MicroRNA biomarkers in frontotemporal dementia and to distinguish from Alzheimer’s disease and amyotrophic lateral sclerosis

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Abstract
Frontotemporal lobar degeneration describes a group of progressive brain disorders that primarily are associated with atrophy of the prefrontal and anterior temporal lobes. Frontotemporal lobar degeneration is considered to be equivalent to frontotemporal dementia. Frontotemporal dementia is characterized by progressive impairments in behavior, executive function, and language. There are two main clinical subtypes: behavioral-variant frontotemporal dementia and primary progressive aphasia. The early diagnosis of frontotemporal dementia is critical for developing management strategies and interventions for these patients. Without validated biomarkers, the clinical diagnosis depends on recognizing all the core or necessary neuropsychiatric features, but misdiagnosis often occurs due to overlap with a range of neurologic and psychiatric disorders. In the studies reviewed a very large number of microRNAs were found to be dysregulated but with limited overlap between individual studies. Measurement of specific miRNAs singly or in combination, or as miRNA pairs (as a ratio) in blood plasma, serum, or cerebrospinal fluid enabled frontotemporal dementia to be discriminated from healthy controls, Alzheimer’s disease, and amyotrophic lateral sclerosis. Furthermore, upregulation of miR-223-3p and downregulation of miR-15a-5p, which occurred both in blood serum and cerebrospinal fluid, distinguished behavioral-variant frontotemporal dementia from healthy controls. Downregulation of miR-132-3p in frontal and temporal cortical tissue distinguished frontotemporal lobar degeneration and frontotemporal dementia, respectively, from healthy controls. Possible strong miRNA biofluid biomarker contenders for behavioral-variant frontotemporal dementia are miR-223-3p, miR-15a-5p, miR-22-3p in blood serum and cerebrospinal fluid, and miR-124 in cerebrospinal fluid. No miRNAs were identified able to distinguish between behavioral-variant frontotemporal dementia and primary progressive aphasia subtypes. Further studies are warranted on investigating miRNA expression in biofluids and frontal/temporal cortical tissue to validate and extend these findings.

Key Words: Alzheimer’s disease; amyotrophic lateral sclerosis; behavioral variant; biomarker; blood plasma; blood serum; brain; cerebrospinal fluid; cortical tissue; frontotemporal dementia; frontotemporal lobar degeneration; microRNA; primary progressive aphasia

Introduction
Frontotemporal lobar degeneration (FTLD) describes a group of progressive brain disorders that primarily are associated with atrophy of the prefrontal and anterior temporal lobes. The clinical features include behavior and personality disturbances, language impairment, and in some cases, accompanying motor neuron disease or parkinsonism. This group of diseases accounts for 5–15% of all cases of dementia (Graff-Radford and Woodruff, 2007), next in frequency to Alzheimer’s disease (AD) that accounts for 50–70% of all dementia cases, and now the most common cause of early-onset dementia in people less than 60 years of age (Bang et al., 2015). FTLD is considered to be equivalent to frontotemporal dementia (FTD) of which there are two major clinical subtypes: behavioral-variant (bvFTD) and primary progressive aphasia (PPA). The first subtype is characterized by behavioral symptoms, while the second one is comprised of a semantic variant PPA (svPPA) and a nonfluent variant PPA (nfvPPA) in which the main feature is a progressive impairment of language and speech (Bang et al., 2015). The bvFTD accounts for greater than 50% of the cases (Warren et al., 2013). The age of the first symptom can be variable, occurring from as early as 30 years of age to as late as 60 or more years of age (UCSF Weill Institute for Neurosciences). At present, there are no cures for FTD.

Genetic, epigenetic, and environmental factors are considered to contribute to FTD disease development (Maloney and Lahiri, 2016). A positive family history of dementia has been found in approximately 40% of patients with FTD (Rosso et al., 2003) and about 25% of patients with FTD have an identified genetic form of the disease (Bang et al., 2015). Mutations were found in several genes, including those encoding the
MicroRNAs (miRNAs) are single-stranded non-coding RNA molecules approximately 22 nucleotides long that recognize sequences in the 3′-untranslated regions of target mRNAs and either induce mRNA degradation (Bagga et al., 2005) or inhibit their translation (He and Hannon, 2004; Meister, 2007). MiRNAs have been found to be dysregulated in a variety of NDs including AD, ALS, Parkinson’s disease, Huntington’s disease, age-related macular degeneration, and multiple sclerosis, and play an important role in FTD. The progranulin gene has been reported to be under the posttranscriptional control of miR-29b, miR-107, and miR-659 (Hébert et al., 2008; Noren Hooten et al., 2010; Piscopo et al., 2016). Moreover, various disease-specific protein aggregates have been observed in FTLD including hyperphosphorylated tau protein in neurons and glia (FTLD-Tau) (Lee and Leugers, 2012), TDP-43 (FTLD-TDP) (Arai et al., 2006; Neumann et al., 2006), FUS-positive inclusions (FTLD-FUS) (Munoz et al., 2009; Neumann et al., 2009a, b), and ubiquitin proteasome system-positive inclusions (FTLD-UPS) (Holm et al., 2007, 2009). Proteins pathologically aggregated in neurodegenerative disorders, such as TDP-43 and FUS, regulate miRNA biogenesis machinery, particularly Drosha and Dicer (Buratti and Baralle, 2010; Kawahara and Mieda-Sato, 2012; Di Carlo et al., 2013). The dysregulation of TDP-43 and FUS activity associated with FTLD and ALS pathogenesis could alter miRNA expression levels (Gascon and Gao, 2014). There have been conflicting results between miRNA studies, probably due to the heterogeneity of cohorts with regard to the underlying pathology (familial or sporadic), and have mainly compared symptomatic patients with healthy controls in determining potential diagnostic biomarkers. Few studies have examined miRNAs as progression biomarkers for FTD subtypes in presymptomatic subjects. Mild cognitive impairment (MCI), which is a heterogeneous syndrome characteristic of the early stages of various NDs, may be detected by analysis of miRNAs enriched in synapses of brain regions affected by the disease e.g., hippocampus in early AD, frontal and temporal lobes in FTD (Sheinerman et al., 2013; Sheinerman and Umansky, 2013). Approximately 20% of MCI patients who progress to dementia are diagnosed with NDs other than AD, such as vascular, Lewy body, Huntington’s, Parkinson’s dementia, and others (Jicha et al., 2006; Stephan et al., 2009). Thus, it might be possible to identify patients in the initial phases of FTD, before becoming demented, by developing a set of biomarkers to detect MCI of the frontotemporal type (FT-MCI) (de Mendonça et al., 2004). The expression of miRNAs in body fluids such as blood plasma, serum or CSF has been shown to correlate with the diagnosis and progression of the disease (Condrat et al., 2020). The CSF might contain unique miRNA signatures specific for various CNS pathologies. Therefore, miRNAs derived from CSF might serve as more valid biomarkers for brain pathologies than those of other body fluids. To date, relatively few studies have been published of miRNA expression in the CSF of FTD and AD patients and which could serve to distinguish between FTD and AD. In most of them AD patients were compared to healthy controls, or a comparison made of AD patients categorized by Braak stages (Cogswell et al., 2008; Alexandrov et al., 2012; Lehmann et al., 2012; Sala Frigerio et al., 2013; Kiko et al., 2014; Liu et al., 2014; Müller et al., 2014). Little is known about the differences in CSF miRNA levels between AD and other types of dementia such as FTD. The limited number of studies comparing miRNA CSF levels in AD patients versus patients with other types of dementia and their conflicting results justifies the need for additional studies to investigate the utility of miRNAs as biomarkers in a clinically relevant setup. Many miRNA studies are performed in small sample groups with subjects of the same genetic and ethnic background (Li et al., 2010). Thus far, few studies have investigated the potential of miRNAs as early biomarkers for the differential diagnosis of various forms of dementia. Studies in which the expression of miRNAs in AD versus FTD and dementia with Lewy bodies (DLB) is analyzed have indicated that miRNAs can play specific roles in dementias other than AD (Hébert et al., 2013; Arrant and Roberson, 2014). The aim of this review was to analyze recent literature on the expression levels of miRNAs in FTD and their potential for guiding clinical diagnosis and treatment with certain medications to manage the behavioral problems or by speech therapy to improve language and communication (Mayo Clinic, 2021).

**MicroRNAs in Frontotemporal Dementia**

We performed a PubMed search for original research articles published during January 2009–March 2021 on possible miRNA biomarkers of FTD compared to nondemented healthy subjects in blood plasma, serum, CSF, and cortical tissue collected from specific brain regions. In addition, we examined these articles for whether they could distinguish between the various FTD subtypes and differentiate FTD from other NDs such as AD and ALS. The steps involved in the review and its contents are shown (Figure 1). A total of 15 articles were found for this review. Of these, 6 had used blood plasma, 3 CSF, 2 blood serum and CSF, 1 blood plasma and CSF, and 3 cortical tissue (collected at postmortem). The relevant findings in the research articles from the PubMed search are summarized as follows.
with miR-877-5p which was > 2-fold higher in FTD group. MiR-206 was also included as it had a high fold change value and was very close to significance. It had also been described as a biomarker for NDs such as AD and ALS (Toivonen et al., 2014; Moon et al., 2016; Waller et al., 2017) and has a key role in the regulation of brain-derived neurotrophic factor (Lee et al., 2012; Tian et al., 2014), which is an important molecule linked to the pathophysiology of FTD (Zanardini et al., 2016). Significant downregulation of miR-663a, miR-502-3p, and miR-206 levels in FTD patients compared to HC was confirmed. The other miRNAs showed the same trend as in the discovery profiling but were not statistically significant. The levels of miR-663a, miR-502-3p, or miR-206 were not significantly correlated with age at onset of FTD and mini-mental state examination (MMSE) scores. Also, no difference was observed in the levels of these miRNAs between the two FTD clinical subtypes bvFTD (n = 17) and PPA (n = 17). ROC analysis using the three miRNA combination miR-663a, miR-502-3p, and miR-206 gave an AUC 0.89 in distinguishing FTD from HC with optimal cut-off point as > 26.83 with sensitivity 0.875 and specificity 0.813. In analyzing by gender, the significant differences of miR-206 levels were specific for males, while in females its levels were similar to controls. MiR-663a and miR-502-3p had significant differences in both genders. A significant difference was found in let-7e-5p when comparing FTD females and HC, but there was no difference in males and the overall FTD population compared to HC.

Piscopo et al. (2018) recruited 54 probable FTD (31 bvFTD, 23 PPA) and 20 AD patients, all of whom were sporadic with no mutations found in the genes most involved in FTD, MAPT, GRN, and C9orf72, as well as 53 HC. MiR-29b, miR-34a, miR-16-5p, miR-17-5p, miR-107, miR-19, let-7b, miR-26b and miR-127-3p in blood plasma were screened by qRT-PCR as possible candidate miRNAs to discriminate FTD from HC. Significant downregulation of miR-127-3p occurred in FTD compared to HC. The other miRNAs were not significantly different between FTD and HC. The level of miR-127-3p expression was significantly lower in FTD compared to AD. When all subjects were stratified by gender, significant difference of miR-127-3p levels between FTD and HC and between FTD and AD were observed both in males and females. By ROC analysis, the AUC for miR-127-3p expression to discriminate FTD from HC was 0.806 and from AD was 0.899. For distinguishing FTD versus HC, when the relative miR-127-3p value was under ∆Ct 5.5, the sensitivity was 0.815 and specificity 0.698. For distinguishing FTD versus AD, when the relative miR-127-3p value was under ∆Ct 5.5, the sensitivity was 0.815 and specificity 0.800. When distinguished by gender, AUC of miR-127-3p to discriminate FTD versus HC was 0.768 in males and 0.826 in females, and to discriminate FTD versus AD was 0.926 in males and 0.871 in females.

Sheinerman et al. (2017) measured the levels of preselected miRNAs in blood plasma from 50 FTD (23 bv, 1 PPA/logopenic variant, 8 PPA/progressive nonfluent aphas, 8 PPA/semantic variant, 10 progressive supranuclear palsy), 50 AD, 50 PD, 50 ALS patients, and 50 HC using RT-PCR. The miRNAs included those present in synapses and enriched in different brain regions affected by the target pathologies, miRNAs associated with inflammatory processes, miR-206 which is highly enriched in muscle tissue and in cerebellum, ubiquitous apoptosis-associated miR-16, and miR-451 which is more effectively excreted from pathologic than normal cells. MiRNA pairs and their combinations (classifiers) capable of differentiating each ND from HC with the highest accuracy were assessed in the training set and confirmed in the validation set, followed by analysis of the combined dataset. In distinguishing between FTD and HC, miR-9-3p/let-7e, miR-
In a discovery cohort consisting of 7 AD patients and 6 noninflammatory neurological disease controls (NINDC), Galimberti et al. (2014) found using miRNA PCR array analysis an overall downregulation of blood serum miRNAs in AD compared to NINDC, with four miRNAs being significantly downregulated miR-125b, miR-223, miR-23a, and miR-26b. In a larger cohort comprising 15 AD, 12 NINDC, 8 inflammatory neurological disease controls (INDC), and 10 FTD patients, significant downregulation of miR-125b, miR-23a, and miR-26b in blood serum of AD patients compared to NINDC was confirmed by RT-PCR. No significant differences occurred in AD patients compared to INDC and FTD patients.

Cerebrospinal fluid

In the GENFI (Genetic Frontotemporal Dementia Initiative) a cohort consisting of 38 mutation carriers (22 GRN, 11 C9orf72, 5 MAPT) and 11 healthy non-mutation carriers was recruited. 23 mutation carriers were presymptomatic and 15 mutation carriers were symptomatic (12 bvFTD, 1 nfvPPA, 1 svPPA, 1 dementia not otherwise specified). A sporadic disease cohort comprised 7 bvFTD, 4 bvFTD/ALS, 3 svPPA, 1 nfvPPA/ALS, 1 svPPA/ALS, 1 nfvPPA, 13 sporadic AD, and 10 HC. Exosomes were isolated from the CSF and miRNAs analyzed using RT-PCR by Schneider et al. (2018). There were no significant changes in miRNA expression between healthy non-mutation carriers and presymptomatic mutation carriers. Relative expression of both miR-204-5p and miR-632 was significantly decreased in symptomatic compared with presymptomatic mutation carriers. Relative expression of miR-204-5p was significantly lower in symptomatic mutation carriers with either GRN or C9orf72 mutations compared with presymptomatic mutation carriers. Relative expression of miR-632 was significantly reduced in symptomatic compared with presymptomatic mutation carriers in the GRN group but not in the C9orf72 group. Relative expression of both miR-204-5p and miR-632 was still significantly lower when bvFTD only was compared with presymptomatic mutation carriers. Age was significantly different between groups with symptomatic mutation carriers being older than presymptomatic mutation carriers. When analyzing for males and females separately, a decrease of miR-204-5p and miR-632 was found in symptomatic compared with presymptomatic female mutation carriers (n = 23) before correcting for multiple comparisons. The number of male mutation carriers was smaller (n = 13) and comparing miR-204-5p and miR-632 between symptomatic and presymptomatic male mutation carriers only revealed a trend towards significance, before correction for multiple comparisons. No significant decrease of miR-204-5p expression was observed in sporadic FTD compared with sporadic AD or HC of similar age; however, miR-632 was significantly decreased in sporadic FTD compared with HC or AD. By ROC analysis, a decrease of miR-204-5p and miR-632 discriminated well between presymptomatic and symptomatic individuals with AUC 0.89 for miR-204-5p and 0.81 for miR-632. A combination of miR-204-5p and miR-632 increased the AUC to 0.93. In the GRN group, miR-632 discriminated well between presymptomatic and symptomatic individuals with AUC 0.85, and there was a trend for miR-204-5p and the combination of miR-204-5p and miR-632. In the C9orf72 group, only 3 individuals were symptomatic, and no significant results were obtained by ROC analysis. For patients with bvFTD, miR-204-5p and miR-632 discriminated well between presymptomatic and symptomatic individuals with AUC 0.91 and 0.83, and there was a trend for the combination of miR-204-5p and miR-632. In distinguishing sporadic FTD from all non-FTD (HC and AD) by miR-632, the AUC was 0.90, and there was a trend for the AUC to distinguish FTD from HC or AD separately.

Blood serum

Denk et al. (2018) examined mRNA expression levels in blood serum of 48 bvFTD, 48 AD patients, and 44 HC by RT-qPCR. A total of 41 of the 48 bvFTD and 20 of the 48 AD cases tested negative for the most prominent gene C9orf72. No mutations in the genes MAPT and GRN were identified in the tested bvFTD (n = 11) and AD (n = 11) cases. Expression levels of miR-143-3p, miR-197-3p, miR-27a-3p, miR-338-3p, miR-491-5p, miR-7b-5p, miR-7g-5p, miR-106a-5p, miR-106b-5p, miR-18b-5p, miR-223-3p, miR-26a-5p, miR-26b-5p, miR-301a-3p, miR-30b-5p were significantly higher in bvFTD compared to HC, and miR-100-5p, miR-335-5p, miR-99a-5p, miR-146a-5p, miR-15a-5p, miR-22-3p, miR-320a, miR-320b, miR-92a-3p, and miR-1246 were significantly lower in bvFTD compared to HC. By ROC analysis, bvFTD cases were distinguished best from HC by miR-301a-3p (upregulated) with an AUC 0.96 and sensitivity 0.96 and specificity 0.84. Also, miR-27a-3p (upregulated) distinguished bvFTD cases from HC with an AUC 0.86 with sensitivity 0.77 and specificity 0.72. AD cases were distinguished from HC by miR-26b-5p (upregulated) with AUC of 0.97 and sensitivity and specificity 0.89. MiR-301a-3p (upregulated) classified AD from HC with an AUC of 0.94.

In a discovery cohort consisting of 7 AD patients and 6
Denk et al. (2018) measured miRNA expression in CSF of 48 bvFTD, 48 AD patients, and 44 HC using RT-PCR. A total of 41 of the 48 bvFTD and 20 of the 48 AD cases tested negative for the most prominent gene C9orf72. No mutations in the genes MAPT and GRN were found in the tested AD (n = 11) and bvFTD (n = 11) cases. In CSF, miR-124-3p, miR-125a-5p, miR-223-3p were significantly increased, while miR-15a-5p was decreased, in bvFTD compared to HC. Interestingly, miR-140-3p, miR-30a-5p, miR-30e-5p, miR-22-3p were significantly decreased in bvFTD compared to AD. By ROC, miR-125a-5p expression (upregulated) best discriminated bvFTD cases with AUC 0.84, sensitivity 0.72 and specificity 0.81, as well as AD cases with AUC 0.75, sensitivity 0.74 and specificity 0.82, from HC. With an AUC 0.73, miR-30a-5p (downregulated) gave the best classification in distinguishing bvFTD from AD cases with sensitivity 0.78 and specificity 0.68.

Sørensen et al. (2016) recruited 10 AD patients and 10 patients with other types of dementia (4 vascular dementia, 4 dementia, 2 DBL). By RT-PCR, let-7i-5p and miR-15a-5p were significantly upregulated and miR-29c-3p was significantly downregulated in CSF of patients with AD compared to patients with other types of dementia. However, none of these were statistically significant on performing the Benjamini-Hochberg procedure for multiple testing. By combining two of the differentially expressed miRNAs in a simple ratio model miR-29c-3p/miR-15a-5p, AD patients were distinguished from patients with other types of dementia (cut-off value 0.92) with sensitivity 0.90 and specificity 1.00.

A multi-center study was reported by Müller et al. (2016) and involved 57 AD, 37 MCI-AD, 37 FTLD, 35 DBL patients, and 40 HC. Non-centrifuged CSF samples had greater levels (decreased Ct-values) of miR-29a compared to centrifuged samples and this was most evident in comparing samples from AD patients. After normalization, these differences due to the centrifugation protocol were only resolved for miR-146a, but differences between centrifuged and non-centrifuged samples were still evident for miR-29a and also for miR-27a and miR-125b. In the ANCOVA to compare miRNA expression between the groups, gender, age, and sample storage, center of origin, and centrifugation status of the samples were included as confounding factors. When the levels were compared between AD patients and dementia-free controls of all three centers, no significant differences were found. Levels of miR-125b showed a trend towards a decreased expression in AD patients, but when results were controlled for confounding factors this trend disappeared. Comparing MCI-AD to AD patients of all centers, levels of miR-27a, miR-125b and miR-146a were increased in MCI-AD patients. However, after correcting for the confounding factors, these differences were lost. Levels of miR-27a, miR-212 and miR-125b were similar in late stage AD, FTD and DBL. Levels of miR-146a were similar in AD and DBL groups but were increased in FTD patients compared to AD patients. However, this difference disappeared when the covariates were included in the group comparisons. No significant differences were identified for FTD patients compared to dementia-free controls.

In a study of miRNA expression in CSF of 22 AD, 10 FTD patients, 18 NINDC and 8 INDC by qRT-PCR, Galimberti et al. (2014) found a significant decrease of miR-125b and miR-26b in AD patients versus NINDCs. No significant differences were found in miR-23a expression levels in AD compared to NINDCs. Also, no differences were found in miR-125b and miR-26b levels in AD patients compared with INDCs and FTD patients.

**Brain tissue**

Jawaid et al. (2019) examined miRNA expression in frontal cortex tissue from 10 ALS, 9–12 FTLD, and 6–8 HC brains postmortem. By RT-qPCR, miR-183/96/182 expression was decreased in frontal cortex of patients with ALS while PP1y, a predominantly nuclear isoform of the memory suppressor protein phosphatase 1, was increased. MiR-183/96/182 expression was similarly decreased in the frontal cortex of patients with FTLD with a comparable increase in PP1y.

A study of miRNA levels in temporal lobe (Brodmann area 20) cortex of brains from 8 AD, 14 FTLD, and 8 HC was made by Hébert et al. (2013). The FTLD group was comprised of 5 FTD, and 9 progressive supranuclear palsy (PSP). By qRT-PCR, there was a significant downregulation of miR-132-3p in temporal cortex in AD, FTD, and PSP cases when compared to non-demented HC. MiR-100 was statistically lower in AD versus HC and tended to be higher in FTD compared to AD and HC (but not statistically significant which was probably due to the small group sizes).

Chen-Plotkin et al. (2012) obtained frontal cortex samples from 12 FTLD-TDP cases (5 with GRN mutations and 7 without GRN mutations) and 6 HC. By qRT-PCR, miR-132-5p, miR-132-3p, and miR-212 all showed < 50% expression in both GRN(−)FTLD-TDP and GRN(+)FTLD-TDP compared with normal controls. This decreased expression relative to normal controls occurred in both GRN(−)FTLD-TDP and GRN(+)FTLD-TDP subgroups, removing the possibility that one subgroup was causing the effect. A significant difference also persisted when quantitation was normalized to the brain-expressed miR, miR-124, removing the possibility that neuronal loss associated with FTLD-TDP was responsible for the effect. Absolute levels of miR-132-5p were ~100 times higher than miR-132-3p and miR-212 in all groups. MiR-132 and miR-212 are dual repressors of TMEM106B through shared binding sites in the 3′-untranslated region.

The findings from the miRNA studies are summarized in Table 1 and 2.

**Discussion**

FTD is the next most common cause of dementia after AD, with between 20–50% of the cases being familial (Olszewska et al., 2016). FTD is characterized by progressive impairments in behavior, executive function, and language (Rascovsky et al., 2011). The most frequent genetic cause of familial FTD and ALS is a hexanucleotide (GGGGCC) repeat expansion in the C9orf72 gene (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Neurodegeneration can be caused by this autosomal dominant mutation through C9orf72 loss of function, aggregates of mutant RNA in nuclear foci and of dipeptide repeats, leading to pathological inclusions of TDP-43. It is imperative to identify biomarkers of preclinical progression for FTD and ALS that could be used to initiate and monitor potential disease-modifying treatments before any irreversible brain damage has occurred. Presymptomatic C9orf72 carriers represent an optimal target population for the development of new therapeutic interventions for FTD and ALS (Eisen et al., 2014; Betrand et al., 2018).
The early diagnosis of FTD is crucial for developing management strategies and interventions for these patients. Without validated biomarkers, the clinical diagnosis depends on recognizing all the core or necessary neuropsychiatric features of FTD (Neary et al., 1998; Mendez and Perryman, 2002). However, early FTD patients often do not show all the necessary core features for the clinical diagnosis of FTD and fail to meet diagnostic criteria on initial assessment (Mendez and Perryman, 2002). Many of the initial symptoms of FTD are compatible with a range of neurologic and psychiatric disorders. Consequently, physicians misdiagnose FTD in patients with AD, or other neurodegenerative diseases, that may present with overlapping cognitive, behavioral, and psychiatric symptoms (Mendez et al., 2006b; Olszewska et al., 2016). Changes in social and emotional behavior are usually the earliest signs of FTD. Within the first few years after onset, neuropsychiatric symptoms usually precede or overshadow any cognitive disabilities (Miller et al., 1991; The Lund and Manchester Groups, 1994; Edmonds-Lea et al., 1997; Pasquier and Petit, 1997). The profile of neuropsychological abnormalities in executive functions and language, with less impaired memory and visuospatial skills than AD (Elfgren et al., 1993; Hodges et al., 2004; Elderkin-Thompson et al., 2004), may be shown only as the disease progresses and lacks sensitivity in the beginning stages of FTD (Hodges, 2001; Mendez and Perryman, 2002; Kertesz et al., 2003). In addition, the earliest behavioral manifestations of FTD vary considerably and are associated with variation in the earliest localization of the disease and possibly in neuropathologic features (McMurtag et al., 2001; Mendez et al., 2006a). Thus, the development of proven biomarker(s) for early FTD would lessen the likelihood of misdiagnosis and benefit patient care. Cost-efficient, and specific biomarkers that can help in diagnosing early FTD and differentiating it from AD and ALS are urgently needed. The t-tau:Ab42 and p-tau:Ab42 ratios measured in CSF have been used to distinguish FTD and AD, and p-tau:Ab42 ratio discriminated PPA from AD (Casoli et al., 2019). However, collecting CSF by lumbar puncture is an invasive procedure and may be difficult to carry out in older patients. It is much more desirable to identify possible biomarkers in blood plasma or serum that can discriminate between FTD and AD which involves collecting peripheral venous blood by a minimally invasive procedure and can be done repeatedly to monitor disease progression and response to intervention.

| Author | Method of miRNA analysis | Comparison | miRNA analysis |
|--------|--------------------------|------------|---------------|
| Kmetts, et al., 2020 | miRNA sequencing | Symptomatic mutation carriers' vs. HC | Upregulated: miR-34a-5p, -345-5p |
| Kmetts, et al., 2020 | miRNA sequencing | Presymptomatic mutation carriers' vs. HC | Upregulated: miR-34a-5p |
| Kmetts, et al., 2020 | miRNA sequencing | Symptomatic mutation carriers vs. presymptomatic mutation carriers | Upregulated: miR-345-5p |
| Siedleck-A-Wullich et al., 2019 | RT-PCR | AD vs. HC | Upregulated: miR-92a-3p, -181c-5p, -210-3p |
| Siedleck-A-Wullich et al., 2019 | RT-PCR | MCI vs. HC | Upregulated: miR-181c-5p, -210-3p |
| Siedleck-A-Wullich et al., 2019 | RT-PCR | FTD vs. HC | No significant differences in miR-92a-3p, -181c-5p, -210-3p |
| Grasso et al., 2019 | RT-PCR | FTD vs. HC | Downregulated: miR-663a, -502-3p, -206 |
| Grasso et al., 2019 | RT-PCR | bvFTD vs. PPA | No significant differences in miR-663a, -502-3p, -206 |
| Grasso et al., 2019 | RT-PCR | Male FTD vs. HC | Downregulated: miR-663a, -502-3p, -206 |
| Grasso et al., 2019 | RT-PCR | Female FTD vs. HC | Downregulated: miR-663a, -502-3p, let-7e-5p |
| Piscopo et al., 2018 | RT-PCR | FTD vs. HC | Downregulated: miR-127-3p |
| Piscopo et al., 2018 | RT-PCR | FTD vs. AD | Downregulated: miR-127-3p |
| Piscopo et al., 2018 | RT-PCR | Male FTD vs. HC | Downregulated: miR-127-3p |
| Piscopo et al., 2018 | RT-PCR | Female FTD vs. HC | Downregulated: miR-127-3p |
| Piscopo et al., 2018 | RT-PCR | Male FTD vs. AD | Downregulated: miR-127-3p |
| Piscopo et al., 2018 | RT-PCR | Female FTD vs. AD | Downregulated: miR-127-3p |
| Sheinerman et al., 2017 | RT-PCR | FTD vs. HC | The ratios miR-9-3p/let-7e, miR-7/miR-451, miR-335-5p/let-7e distinguished FTD from HC |
| Sheinerman et al., 2017 | RT-PCR | FTD vs. AD | The ratios miR-125b/miR-29a, miR-125b/miR-874, miR-107/miR-335-5p distinguished FTD from AD |
| Sheinerman et al., 2017 | RT-PCR | FTD vs. ALS | The ratios miR-129-3p/miR-206 and miR-338-3p/let-7e distinguished FTD from ALS |
| Sørensen et al., 2016 | RT-PCR | AD vs. other dementia types (vascular, FTD, DLB) | Upregulated: miR-590-5p, -142-5p but not significant by Benjamini-Hochberg |
| Sheinerman et al., 2017 | RT-PCR | MCI vs. HC | Downregulated: miR-194-5p but not significant by Benjamini-Hochberg |
| Sheinerman et al., 2012 | RT-PCR | MCI vs. HC | The ratios miR-128/miR-491-5p, miR-132/miR-491-5p, miR-874/miR-491-5p, miR-134/miR-370, miR-323-5p/miR-370, miR-382/miR-370 distinguished MCI from HC |
| Galimberti et al., 2014 | RT-PCR | bvFTD vs. HC | Upregulated: miR-143-3p, -193-3p, -222-3p, -223-3p, -26a-5p, -26b-5p, -30a-5p, -30b-5p |
| Galimberti et al., 2014 | RT-PCR | AD vs. NIHDC | Downregulated: miR-100-5p, -335-5p, -99a-5p, -146a-5p, -15a-5p, -22-3p, -320a, -320b, -92a-3p, -1246 |
| Galimberti et al., 2014 | RT-PCR | AD vs. FTD and INDC | Downregulated: miR-125b, -23a, -26b-5p |
| Galimberti et al., 2014 | RT-PCR | FTD vs. INDC | No significant differences in miR-125b, -23a, -26b-5p |

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; bvFTD: behavioral variant FTD; DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; HC: non-demented healthy controls; INDC: inflammatory neurologic disease controls; MCI: mild cognitive impairment; NINDC: non-inflammatory neurologic disease controls; PPA: primary progressive aphasia; RT-PCR: real-time polymerase chain reaction. 'Symptomatic mutation carriers consisted of 15 FTD, 4 FTD/ALS, 3 ALS patients carrying a C9orf72 expansion; 'Presymptomatic mutation carriers were 46 asymptomatic first-degree relatives of FTD, DLB).
A very large number of miRNAs was found to be dysregulated in the different studies reviewed herein, but with limited overlap between individual studies (Tables 1 and 2). Important findings in blood plasma were miR-663a, miR-502-3p, miR-206 being downregulated in FTD patients compared to HC (Grasso et al., 2019), as was miR-127-3p (Piscopo et al., 2018), and also the ratios miR-9-3p/let-7e, miR-7/miR-451, miR-335-5p/let-7e distinguished FTD from HC (Sheinerman et al., 2017). Moreover, miR-127-3p was downregulated in FTD compared to AD (Piscopo et al., 2018), and the ratios miR-125b/miR-29a, miR-125b/miR-874, miR-107/miR-335-5p distinguished FTD from AD (Sheinerman et al., 2017). FTD was distinguished from ALS by the ratios miR-129-3p/miR-206 and miR-338-3p/let-7e HC (Sheinerman et al., 2017). No significant differences in miR-663a, miR-502-3p, miR-206 were found in bvFTD compared to PPA (Grasso et al., 2019). Symptomatic mutation carriers consisting of FTD, FTD/ALS, and ALS patients carrying a C9orf72 expansion had upregulated miR-34a-5p, miR-345-5p and downregulated miR-200c-3p, miR-10a-3p compared to HC. Presymptomatic mutation carriers who were asymptomatic first-degree relatives of C9orf72 patients with a pathogenic expansion had upregulated miR-34a-5p compared to HC. Symptomatic mutation carriers were distinguished from presymptomatic mutation carriers by an upregulation of miR-34a-5p and downregulation of miR-200c-3p, miR-10a-3p (Kmetsch et al., 2021). Important findings in blood serum included upregulation of miR-143-3p, miR-197-3p, miR-27a-3p, miR-338-3p, miR-491-5p, miR-7b-5p, miR-7g-5p, miR-106a-5p, miR-106b-5p, miR-18b-5p, miR-223-3p, miR-26a-5p, miR-26b-5p, miR-301a-3p, miR-30b-5p and downregulation of miR-100-5p, miR-335-3p, miR-99a-5p, miR-146a-5p, miR-15a-5p, miR-22-3p, miR-320a, miR-320b, miR-92a-3p, miR-1246 in bvFTD compared to HC (Denk et al., 2018). In exosomes isolated from CSF, miR-204-5p, miR-632 were downregulated in symptomatic mutation carriers compared to asymptomatic presymptomatic mutation carriers. Symptomatic mutation carriers consisted of GRN, C9orf72, MAPT mutation carriers and comprised 12 bvFTD, 1 nfvPPA, 1 svPPA, 1 dementia not otherwise specified. Presymptomatic mutation carriers consisted of 23 patients.
2018). Upregulation of miR-124-3p, miR-125a-5p, miR-223-3p and downregulation of miR-15a-5p distinguished bvFTD from HC. Moreover, downregulation of miR-140-3p, miR-30a-5p, miR-30e-5p, miR-22-3p distinguished bvFTD from AD (Denk et al., 2018). Upregulation of miR-223-3p and downregulation of miR-15a-5p had been found in blood serum in bvFTD compared to HC (Denk et al., 2018). Downregulation of miR-22-3p in blood serum and CSF distinguished bvFTD from HC and AD, respectively. Thus, measurement of specific miRNAs singly or in combination, or as miRNA pairs (as a ratio) in blood plasma, serum or CSF enabled FTD to be discriminated from HC, AD, and ALS as shown by ROC analysis. Also, bvFTD could be distinguished from HC or AD. No miRNAs were identified as being able to distinguish between the bvFTD and PPA subtypes in the studies reviewed. Downregulated expression in frontal cortex of miR-183/96/182 (Jawaid et al., 2019) and miR-132-3p (Chen-Plotkin et al., 2012) occurred in FTLD compared to HC. Downregulation of miR-132-3p in temporal cortex in FTD compared to HC was also reported (Hébert et al., 2013). None of these miRNAs had altered expression in blood plasma, serum, or CSF in FTD patients. Possible strong miRNA biofluid biomarker contenders for bvFTD are miR-223-3p, miR-15a-5p, and miR-22-3p. MI-124 had been reported to modulate social behavior in FTD (Arrant and Roberson, 2014) and was found to be upregulated in CSF in FTLD versus HC and AD (Derkow et al., 2018) and could also be a potential biomarker contender. Table 3 provides further information on the composition of the groups in the studies by Denk et al. (2018) and Derkow et al. (2018). In the study by Denk et al. (2018) a total of 41 of the 48 bvFTD and 20 of the 48 AD cases were tested negative for the most prominent gene C9orf72, and no mutations in the genes MAPT and GRN were identified in the tested AD (n = 11) and bvFTD (n = 11) cases. No information on gene mutations in the cases was provided by Derkow et al. (2018). Interestingly, miR-132, miR-29b and miR-659 are reported to regulate GRN gene, and TDP-43 seems to regulate miR-9a and increases its stability (Piscopo et al., 2016b). Also, miR-30d is predicted to target C9orf72 gene (Kovanda et al., 2018). However, none of these miRNAs had altered expression in the studies reviewed. MiR-223-3p targets the G6PT gene (Paul et al., 2020). It is suggested that miR-223-3p is upregulated in bvFTD patients in response to inflammation to mediate a neuroprotective effect; overexpression of miR-223-3p was found to protect dissociated cortical neurons from condition media-mediated degeneration (Morquette et al., 2019). The target gene of miR-124 is AMPAR (Piscopo et al., 2016a) and research suggests that AMPA receptors are associated with the regulation of social behavior (Gascon et al., 2014). Upregulation of miR-124 would lead to a decrease in AMPAR and AMPA receptors, thereby affecting the regulation of social behavior. MiR-15a is positively linked with amantadine which acts as an N-methyl-D-aspartate receptor antagonist. Research has shown amantadine to be associated with the treatment of behavioral disturbances (Huey et al., 2006). MiR-15a-5p targets the BDNF gene (Dentham et al., 2018), which is also targeted by miR-22-3p in addition to the PTEN and SIRT1 genes (Lauretti et al., 2020; Liu et al., 2020).

The main limitations identified in these studies included the small sizes of some groups, gender and/or age disproportion in some groups, and whether normalization of miRNA data had been employed. For example, in a study by Sørensen et al. (2016) miRNA expressions were compared in 10 AD patients versus 10 patients with other types of dementia (consisting of 4 vascular dementia, 4 FTD, 2 DLB). When applying multiple testing of P values with the Benjamini-Hochberg procedure, none of the previously found differences remained significant. With small group sizes it is difficult to show statistically significant changes, and no power calculations were included in any of the reviewed articles. Also, Piscopo et al. (2018) studied miRNA expression in 54 probable FTD cases (19 male/35 female) and 20 AD cases (10 male/10 female); however, testing of data to take account of gender differences was not considered.

Table 3 | Possible miRNA biomarker candidates in frontotemporal dementia from studies by Denk et al. (2018) and Derkow et al. (2018) and related mechanistic pathways

| Author | Number of FTD patients, gender, ages | Subjects for comparison, number, Sample assayed | Altered miRNA expression | Related pathway to FTD |
|--------|-------------------------------------|-------------------------------------------------|--------------------------|------------------------|
| **bvFTD vs. HC** | | | | |
| Denk et al., 2018 | 48 bvFTD³, 30M/18F, 65±9.2 yr (48 serum) | 44 HC, 20M/24F, 64±11.3 yr (38 serum) | Serum | miR-223-3p upregulated | Possible protection of surviving neurons by miR-223-3p. MiR-223-3p targets G6PT gene |
| | | | | | A positive linkage of miR-15a with amantadine, which is associated with the treatment of behavioral disturbances |
| | | | | | MiR-15a-5p targets BDNF gene |
| | | | | | MiR-22-3p targets BDNF, PTEN, and SIRT1 genes |
| Denk et al., 2018 | 48 bvFTD³, 30M/18F, 65±9.2 yr (48 CSF) | 44 HC, 20M/24F, 64±11.3 yr (44 CSF) | CSF | miR-223-3p upregulated | Possible protection of surviving neurons by miR-223-3p. MiR-223-3p targets G6PT gene |
| | | | | | The target gene of miR-124 is AMPAR. AMPA receptors are associated with the regulation of social behavior |
| | | | | | A positive linkage of miR-15a with amantadine, which is associated with the treatment of behavioral disturbances |
| | | | | | MiR-15a-5p targets BDNF gene |
| | | | | | MiR-22-3p targets BDNF, PTEN, and SIRT1 genes |
| **FTLD vs. HC** | | | | |
| Derkow et al., 2018 | 8 FTLD, 3M/5F, 64±11.5 yr | 10 HC, 7M/3F, 58±11 yr | CSF | miR-124 upregulated | The target gene of miR-124 is AMPAR. AMPA receptors are associated with the regulation of social behavior |
| **FTLD vs. AD** | | | | |
| Derkow et al., 2018 | 8 FTLD, 3M/5F, 64±11.5 yr | 12 AD, 2M/10F, 71±8.5 yr | CSF | miR-124 upregulated | The target gene of miR-124 is AMPAR. AMPA receptors are associated with the regulation of social behavior |

AD: Alzheimer’s disease; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazoletropic acid; CSF: cerebrospinal fluid; F: Female; FTD: frontotemporal dementia; bvFTD: behavioral variant FTD; FTLD: frontotemporal lobar degeneration; HC: healthy controls; M: Male; yr: years. Total of 41 of the 48 bvFTD and 20 of the 48 AD cases were tested negative for the most prominent gene C9orf72, and no mutations in the genes MAPT and GRN were identified in the tested AD (n=11) and bvFTD (n = 11) cases.
in these two groups by multiple comparisons was not made. Furthermore, the gender composition of the AD, FTD, NINC and INDC groups in the study by Galimberti et al. (2014) was not reported. A significant age difference occurred between symptomatic mutation carriers and presymptomatic mutation carriers in the study by Schneider et al. (2018). Also, in a multi-center study of miRNAs in CSF by Müller et al. (2016), several confounding factors were identified that included gender, age, sample storage, center of origin, and centrifugation status of the samples, and notably when the results were controlled for these confounding factors, the differences identified in miRNA levels between the different groups were lost. Normalization of experimental data was reported in eight of the 15 studies, but it was unclear whether this had been performed in the other studies. It was surprising that there were only three studies performed with frontal or temporal cortical tissue. In one of these studies fresh frontal cortices were used (Jawai et al., 2019) while frontal cortex (Chen-Plotkin et al., 2012) and temporal cortex (Hébert et al., 2013) were obtained from a research brain bank. The other studies examined either cerebrospinal fluid (CSF), frontal or temporal cortical tissue. In one of these studies it is hoped that a sensitive and specific, minimally invasive test can be developed to identify patients with FTLD and assist with regular monitoring and initiate treatment to slow disease progression. A multimodal assessment combining potential novel biofluid biomarkers with clinical, neuroimaging, and genetic markers may enable FTLD subtypes to be more accurately distinguished.

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