with FTD (123, 124) although not always significant (125). Two recent studies reported lower (26–28%) Aβ42 concentrations in the CSF of DLB patients compared with FTD (120, 126) and this could confirm previous observations (123, 124). Tau, pTau181 and Aβ42 are not different between FTD and PD with dementia (PDD) (120). In recent years, studies had found that focusing on the Aβ42/pTau181 ratio allows better differentiation between AD and FTD patients (120). This was supported by two other studies reporting increased sensitivity (80–86%) and specificity (82%) of the Aβ42/pTau181 ratio, compared with the three biomarkers individually (122, 127). A similar improvement was observed for the combination of Aβ42/Tau ratio, with sensitivities and specificities of 70–79% and 84–94% (122), in line with previous observations (128).

4.2. Neurofilament light chain (NfL)

A few new biomarker candidates were suggested to differentiate the diagnosis of AD and FTD. Neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain, are important proteins of the axonal cytoskeleton and increased concentrations of these proteins in CSF are considered as markers of axonal damage (129). In FTD, NfL concentration in CSF has been shown to be higher when compared with AD (124, 130). A large cohort study confirmed that there is an increased (70%) NfL concentrations in FTD (131), and the elevation of NfL is in agreement with the more pronounced white matter degeneration observed in FTD compared to AD (132).

4.3. Neurogranin

One publication reported a very selective increase in neurogranin concentrations, another new biomarker candidates, in AD compared with FTD (90%)(133). Neurogranin is a post-synaptic protein implicated in synaptic plasticity and learning (133). Its use in combination with CSF Aβ42, Tau, pTau181 and endostatin/Aβ42 ratio had been shown to improve the diagnostic accuracy of bvFTD versus AD (134, 135).

5. NEUROPSYCHIATRIC ASSESSMENT FOR FTD

A comprehensive language assessment significantly contribute to the correct diagnosis of FTD, and language testing is crucial in the early differentiation between the behavioral and language variants of FTD(136).

5.1. bvFTD

Patients with bvFTD tend to demonstrate difficulty naming action words, associated with dysfunction in executive abilities. As the disease progresses, many patients develop semantic problems typical for semantic dementia (137). Subjects with bvFTD frequently present with severe pragmatic disturbance, disinhibited output, and stereotypic thematic perseverations.

5.2. PPA

5.2.1. nfvPPA

Patients with nfvPPA typically have effortful and halting speech due to difficulty in articulation, and most subjects begin to experience progressive problems with sentence construction and syntax

Table 2. Clinical trials and treatment in FTD

	Mechanism	Phase	Results
TPI-287	Microtubule stabilizer	I	Unavailable
C2N-8E12	Anti-tau antibody	I	Unavailable
BMS-986168	Anti-tau antibody	I	Unavailable
Salsalate	Tau acetylation inhibitor	I	Unavailable
Nimodipine	Increase progranulin release	I	Unavailable
Davunetide	Microtubule stabilizer	II/III	No effect
Tideglusib	Glycogen synthase kinase-3 inhibitor	II	No effect
FRM-0334	Increase progranulin expression	II	Unavailable
LMTx	Tau aggregation inhibitor	III	Unavailable

Adapted with permission from (157)

relatively early in the course of disease (9, 138) . Therefore, speech becomes agrammatic and difficult to comprehend, often due to a significant lack of verbs as well as phonological errors in conversational speech (139, 140). Additionally, many subjects experience difficulties in reading and writing (141).

5.2.2. svPPA

Patients with svPPA lose the ability to recognize the meaning of words, seen particularly in the context of naming and single-word comprehension (142-144). As the disease progresses, it becomes semantically jargonic, frequently irrelevant to the questions being asked or the topic discussed(145). Problems with single-word comprehension become more evident in the latter stages of disease, even for more common words (146).

5.2.3. lvPPA

Patients with lvPPA do not produce telegraphic speech, have missing function words and morphemes (147), and they usually have severe difficulty repeating and/or comprehending sentences and longer phrases, while reproduction of short phrases and single words remains spared. As the disease progresses, subjects with lvPPA often present with episodic memory impairment (148) as well as acalculia(149).

6. CLINICAL TREATMENT OF FTD

FTD treatment strategies generally rely on the use of medications for symptomatic management, but most therapies lack quality evidence from randomized, placebo-controlled clinical trials(150). Selective serotonin reuptake inhibitors may be effective in the case of behavioral symptoms, while antipsychotics or antiepileptic drugs are also effective in some case reports, but use of these latter agents is limited by the concern of side effects. There is some evidence suggests that glutamate excitotoxicity may play a role in the pathogenesis of bvFTD, therefore the therapeutic effects of memantine (a moderate affinity non-competitive NMDA glutamate and serotonin-3 receptor antagonist) may extend beyond AD and be useful in treating the neuropsychiatric features of FTD(151). However, there is no effective treatment of cognitive declines in FTD, which often involve executive function, memory and language. Motor difficulties associated with FTD may present with parkinsonian symptoms or motor neuron disease, for which riluzole is the preferred therapy. The parkinsonian symptoms usually do not respond to dopamine replacement therapy, although a small number of patients may still experience improvement with a trial of carbidopa-levodopa. Physiotherapy and occupational therapy play an important role in the management of FTD motor symptoms. Speech therapy can also help patients manage symptoms associated with aphasia, aphasia and associated mood disorders (152).

Recently, salsalate, a non-steroidal anti-inflammatory drug was found to inhibit tau acetylation, thus resulting in lower levels of total tau. Salsalate was shown to preserve hippocampal volume and improve memory deficits when given to transgenic mouse modelled to have FTD (153). Salsalate is currently being tested in PSP patients in a small clinical trial (NCT02422485). Additionally, TPI-287, a synthetic taxol-derived compound that crosses the blood-brain barrier developed for neuro-oncology has been studied as a potential therapeutic agent in FTD, and a phase I clinical trial for its use in PSP and CBS is currently being conducted (NCT02133846).

Alkalilzing drugs such as chloroquine, bepridil, and amiodarone that affect endosomal sorting may stimulate PGRN production (154). Unfortunately, a recent pilot study using amiodarone in 5 FTD patients with GRN mutation failed to demonstrate any elevated granulin levels or alter the disease progression (155). A

phase I clinical trial examining the effect of nimodipine, a CNS-penetrant calcium channel blocker in *GRN* mutation carriers was recently completed and results of its effects on serum and CSF PGRN levels should be available soon. A phase 2 clinical trial utilizing FRM-0334, a proprietary histone deacetylase inhibitor that crosses the blood-brain barrier and enhances PGRN expression in preclinical models, is also currently underway in GRN mutation carriers (NCT02149160).

Antisense oligonucleotides (ASO) are synthetic nucleic acids that can inactivate the mRNA of a target gene by direct binding or inducing RNAse H mediated cleavage via a DNA/RNA heteroduplex. ASO may prove to be a viable strategy for FTD patients with *C9orf72* repeat expansions. This therapeutic modality has already been successfully tested in ALS patients with super-oxide dismutase 1 mutation via intrathecal administration, and may serve as a roadmap for treatment development for FTD (156). Several ASO candidates are in pre-clinical development and demonstrated reduction in RNA aggregation without toxic effects preliminarily (157).

7. CONCLUSION

The field of genomic sequencing and novel biomarkers in FTD has made significant advances over the past 5 years. New techniques such as next generation sequencing have led to the identification of new genetic risk factors for the disease. Unfortunately, to date, it still lacks an effective treatment to alter the course of progression in FTD. Further identification of neuroimaging and neurochemical biomarkers that can reliably detect the disease prior to the onset of symptoms would be required in order to achieve pre-symptomatic identification of FTD and potential therapeutic modalities to halt disease progression. Hopefully, the era of precision medicine for FTD to establish the diagnosis and individualized treatment will soon be materialized with the continual advances of genetics and molecular biomarkers in the near future.

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