Molecular imaging biomarkers in familial frontotemporal lobar degeneration: Progress and prospects

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Familial frontotemporal lobar degeneration (FTLD) is a pathologically heterogeneous group of neurodegenerative diseases with diverse genotypes and clinical phenotypes. Three major mutations were reported in patients with familial FTLD, namely, progranulin (GRN), microtubule-associated protein tau (MAPT), and the chromosome 9 open reading frame 72 (C9orf72) repeat expansion, which could cause neurodegenerative pathological changes years before symptom onset. Noninvasive quantitative molecular imaging with PET or single-photon emission CT (SPECT) allows for selective visualization of the molecular targets in vivo to investigate brain metabolism, perfusion, neuroinflammation, and pathophysiological changes. There was increasing evidence that several molecular imaging biomarkers tend to serve as biomarkers to reveal the early brain abnormalities in familial FTLD. Tau-PET with \textsuperscript{18}F-flortaucipir and \textsuperscript{11}C-PBB3 demonstrated the elevated tau position in patients with FTLD and also showed the ability to differentiate patterns among the different subtypes of the mutations in familial FTLD. Furthermore, dopamine transporter imaging with the \textsuperscript{11}C-DOPA and \textsuperscript{11}C-CFT in PET and the \textsuperscript{123}I-FP-CIT in SPECT revealed the loss of dopaminergic neurons in the asymptomatic and symptomatic patients of familial FTLD. In addition, PET imaging with the \textsuperscript{11}C-MP4A has demonstrated reduced acetylcholinesterase (AChE) activity in patients with FTLD, while PET with the \textsuperscript{11}C-DAA1106 and \textsuperscript{11}C-PK11195 revealed an increased level of microglial activation associated with neuroinflammation even before the onset of symptoms in familial FTLD. \textsuperscript{18}F-fluorodeoxyglucose (FDG)-PET indicated hypometabolism in FTLD with different mutations preceded the atrophy on MRI. Identifying molecular imaging biomarkers for familial FTLD is important for the in-vivo assessment of underlying pathophysiological changes with disease progression and future disease-modifying therapy. We review the recent progress of molecular imaging in familial FTLD with focused on the possible implication of these techniques and their prospects in specific mutation types.

\textbf{KEYWORDS}  
familial frontotemporal lobar degeneration, molecular imaging, biomarkers, MAPT, GRN, C9orf72
Introduction

Frontotemporal lobar degeneration (FTLD) encompasses a set of clinical syndromes characterized by progressive abnormalities in behavior, executive function, language, or motor function. Patients with FTLD may present clinical syndromes with the behavioral variant of frontotemporal dementia (bvFTD), the nonfluent variant of a primary progressive aphasia (nfvPPA), a semantic variant of PPA (svPPA), and some patients also have amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) (1). Approximately, 40% of patients with FTLD have a positive family history of autosomal dominant inheritance (2). Three major mutations were reported in patients with familial FTLD, namely, the microtubule-associated protein tau (MAPT), progranulin (GRN), and the repeat expansions in the chromosome 9 open reading frame 72 (C9orf72). These mutations could lead to neurodegenerative pathological changes years before symptom onset (2, 3).

Mutations in the MAPT gene located on chromosome 17q21 first reported in 1998 (4) were discovered in numerous pedigrees of familial FTLD. The majority of known mutations in the coding region occur in the repeats, causing the decreased ability of tau proteins to interact with microtubules, and resulting in hyperphosphorylated tau accumulation in neurons and glial cells (5). MAPT mutations of different subtypes have been linked to various tauopathies. Generally, the mutations inside exon 10 (i.e., N279K, S305N, P301L) and intron 10 (i.e., IVS 10 + 16) tend to form four tandem microtubule-binding domain repeat (4R-tau) pathology, while mutations outside exon 10 (i.e., V337M, R406W, Q351R) tend to form mixed 3R/4R tauopathy similar to the tauopathy in Alzheimer’s disease (6).

Mutations in the GRN linked to chromosome 17q21 initially reported in 2006 (7, 8) could result in a lack of progranulin by haploinsufficiency and the accumulation of TAR DNA-binding protein (TDP)-43 protein (9). GRN mutation carriers have a wide range of clinical phenotypes and illness onset ages. The bvFTD, CBS, and PPA are the most common clinical syndromes in patients with GRN mutation (10, 11).

The hexanucleotide GGGGCC (G4C2) repeat expansions of the C9orf72 were identified as a common genetic cause of FTLD and ALS in 2011 (12, 13). TDP-43 aggregations were pathologically discovered in cases with C9orf72 expansions (14). The most prevalent clinical syndromes were bvFTD, ALS, or a mixture of both in C9orf72 mutation carriers (14, 15).

Currently, the visual inspection of MRI was demonstrated to easily increase the diagnostic confidence of underlying FTLD (16, 17). The cortical microstructure was found to be more sensitive than cerebral atrophy within patients with GRN mutations (18), suggesting the powerful value of MRI to correctly diagnose and capture the early abnormalities in familial FTLD. Noninvasive quantitative molecular imaging with PET or single-photon emission CT (SPECT) provided another perspective and allowed for selective visualization of the molecular targets in vivo to investigate the brain topographic and pathophysiological changes. The former included metabolism, perfusion, neuroinflammation, synaptic function, and neurotransmitters’ activity, and the latter comprised Tau and Aβ aggregation. There was increasing evidence that several molecular imaging biomarkers tend to serve as biomarkers to reveal the early brain abnormalities in familial FTLD. Identifying molecular imaging biomarkers for familial FTLD is important for the in-vivo assessment of underlying pathophysiological changes with disease progression and future disease-modifying therapy. Thus, we review the recent progress of molecular imaging in familial FTLD with a focus on the possible implication of these techniques and their prospects in specific mutation types.

Methods

Search strategy

We performed electronic searches of Medline, PubMed, and Embase databases using the combination of a number of medical subject headings, Emtree subject headings, and free-text terms (“frontotemporal lobar degeneration,” “frontotemporal dementia” for clinical categories; “microtubule-associated protein tau” or “MAPT,” “progranulin” or “GRN,” and “chromosome 9 open reading frame 72” or “C9orf72” for genes; “positron emission tomography” or “PET,” “single-photon emission CT” or “SPECT,” and “dopamine transporter imaging” for molecular imaging biomarkers). The retrieval deadline was 1 December 2021. All the relevant articles were retrieved, placing restrictions on #elds (free-text terms searched exclusively in the title or abstract of the articles) and publication type (original articles).

Discussion

Pathophysiological biomarkers

Tau studies

Tau-PET is currently being explored as a promising method to identify the tau protein in vivo (19). Several types of tracers have been applied to map the pattern of tau accumulation in familial FTLD, especially in individuals with MAPT mutations thought to be tauopathy. 18F-flortaucipir, the most commonly used tau tracer, has been proven to bind paired helical filaments composed of 3R/4R tau in Alzheimer’s disease (AD) (20, 21). In recent years, other tracers, including 11C-PBB3 (22), 18F-MK6240 (23), and 18F-PMPBB3 (24), started to be applied in MAPT mutation carriers. 11C-PBB3 could capture wide-ranging Tau pathologies, including 3R/4R tau and 4R tau (25, 26) compared to 18F-flortaucipir (27). For 18F-MK6240 and
| No. | References | No. of subjects | Techniques | Findings |
|-----|------------|----------------|------------|----------|
| 1   | Arvanitakis et al. (43) | (2 sMApT+, 5 sMApT+) vs. 3 NC | ^18^F-FDG PET | Asymmetric temporal lobe hypometabolism in 7 sMApT+ carriers than sMApT- carriers |
| 2   | Laws et al. (44) | (31 sMApT_H1+ 10 sMApT_H2) vs. 16 HC | ^18^F-FDG PET | More pronounced hypometabolism in frontal brain areas of H2 carriers than H1 carriers |
| 3   | Deters et al. (45) | (3 sMApT+, 8 sMApT+) vs. 8 NC | ^18^F-FDG PET | Hypometabolism bilaterally in the medial temporal lobe, and the parietal and frontal cortices |
| 4   | Yang et al. (46) | 2 sMApT+ vs. 1 NC | ^18^F-FDG PET | Hypometabolism in extensive prefrontal areas, and hypermetabolism in the putamen, globus pallidum, cerebellum, and sensorimotor cortex |
| 5   | Su et al. (24) | 1 sMApT+ vs. HC | ^18^F-FDG PET | Brain metabolism significantly decreased in bilateral temporal lobes and moderately decreased in bilateral frontal lobes with more remarkable in the left side |
| 6   | Clarke et al. (47) | 6 sMApT+ vs. 12 NC | ^18^F-FDG PET | Hypometabolism in the anterior cingulate |
| 7   | Bevan Jones et al. (36) | 1 sMApT+ vs. 12 HC | ^18^F-flortaucipir PET | Increased tau accumulation in the anterior temporal lobes and ventral anterior cingulate cortex |
| 8   | Smith et al. (39) | 3 sMApT+ vs. 4 HC | ^18^F-flortaucipir PET | Increased tau accumulation mainly in the hippocampus and adjacent temporal lobe regions of 2 sMApT+ with short disease duration and isolated memory impairment; the temporal, frontal lobes, and basal ganglia of 1 sMApT+ with long disease duration and behavioral deficits |
| 9   | Spina et al. (41) | 1 sMApT+ vs. 20 HC | ^18^F-flortaucipir PET | Increased tau accumulation in the bilateral frontal pole, medial orbitofrontal cortex, inferior temporal lobe, insular cortex, anterior cingulate, dorsolateral prefrontal cortex, and lateral temporal cortex |
| 10  | Jones et al. (34) | (3 sMApT+, 10 sMApT+) vs. 241 HC vs. 30 AD | ^18^F-flortaucipir PET | The greatest tau accumulation in AD and minimal regional tau accumulation in MAPT+ with mutations in exon 10 |
| 11  | Bevan Jones et al. (35) | 1 sMApT+ vs. 13 HC | ^18^F-flortaucipir PET | A lack of tau aggregation in frontotemporal regions |
| 12  | Tsai et al. (42) | 6 sMApT+ vs. 53 HC | ^18^F-flortaucipir PET | Tau depositions in left insula and bilateral temporal poles |
| 13  | Convery et al. (37) | 1 sMApT+ vs. 6 HC | ^18^F-flortaucipir PET | Baseline: tau aggregation in the insula region cortically, and the medial temporal, putamen, and pallidum regions subcortically Follow-up: tau aggregation in the same regions as at baseline but also the temporal region cortically and caudate and thalamus regions subcortically |
| 14  | Soleimani-Meigooni et al. (40) | 2 sMApT+ vs. 14 HC | ^18^F-flortaucipir PET | Tau depositions in the temporal lobes, temporal white matter, and basal ganglia |
| 15  | Malpetti et al. (48) | 2 sMApT+ vs. 15 HC | ^18^F-flortaucipir PET | Consistent tau deposition distribution in frontotemporal regions in 2 sMApT+ |
| 16  | Ikeda et al. (22) | 4 sMApT+ vs. 13 HC | ^11^C-PBB3 PET | Mild tau depositions in the midbrain and medial temporal areas of 2 sMApT+ from kindred with slow progression; profoundly increased tau depositions in widespread regions of 2 sMApT+ from kindreds with rapid progression |
| 17  | Su et al. (24) | 1 sMApT+ vs. HC | ^18^F-PMPBB3 PET | Slightly diffuse tau deposition especially in the left frontal lobe |
| 18  | Levy et al. (23) | (3 sMApT+, 3 sMApT+) vs. 83 HC | ^18^F-MK-6240 PET | At least mild but significant tau deposition in 3 sMApT+; modest tau deposition in 2 sMApT+ within 5 years from estimated onset; no tau deposition in 1 sMApT+ about 30 years from estimated onset |
| 19  | Miyoshi et al. (49) | 3 sMApT+ vs. 9 HC | ^11^C-DOPA PET | Low dopamine synthesis in putamen |
| 20  | Yang et al. (46) | 2 sMApT+ vs. 1 NC | ^11^C-CFT PET | Dopaminergic dysfunction in the caudate nucleus and putamen |

(Continued)
The heterogeneous results might be due to the fact that MAPT mutation carriers, temporal, frontal lobes, and the basal ganglia might be an early biomarker for disease progression in symptomatic MAPT mutation carriers. However, the majority of research was based on case reports or cross-sectional studies with small sample size. Longitudinal data with larger cohorts will be required for such investigations.

Two studies applied $^{11}$C/$^{18}$F-PBB3 tracking both the 3R/4R tau and 4R tau in symptomatic MAPT mutation carriers (22, 24). In four patients with MAPT N279K mutation, the kindreds with slow progression exhibited mild binding; in contrast, kindreds with rapid progression showed profoundly increased binding in widespread regions from an early disease stage (22). Recently, a study of $^{18}$F-MK-6240 in two asymptomatic MAPT P301L mutation carriers showed modest tau deposition about 5 years from estimated onset (23), indicating that $^{18}$F-MK-6240 uptake might be an early biomarker for MAPT P301L mutation carriers (Table 1).
Similarly, findings among symptomatic GRN
 carriers. Therefore, novel tracers for multiform tau
pathologies need to be further explored in longitudinal
studies with larger cohorts.

**GRN/C9orf72_Tau-PET**

Three studies reported $^{18}$F-flortaucipir binding in the
frontotemporal region in five symptomatic GRN
mutation carriers (38, 40, 42), whereas another research
found no $^{18}$F-flortaucipir binding in a patient with GRN
mutation (53) (Table 2). Similarly, findings among symptomatic C9orf72
mutation carriers were contradictory. Ten patients with C9orf72
mutation had increased $^{18}$F-flortaucipir binding in the frontal
lobe (38, 40, 42, 64), while another study found no tau
deposition in six patients with C9orf72 mutation (65) (Table 3).

**TABLE 2** Studies investigated asymptomatic/symptomatic GRN carriers.

| No. | References   | No. of subjects | Techniques           | Findings                                      |
|-----|--------------|-----------------|----------------------|-----------------------------------------------|
| 1   | Huey et al.  | 2 sGRN+         | $^{18}$F-FDG PET     | Predominant right-sided hypometabolism        |
| 2   | Jacova et al. | 9 GRN+ (4 sGRN+) vs. 11 NC | $^{18}$F-FDG PET | GRN+ showed an overall pattern of right anterior cerebral hypometabolism |
| 3   | Josephs et al. | 3 sGRN+ vs. 3 sNC vs. 26 HC | $^{18}$F-FDG PET | sGRN+ and sNC vs. HC: left temporoparietal hypometabolism |
| 4   | Caroppo et al. | Baseline: 16 sGRN+ VS 17 NC | Follow-up: 14 sGRN+ VS 14 NC | Baseline: left middle temporal gyrus hypometabolism |
| 5   | Licata et al. | 10 sGRN+ vs. 23 HC | $^{18}$F-FDG PET | Inter-individual variability of FDG uptake pattern in sGRN+. All sGRN+ showed frontal hypometabolism. Asymmetrical metabolism in half of sGRN+ |
| 6   | Deng et al.  | 1 sGRN+         | $^{18}$F-FDG PET     | Bifrontal and bitemporal hypometabolism       |
| 7   | Ljubenkov et al. | 26 GRN+ (18 sGRN+) vs. 52 HC | $^{18}$F-FDG PET | Left-predominant hypometabolism in dorsal prefrontal, anterior cingulate, orbitofrontal, inferior frontal gyrus, insular, lateral parietal, lateral temporal, posterior cingulate, caudate, and thalamic regions |
| 8   | Lagarde et al. | 1 sGRN+ vs. 8 sporadic FTLD | $^{18}$F-flortaucipir PET | No tau binding in sGRN+; tau binding in 5/8 sNC |
| 9   | Careccio et al. | 1 sGRN+        | DaTScan (I-123 ioflupane SPECT) | Reduced tracer uptake in the left putamen |
| 10  | Deng et al.  | 1 sGRN+         | $^{18}$F-DOPA PET    | $^{18}$F-DOPA: reduced DOPA metabolism in bilateral corpus striatum |
| 11  | Josephs et al. | 3 sGRN+ vs. 3 sporadic FTLD vs. 26 HC | Amyloid-PET (C-11 C-Pb) | Negative in all participants (cut-off score of <1.5). sGRN+ had lower PiB-PET ratios compared to sNC |
| 12  | Dopper et al. | 1 sGRN+         | $^{99m}$Tc-HMPAO SPECT | Symmetrical frontoparietal hypoperfusion. |
| 13  | Premi et al. | 13 sGRN+ vs. 13 sporadic FTLD vs. 13 HC | $^{99m}$Tc-ECD SPECT | sGRN+ and sNC vs. HC: hyperperfusion in frontotemporal areas sGRN+ vs. sNC: hyperperfusion in anterior cingulate cortex and left dorsolateral prefrontal cortex |
| 14  | Careccio et al. | 1 sGRN+        | perfusion SPECT      | Left predominant bifrontal with homolateral parieto-temporal hypoperfusion |

GRN+, GRN mutation carriers; NC, non-carriers; HC, healthy controls; sGRN+, symptomatic GRN mutation carriers; aGRN+, asymptomatic GRN mutation carriers; FDG, fluorodeoxyglucose; ECD, ethylcysteinate dimer; HMPAO, hexamethylpropylene amine oxime; PiB, Pittsburgh compound B; DaTscan, dopamine transporter scan; PET, positron emission tomography; SPECT, single photon emission computed tomography.

In MAPT mutation carriers, the value of tau PET for capturing tau accumulation has been primarily proved, and the tau aggregation patterns were associated with the subtypes of mutations and tracers. Therefore, novel tracers for multiform tau pathologies need to be further explored in longitudinal studies with larger cohorts.
To detect the underlying AD pathology, amyloid-PET with tracers, including \(^{11}\)C-Pittsburgh compound B (PIB) (42, 67, 70, 76), \(^{18}\)F-florbetapir (24), \(^{18}\)F-florbetaben (23), \(^{18}\)F-flutafuranol (78), \(^{18}\)F-flutemetamol (39, 79), etc., is applied in patients with familial FTLD. Most patients with MAPT mutation indicated negative results with \(^{11}\)C-PiB or \(^{18}\)F-florbetapir PET (23, 24, 39, 42), while two patients with MAPT P301L mutation had a positive \(^{11}\)C-PiB scan (40, 42). However, one might imply an incidental rather than preclinical \(\beta\)-amyloid pathology since the SUVs were well below those seen in AD (42); in contrast, the other regarded as combining with AD presented higher SUVs close to AD (40). Negative results with \(^{11}\)C-PiB or \(^{18}\)F-flutafuranol were reported in patients with GRN and C9orf72 mutation carriers so far (23, 42, 56, 76). Thus, amyloid-PET may help discriminate true underlying AD co-pathology from incidental \(\beta\)-amyloid pathology (80) (Table 4).

### Amyloid studies

To detect the underlying AD pathology, amyloid-PET with tracers, including \(^{11}\)C-Pittsburgh compound B (Pib) (42, 67, 70, 76), \(^{18}\)F-florbetapir (24), \(^{18}\)F-florbetaben (23), \(^{18}\)F-flutafuranol (78), \(^{18}\)F-flutemetamol (39, 79), etc., is applied in patients with familial FTLD. Most patients with MAPT mutation indicated negative results with \(^{11}\)C-PiB or \(^{18}\)F-florbetapir PET (23, 24, 39, 42), while two patients with MAPT P301L mutation had a positive \(^{11}\)C-PiB scan (40, 42). However, one might imply an incidental rather than preclinical \(\beta\)-amyloid pathology since the SUVs were well below those seen in AD (42); in contrast, the other regarded as combining with AD presented higher SUVs close to AD (40). Negative results with \(^{11}\)C-PiB or \(^{18}\)F-flutafuranol were reported in patients with GRN and C9orf72 mutation carriers so far (23, 42, 56, 76). Thus, amyloid-PET may help discriminate true underlying AD co-pathology from incidental \(\beta\)-amyloid pathology (80) (Table 4).

### Topographic biomarkers

#### Brain metabolism

\(^{18}\)F-fluorodeoxyglucose (FDG)-PET is a technique for measuring glucose metabolism in vivo (82). Studies of FDG-PET could capture the different patterns of brain hypometabolism and even precede brain atrophy in familial FTLD mutation carriers (43, 45, 47, 55, 57, 72, 83).

### MAPT_FDG-PET

A few cross-sectional FDG-PET studies demonstrated brain hypometabolism in both the asymptomatic and symptomatic
### TABLE 4  Studies investigating multiple different mutations in FTLD.

| No. | References | No. of subjects | Techniques | Findings |
|-----|------------|-----------------|------------|----------|
| 1   | Tsai et al. (42) | 6 sMAPT+ vs. 5 sC9+ vs. 1 sGRN+ vs. 53 HC | 18F-flortaucipir PET | Tau deposition in the left insula and bilateral temporal poles of sMAPT+; the left lateral frontal, parietal and temporal lobes of sGRN+; the frontal poles of sC9+ with varying degrees |
| 2   | Soleimani-Meigooni et al. (40) | 2 sMAPT+ vs. 1 sC9+ vs. 1 sGRN+ vs. 14 HC | 18F-flortaucipir PET | Tau deposition was less than Alzheimer's disease, though higher than HC, and did not reliably correspond with post-mortem tau pathology for all mutation groups |
| 3   | Malpetti et al. (48) | 2 sMAPT+ vs. 3 sC9+ vs. 2 sGRN+ vs. 15 HC | 18F-flortaucipir PET | Consistent tau deposition distribution (overlapped with that of 11C-PK11195, but was more extensive) in 2 sMAPT+, heterogeneous tau deposition distributions among sGRN+ and sC9+ |
| 4   | Levy et al. (23) | (3 sMAPT+, 3 sMAPT+) vs. 2 sC9+ vs. 2 sGRN+ vs. 83 HC | 18F-MK-6240 PET | At least mild but significant tau deposition in 3 sMAPT+; modest tau deposition in 2 sMAPT+ within 5 years from estimated onset; no tau deposition in 1 sMAPT+ about 30 years from estimated onset Negative for 2 sGRN+; and 1 advanced sC9+ showed minimal regionally non-specific binding |
| 5   | Tsai et al. (42) | 5 sMAPT+ vs. 4 sC9+ vs. 1 sGRN+ vs. 53 HC | Amyloid-PET (11C-PiB) | Positive in 1 sMAPT+ and 1 sGRN+ |
| 6   | Levy et al. (23) | (3 sMAPT+, 3 sMAPT+) vs. 2 sC9+ vs. 2 sGRN+ vs. 83 HC | Amyloid-PET (18F-flutafuranol) | Negative in all participants |
| 7   | Seelaar et al. (51) | 10 sMAPT+ vs. 19 FTLD-TDP (6 GRN+, 5 Ser82ValX174+, 1 Gln125X+, 13 unknown gene defect) vs. 10 HC | 99mTc-HMPAO SPECT | Hypoperfusion in the right frontal lobe, precuneus, cuneus, and inferior parietal lobule of familial FTLD-TDP; in the left temporal and inferior frontal gyri of MAPT+ |
| 8   | Lant et al. (81) | 10 sMAPT+ vs. 9 sC9+ vs. 8 sGRN+ vs. 13 AD vs. 13 HC | 11C-PK11195 PET | Significantly microglial activation in all four regions (cortical gray and subcortical white matter of frontal and temporal) of FTLD-Greater microglial activation of frontal subcortical white matter in FTLD than AD, temporal cortical gray matter in contrast Microglial activation was higher in FTLD-MAPT than other genetic forms (GRN, C9) |
| 9   | Malpetti et al. (48) | 2 sMAPT+ vs. 3 sC9+ vs. 2 sGRN+ vs. 15 HC | 11C-PK11195 PET | Increased microglial activation predominantly in frontotemporal regions for all mutation groups |

*FTLD, frontotemporal lobar degeneration; TDP, TAR DNA binding protein; sMAPT+, asymptomatic MAPT mutation carriers; sMAPT-, symptomatic MAPT mutation carriers; sC9+, symptomatic C9orf72 mutation carriers; sGRN+, symptomatic GRN mutation carriers; HC, healthy controls; NC, non-carriers; HMPAO, hexamethylpropylene amine oxime; PiB, Pittsburgh compound B; PET, positron emission tomography; SPECT, single photon emission computed tomography.*

**MAPT** mutation carriers (24, 43, 45–47). Hypometabolism in the temporal lobe (43, 45) and anterior cingulate cortex (47) was reported in asymptomatic **MAPT** mutation carriers, while temporal lobe hypometabolism even preceded the brain atrophy on MRI in the asymptomatic stage (43). In symptomatic **MAPT** mutation carriers, hypometabolism regions spread extensively to the frontotemporal lobes (24, 43, 46), while hypermetabolism was also found in the putamen, globus pallidum, cerebellum, and sensorimotor cortex (46). These findings all pointed to early involvement of the temporal lobe in asymptomatic **MAPT** mutation carriers. Furthermore, only one study compared three asymptomatic **MAPT** mutation carriers and 8 symptomatic
MAPT mutation carriers, but found no difference in FDG uptake [45], which was mainly due to the small sample size. However, most current studies were cross-sectional with a small cohort, and further studies are needed to characterize the trajectories of metabolism patterns from asymptomatic to symptomatic MAPT mutation carriers.

GRN_FDG-PET

Two studies indicated asymmetric temporal lobe hypometabolism with FDG-PET in asymptomatic GRN mutation carriers [55, 57]. After 20 months of follow-up, hypometabolism spread to the frontal lobe and thalamus [57]. The metabolic changes appeared before brain atrophy on MRI and approximately more than 10 years before clinical onset [57], suggesting that FDG-PET changes can be detected as early biomarkers in GRN mutation carriers. In symptomatic GRN mutation carriers, the asymmetrical hypometabolism of temporoparietal [56] and frontal [58] lobes was reported primarily based on a small number of cross-sectional studies or case reports. Hypometabolism patterns were observed to correlate with clinical manifestations [56], but another study failed to find clear metabolic change pattern in each clinical subtype [58].

C9orf72_FDG-PET

In asymptomatic C9orf72 mutation carriers, extensive hypometabolism was observed in frontotemporal and subcortical regions in two studies [75, 77]. Thalami hypometabolism was found in both the asymptomatic [75, 77] and symptomatic [72] individuals with C9orf72 mutation, especially when compared to sporadic FTLD patients [72], suggesting that thalami could be a distinguishing early biomarker for C9orf72 mutation carriers. In symptomatic C9orf72 mutation carriers, some studies showed that the hypometabolism patterns were consistent with the clinical diagnosis and correlated well with the brain atrophy on MRI, for example, prevalent frontal hypometabolism in patients with bvFTD and temporal polar and lateral temporal hypometabolism in patient with svPPA [66, 69, 71, 74]. However, the cross-sectional studies above with small sample sizes still need to be replicated in longitudinal studies with larger cohorts.

Most studies demonstrated the concordance between structural MRI and FDG-PET in MAPT [43, 45], GRN [84, 85], and C9orf72 [74, 77] mutation carriers. However, controversy still existed regarding the earlier or more sensitive biomarkers [43, 45, 77]. Some studies showed that additional informative MRI modalities such as diffusion tensor imaging (DTI) and arterial spin labeling (ASL) had equivalent or even better diagnostic utility of FTLD compared with FDG-PET [86–89], but others found a gap in sensitivity or accuracy that still remained [90, 91]. Further investigations of familial FTLD need to compare the clinical value of microstructural MRI and PET.

Dopaminergic system

Dopamine functional deficits can be measured in vivo via PET or SPECT with various types of tracers assessing dopamine synthesis and storage [18F-DOPA, 11C-DOPA, 11C-dihydroxydopamine (DTRZ), 18F-fluoropropyl-DTBZ, etc.], transporter density [123I-FP-CIT, 123I-ioflupane, 11C-CFT, 99mTc-TRODAT, etc.], or postsynaptic terminals [11C-carfentanil, 123I-i-doibenzoamide (IBZM), etc.] [92]. Dopaminergic deficits were evaluated by the techniques mentioned above, especially in patients with familial FTLD with Parkinsonism.

Parkinsonism may present as the initial symptom in MAPT mutation carriers, particularly individuals with MAPT N279K mutation. Tracers such as 11C-DOPA and 2b-carbomethoxy-3b-(4-trmethylstannylphenyl) tropane (11C-CFT) were used to reveal dopaminergic function. The 11C-CFT uptake in the putamen was mildly low in asymptomatic MAPT N279K mutation carriers [49, 50]. In symptomatic patients, both the caudate nucleus and putamen were involved more heavily [46, 50].

Individuals with GRN mutations and Parkinsonism could show reduced DOPA metabolism in bilateral corpus striatum by 18F-DOPA PET [59] or reduced tracer uptake in left putamen by 123I-ioflupane SPECT [61]. Parkinsonism is not uncommon in GRN mutation carriers and sporadic patients with FTLD.

Brain perfusion

Perfusion SPECT is a well-established technique for measuring regional cerebral blood flow (rCBF) to assess brain function [93]. The tracers utilized in brain perfusion SPECT are technetium-99m-hexamethylpropyleneamineoxime (99mTc-HMPAO) and technetium-99m-ethylcysteinate dimer (99mTc-ECD), both which are distributed proportionally to rCBF [93]. Perfusion imaging has been widely used in the clinical evaluation of patients with neurological and psychiatric diseases [94], including FTLD.

In 11 MAPT mutation carriers, including eight in P301L, two in G272V, and one in G389R, significant hypoperfusion detected by 99mTc-HMPAO SPECT was found in the asymmetric frontotemporal lobes [51, 52]. Several studies indicated that hypoperfusion occurred in frontotemporal areas of GRN mutation carriers [61–63]. Compared with MAPT mutation carriers, patients with GRN mutation exhibited relatively more posterior hypoperfusion, including the precuneus and inferior parietal lobule detected by 99mTc-HMPAO SPECT [51]. Perfusion SPECT might be a potential biomarker to identify MAPT and GRN mutation carriers.

Neuroinflammation

Previous studies of genome-wide association [95] and animal [96] suggest that neuroinflammation might be an
earlier process in FTLD, even preceding tau accumulation. The neuroinflammation is accompanied by the activation of microglia, and 18 kDa TSPO, previously known as peripheral benzodiazepine receptors, is highly expressed (97). Thus, radioligands (\(^{11}\)C-PK11195, \(^{11}\)C-DAA1106) have been developed to target TSPO to visualize neuroinflammation in vivo (98, 99).

In asymptomatic MAPT mutation carriers, two studies with \(^{11}\)C-PK11195 PET (35) or \(^{11}\)C-DAA1106 PET (49) revealed increased levels of microglial activation, even despite a lack of significant atrophy or \(^{18}\)F-flortaucipir uptake (35). In symptomatic patients, \(^{18}\)F-flortaucipir binding overlapped with \(^{11}\)C-PK11195 binding and was more extensive across the brain (38). These findings suggest that neuroinflammation might facilitate tau aggregation initially, then tau-mediated neurodegeneration takes the dominant role. Combining different modalities in a relatively homogeneous group such as familial FTLD with a specific mutation subtype would better understand the underlying mechanism of disease progression.

Across different mutation subtypes, familial patients with FTLD with MAPT, GRN, and C9orf72 mutations all showed increased \(^{11}\)C-PK11195 binding predominantly in frontotemporal regions (38), and \(^{11}\)C-PK11195 binding was significantly higher in temporal subcortical white matter in MAPT mutation carriers than in other genetic (GRN, C9orf72) mutation carriers or sporadic FTLD (81). Future studies could add more details to the neuroinflammation patterns of subtypes of familial FTLD.

**Synaptic function and acetylcholinesterase activity**

The synaptic vesicle glycoprotein 2A (SV2A) is a transmembrane protein ubiquitously expressed in secretory vesicles of synapsis in all the brain areas (100). It is critical for synaptic function (101), and it has been related to neurologic disorders such as AD and epilepsy (102–104). The density of SV2A could be quantified by the newly developed tracer \(^{11}\)C-UCB-J (105). Reduced synaptic density in the thalamus detected by \(^{11}\)C-UCB-J was found in three asymptomatic C9orf72 mutation carriers compared to healthy controls. It proved the role of the thalamus in C9orf72 mutation carriers again, especially before symptom onset (48). There is a lack of studies on synaptic density mapping in other early staged mutation carriers. Thus, its value and correspondence with other imaging techniques remain unknown.

\(^{11}\)C-MP4A PET could reflect acetylcholinesterase (AChE) activity in vivo. A study showed reduced AChE activity in the temporoparietal cortex in one of three asymptomatic MAPT N279K mutation carriers (49). Therefore, more studies with larger sample sizes are needed to provide further evidence for \(^{11}\)C-MP4A PET in familial FTLD.

**Challenges and limitations of molecular imaging**

Even though more and more tracers were approved by the US Food and Drug Administration and by the European Medicines Agency for clinical usage (106), the higher cost and longer acquisition times compared to MRI might limit the wide applications in clinical practice (107). Changes in the levels of human fluid components could reflect underlying pathophysiological processes, and several fluid biomarkers were available or showed potential values such as A\(\beta\), tau, NfL, and progranulin. A lack of multicenter standardization of procedures and quality control would compromise the stability and reliability of outcomes (108). By contrast, molecular imaging could provide more robust and comprehensive (quantitative and spatial distribution) information. However, the unspecific binding was still a challenge. Off-target binding of first-generation tau tracers such as \(^{18}\)F-flortaucipir might interfere with the quantification in several brain regions (109). Further development of 4R tau and TDP-43 specific tracers was needed to move toward precise diagnoses in FTLD. Several studies demonstrated that some molecular imaging biomarkers of FTLD with mutations could be different from sporadic individuals (72, 81), suggesting findings in genetic FTLD that may not translate to sporadic FTLD.

**Conclusion**

This review summarized recent molecular imaging findings in familial frontotemporal lobar degeneration regarding common genetic mutations. The application of advanced neuroimaging techniques in monogenetic familial FTLD provides a unique opportunity to study specific proteinopathies and their clinical phenotypes. Although various study designs and data analysis methods generated heterogeneous nonspecific results, some key biomarkers could still be identified, pointing to specific brain regions worth further exploring. The combination of multimodal neuroimaging would also help identify the underlying mechanism of these biomarkers. To date, this research topic has been limited by a large multicenter longitudinal cohort study and a comparison between asymptomatic/symptomatic mutation carriers and sporadic patients with FTLD. Thus, the changes in different time points of these biomarkers between FTLD mutation carriers and sporadic ones are largely unknown, and the prognostic value of these biomarkers is still unclear. Future
studies could focus on these issues and provide more insight into the significance of these molecular imaging methods and their findings.

**Author contributions**

RW contributed to data collection, analysis and interpretation of the data, and drafting of the manuscript. HG contributed to analysis and interpretation of the data and drafting of the manuscript. HX and ZJ revised the manuscript. QC contributed to design the study, interpretation of the data, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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