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Review

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

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From the Contents

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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

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microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), chromosome 9 open reading frame 72 (*C9orf72*), TAR DNA-binding protein 43 (*TDP-43*), fused in sarcoma-binding protein (*FUS*), valosin-containing protein (*VCP*), and charged multivesicular body protein 2B (*CHMP2B*) (Sieben et al., 2012; Fontana et al., 2015). Screening for mutations in these genes provides an opportunity to study the disease in its presymptomatic phase. However, single research groups have only been able to study small numbers of patients with genetic FTD. The large majority of sporadic FTD cases are of unknown etiology, although genetic alterations may be expected there (Blauwendraat et al., 2018). Some symptoms of FTD can be detected in nearly 50% of amyotrophic lateral sclerosis (ALS) patients (FTD-ALS) (Ferrari et al., 2011), and these two diseases have common pathophysiological mechanisms and genetic causes (Mackenzie et al., 2010).

Currently, the diagnosis of FTD is based primarily on medical history, neuropsychological testing to better assess the pattern of cognitive loss in an individual and the exclusion of other neurodegenerative disorders, as well as neuroimaging to determine the location and the extent that specific brain regions have atrophied. FTD presents chiefly as a disturbance of personality and behavior or a progressive aphasia that may be misdiagnosed as a psychiatric disorder (Warren et al., 2013). Moreover, the clinical diagnosis of FTD is hampered by the considerable overlap of the clinical symptoms and neuropsychological profiles within its subtypes and with AD and other neurodegenerative diseases (NDs) (Olszewska et al., 2016), which often results in misdiagnoses (Vijverberg et al., 2016). A total of 10–30% of patients presenting with an FTD clinical syndrome were found to have AD at postmortem (Rabinovici and Miller, 2010). No single diagnostic test is available that can confirm or rule out a diagnosis of FTD. Cost-efficient, and specific biofluid biomarkers that can help in diagnosing early FTD and could support MRI neuroimaging findings are urgently needed (Bruun et al., 2019).

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 post-transcriptional 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 et al., 2001; 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 FTD 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.

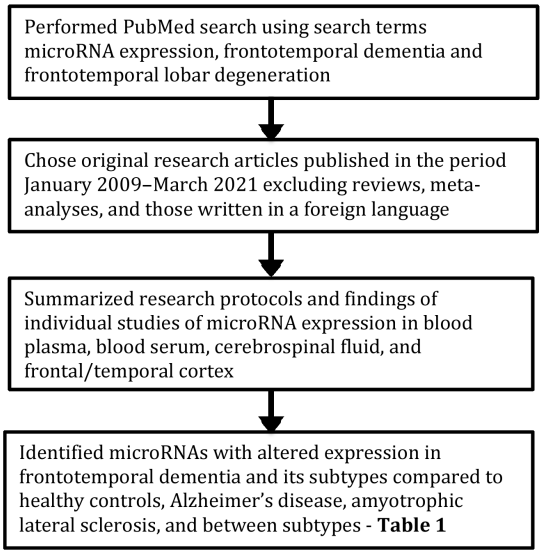

Figure 1 | **Flow diagram to indicate how the review was performed and its contents.**

Blood plasma

Kmetsch et al. (2021) recruited 22 patients consisting of 15 FTD, 4 FTD/ALS and 3 ALS carrying a *C9orf72* expansion, together with 89 asymptomatic first-degree relatives of *C9orf72* patients in which a pathogenic expansion was found in 46 of them and were referred to as the 'presymptomatic' group. The control group consisted of the 43 asymptomatic individuals who did not carry an expansion. By miRNA sequencing, miR-34a-5p and miR-345-5p were upregulated while miR-200c-3p and miR-10a-3p were downregulated in blood plasma of symptomatic mutation carriers compared to controls. MiR-34a-5p was also significantly upregulated in presymptomatic mutation carriers compared to controls. MiR-345-5p was significantly upregulated in patients compared to presymptomatic carriers, while miR-200c-3p and miR-10a-3p showed decreased expression compared to presymptomatic carriers. Using receiver operating characteristic (ROC) analysis, the four miRNA signature gave AUC value 0.90 in distinguishing presymptomatic carriers and controls, AUC 0.90 for patients and controls, and AUC 0.80 to distinguish patients and presymptomatic carriers.

Siedlecki-Wullich et al. (2019) examined miRNA expression in the blood plasma of two cohorts using RT-PCR. In cohort 1 consisting of 56 sporadic AD, 26 MCI patients, and 14 healthy controls (HC), a significant increase was observed in the blood plasma levels of miR-92a-3p, miR-181c-5p and miR-210-3p of AD patients compared with HC. A significant increase of miR-181c-5p and miR-210-3p was also observed in blood plasma for MCI patients. In cohort 2 consisting of 27 FTD and 24 HC, there were no significant differences in blood plasma levels of miR-92a-3p, miR-181c-5p and miR-210-3p of FTD patients compared with HC. It was suggested that the increase in miR-92a-3p, miR-181c-5p and miR-210-3p levels could be specific for AD.

Analysis of blood plasma samples of 10 FTD patients and 10 HC in a discovery set by Grasso et al. (2019) using RT-PCR revealed eight miRNAs were downregulated miR-663a, -502-3p, -375, -10b-5p, -30a-5p, let-7e-5p, -548c-5p, -548a-3p, and two were upregulated miR-454-3p, -877-5p in FTD patients compared to HC. In a validation set of plasma samples from 48 FTD patients and 46 HC, six of these miRNAs miR-663a, -502-3p, -375, -10b-5p, let-7e-5p, -548c-5p were selected as they had an expression level ~2-fold lower in FTD group together 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 ΔCt 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 ΔCt 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 aphasia, 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-

7/miR-451, and miR-335-5p/let-7e had AUC 0.79, 0.75, 0.83, respectively, and their combination had AUC 0.94, sensitivity 0.86 and specificity 0.90. In distinguishing between FTD and AD, miR-125b/miR-29a, miR-125b/miR-874, miR-107/miR-335-5p had AUC 0.78, 0.75, 0.80, respectively, and their combination had AUC 0.87, sensitivity 0.78 and specificity 0.76. In distinguishing between FTD and ALS, miR-129-3p/miR-206 and miR-338-3p/let-7e had AUC 0.86 and 0.81, respectively, and their combination had AUC 0.94, sensitivity 0.84 and specificity 0.86. Also, for distinguishing between FTD and HC (all male and female participants), miR-335/let-7e and miR-99b/let-7e and miR-9-3p/miR-181a classifier had AUC 0.94. This was also the best classifier for males with AUC 0.98. For females the best classifier was miR-491/let-7e and miR-107/miR-9 and miR-28/miR-181a with AUC 0.98.

Sørensen et al. (2016) performed miRNA analysis by RT-PCR of blood plasma from 10 AD and 10 patients with other types of dementia (4 vascular dementia, 4 FTD, 2 DLB). MiR-590-5p (FC = 1.35) and miR-142-5p (FC = 1.22) were significantly upregulated and miR-194-5p (FC = 0.54) was significantly downregulated in AD patients compared to the group with other types of dementia. However, none of these were statistically significant upon adjusting all *P* values with the Benjamini-Hochberg procedure for multiple testing.

In a pilot study, Sheinerman et al. (2012) measured the levels of brain- and neuron-enriched miRNAs in blood plasma of 10 amnestic MCI patients and 10 HC using RT-PCR. Thirteen miRNAs, miR-7, miR-125b, miR-128, miR-132, miR-134, miR-323-3p, miR-382, miR-874, miR-9, miR-127-3p, miR-181a, miR-370, miR-491-5p, formed pairs differentiating MCI from HC. In the main study, the levels of these 13 miRNAs were measured in the blood plasma of 20 amnestic MCI, 20 AD, and 20 HC by qRT-PCR. ROC analysis showed the biomarker pairs miR-128/miR-491-5p, miR-132/miR-491-5p and miR-874/miR-491-5p (Set1, miR-132 family) differentiated MCI from HC with AUC 0.95, 0.93 and 0.95, respectively, and with sensitivity 0.79–0.89 and specificity 0.83–1.00. Furthermore, the biomarker pairs miR-134/miR-370, miR-323-3p/miR-370 and miR-382/miR-370 (Set 2, miR-134 family) differentiated MCI from HC with AUC 0.91, 0.94 and 0.92, respectively, and with sensitivity 0.80–0.95 and specificity 0.79–0.84.

Blood serum

Denk et al. (2018) examined miRNA 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 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 an 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.

Derkow et al. (2018) examined miRNA expression in CSF of 8 FTLD, 12 AD, 8 MDE (major depressive episode) patients, and 10 HC using RT-PCR. Significantly elevated levels of let-7b and let-7e, and of let-7e only when adjusted for gender and age, were found in CSF from AD patients compared to HC. Copy numbers of let-7b and let-7e did not differ between the FTLD and HC, while levels of let-7b and let-7e, and let-7e only when adjusted for age and gender, were elevated in MDE patients compared to HC. Ct-values for miR-124 expression were lower in CSF from FTLD patients, indicating an increase in level, compared to all other tested groups.

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 FTD, 2 DLB). 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 FTD, 35 DLB patients, and 40 HC. Non-centrifuged CSF samples had greater levels (decreased Ct-values) of miR-29a and miR-146a 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-29a and miR-125b were similar in late stage AD, FTD and DLB. Levels of miR-146a were similar in AD and DLB 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 FTD, and 6–8 HC brains postmortem. By RT-qPCR, miR-183/96/182 expression was decreased in frontal cortex of patients with ALS while PP1γ, 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 PP1γ.

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 **Tables 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).

Table 1 | **Alterations of miRNA expression in frontotemporal degeneration in blood plasma and blood serum**

Author	Method of miRNA analysis	Comparison	miRNA analysis
Blood plasma			
Kmetsch et al., 2020	miRNA sequencing	Symptomatic mutation carriers[1] *vs*. HC	Upregulated: miR-34a-5p,-345-5p Downregulated: miR-200c-3p,-10a-3p
Kmetsch et al., 2020	miRNA sequencing	Presymptomatic mutation carriers[2] *vs*. HC	Upregulated: miR-34a-5p
Kmetsch et al., 2020	miRNA sequencing	Symptomatic mutation carriers *vs*. presymptomatic mutation carriers	Upregulated: miR-345-5p Downregulated: miR-200c-3p,-10a-3p
Siedlecki-Wullich et al., 2019	RT-PCR	AD *vs*. HC	Upregulated: miR-92a-3p,-181c-5p,-210-3p
Siedlecki-Wullich et al., 2019	RT-PCR	MCI *vs*. HC	Upregulated: miR-181c-5p,-210-3p
Siedlecki-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
			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-323-3p/miR-370, miR-382/miR-370 distinguished MCI from HC
Blood serum			
Denk et al., 2018	RT-PCR	bvFTD *vs*. HC	Upregulated: miR-143-3p,-197-3p,-27a-3p,-338-3p,-491-5p,-7b-5p,-7g-5p,-106a-5p,-106b-5p,-18b-5p,-223-3p,-26a-5p,-26b-5p,-301a-3p,-30b-5p
			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*. NINDC	Downregulated: miR-125b,-23a,-26b-5p
Galimberti et al., 2014	RT-PCR	AD *vs*. FTD and 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. [1]Symptomatic mutation carriers consisted of 15 FTD, 4 FTD/ALS, 3 ALS patients carrying a *C9orf72* expansion; [2]Presymptomatic mutation carriers were 46 asymptomatic first-degree relatives of *C9orf72* patients in which a pathogenic expansion was found.

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 neurological disorders, and primary psychiatric conditions (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; Edwards-Lee 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 (McMurtay et al., 2006; 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:$A\beta_{42}$ and p-tau:$A\beta_{42}$ ratios measured in CSF have been used to distinguish FTD and AD, and p-tau:$A\beta_{42}$ 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.

Table 2 | **Alterations of miRNA expression in frontotemporal degeneration in CSF and frontal/temporal cortical tissue**

Author	Method of miRNA analysis	Comparison	miRNA analysis
CSF			
Schneider et al., 2018	RT-PCR	Symptomatic mutation carriers[1] *vs.* presymptomatic mutation carriers[2]	Downregulated: miR-204-5p,-632 in exosomes
Schneider et al., 2018	RT-PCR	Symptomatic mutation carriers with either *GRN* or *C9orf72* mutations *vs.* presymptomatic mutation carriers	Downegulated: miR-204-5p in exosomes
Schneider et al., 2018	RT-PCR	Symptomatic mutation carriers with GRN but not with *C9orf72* mutations *vs.* presymptomatic mutation carriers	Downregulated: miR-632 in exosomes
Schneider et al., 2018	RT-PCR	bvFTD *vs.* presymptomatic mutation carriers	Downregulated: miR-204-5p,-632 in exosomes
Schneider et al., 2018	RT-PCR	FTD *vs.* HC	Downregulated: miR-632 in exosomes
Schneider et al., 2018	RT-PCR	FTD *vs.* AD	Downregulated: miR-632 in exosomes
Derkow et al., 2018	RT-PCR	AD *vs.* HC	Upregulated: let-7e
Derkow et al., 2018	RT-PCR	MDE *vs.* HC	Upregulated: let-7e
Derkow et al., 2018	RT-PCR	FTLD *vs.* HC	Upregulated: miR-124
Derkow et al., 2018	RT-PCR	FTLD *vs.* AD	Upregulated: miR-124
Derkow et al., 2018	RT-PCR	FTLD *vs.* MDE	Upregulated: miR-124
Denk et al., 2018	RT-PCR	bvFTD *vs.* HC	Upregulated: miR-124-3p,-125a-5p,-223-3p Downregulated: miR-15a-5p
Denk et al., 2018	RT-PCR	bvFTD *vs.* AD	Downregulated: miR-140-3p,-30a-5p,-30e-5p,-22-3p
Sørensen et al., 2016	RT-PCR	AD *vs.* other types of dementia	The ratio miR-29c-3p/miR-15a-5p distinguished AD from other types of dementia
Galimberti et al., 2014	RT-PCR	AD *vs.* NINDC	Downregulated: miR-125b,-26b
Galimberti et al., 2014	RT-PCR	AD *vs.* NINDC	No difference in miR-23a
Galimberti et al., 2014	RT-PCR	AD *vs.* FTD and INDC	No differences in miR-125b,-26b
Brain tissue			
Jawaid et al., 2019	RT-PCR	ALS *vs.* HC	Downregulated: miR-183/96/182 in frontal cortex
Jawaid et al., 2019	RT-PCR	FTLD *vs.* HC	Downregulated: miR-183/96/182 in frontal cortex
Hébert et al., 2013	RT-PCR	AD *vs.* HC	Downregulated: miR-132-3p,-100 in temporal cortex
Hébert et al., 2013	RT-PCR	FTD *vs.* HC	Upregulated: possibly miR-100 in temporal cortex Downregulated: miR-132-3p in temporal cortex
Hébert et al., 2013	RT-PCR	PSP *vs.* HC	Downregulated: miR-132-3p in temporal cortex
Hébert et al., 2013	RT-PCR	FTD *vs.* AD	Upregulated: possibly miR-100 in temporal cortex
Chen-Plotkin et al., 2012	RT-PCR	GRN(-)FTLD-TDP *vs.* HC	Downregulated: miR-132-5p,-132-3p,-212 in frontal cortex
Chen-Plotkin et al., 2012	RT-PCR	GRN(+)FTLD-TDP *vs.* HC	Downregulated: miR-132-5p,-132-3p,-212 in frontal cortex

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; bvFTD: behavioral variant FTD; CSF: cerebrospinal fluid; FTD: frontotemporal dementia; FTLD: frontal temporal lobar degeneration; INDC, inflammatory neurologic disease control; MDE: major depressive episode; NINDC: non-inflammatory neurologic disease control; PPA: primary progressive aphasia; PSP: progressive supranuclear palsy; RT-PCR: real time polymerase chain reaction. [1]Symptomatic mutation carriers consisted of *GRN*, *C9orf72*, *MAPT* mutation carriers and consisted of 12 bvFTD, 1 nfvPPA, 1 svPPA, 1 dementia not otherwise specified; [2]Presymptomatic mutation carriers consisted of 23 patients.

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-335-5p, 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 (Schneider et al., 2018). These dysregulated miRNAs were different to what had been found in the blood plasma of symptomatic mutation carriers having a *C9orf72* expansion compared to presymptomatic mutation carriers (Kmetsch et al., 2021). In addition, miR-204-5p, miR-632 were downregulated in exosomes from CSF for bvFTD compared to presymptomatic mutation carriers, and miR-632 downregulation was found for sporadic FTD compared to HC or AD (Schneider et al., 2018). In CSF, miR-124 upregulation occurred in FTD compared to HC, AD and MDE (Derkow et al.,

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. MiR-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

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, gender, ages	Sample assayed	Altered miRNA expression	Related pathway to FTD
bvFTD vs. HC					
Denk et al., 2018	48 bvFTD[1], 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
				miR-15a-5p downregulated	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 downregulated	MiR-22-3p targets *BDNF*, *PTEN*, and *SIRT1* genes
Denk et al., 2018	48 bvFTD[1], 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
				miR-124-3p upregulated	The target gene of miR-124 is AMPAR. AMPA receptors are associated with the regulation of social behavior
				miR-15a-5p downregulated	A positive linkage of miR-15a with amantadine, which is associated with the treatment of behavioral disturbances
					MiR-15a-5p targets *BDNF* gene
Denk et al., 2018	48 bvFTD[1], 30M/18F, 65±9.2 yr (48 CSF)	48 AD[1], 22M/26F, 65±9.3 yr (48 CSF)	CSF	miR-22-3p downregulated	MiR-22-3p targets *BDNF*, *PTEN*, and *SIRT1* genes
FTLD vs. HC					
Derkow et al., 2018	8 FTD, 3M/5F, 64±11.5 yr	10 HC, 7M/3F, 58.3±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 FTD, 3M/5F, 64±11.5 yr	12 AD, 2M/10F, 71.5±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-isoxazolepropionic acid; CSF: cerebrospinal fluid; F: female; FTD: frontotemporal dementia; bvFTD: behavioral variant FTD; FTLD: frontotemporal lobar degeneration; HC: healthy controls; M: male; yr: years. [1]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.

disproportion in these two groups by multiple comparisons was not made. Furthermore, the gender composition of the AD, FTD, NINCD 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 (Jawaid 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 in the other two. Further studies are warranted on miRNA expression in biofluids and frontal/temporal cortical tissue of patients and to examine for similarities.

No effective treatments are available for FTD disease at present, but promising clinical trials are being undertaken. Two of the greatest challenges in conducting clinical trials in FTD are the heterogeneity of FTD cases causing difficulties in efficiently determining treatment effects, and the rarity of FTD disorders leading to difficulties in recruitment. The results of two large industry-sponsored trials in bvFTD (TRx0237 treatment, a tau protein aggregation inhibitor; NCT01626378) and FTD due to GRN mutations (FTLFD-GRN) (FRM-0334 treatment, a histone deacetylase inhibitor; NCT02149160) have not yet been published. Tau immunotherapy trials are being conducted by groups exploiting the clinical homogeneity of patients with nfvPPA (Santos-Santos et al., 2016) that is considered a “pure” 4 repeat taupathy with a well-defined history of disease progression. Antisense oligonucleotide (ASO) therapy has been shown to be effective in treating spinal muscular atrophy (Iwamoto et al., 2017; Wood et al., 2017). Two ASO programs targeting the C9orf72 mutation (NCT03070119, NCT03626012; Ly and Miller, 2018) are approaching the clinical stage for ALS and an anti-*MAPT* ASO trial is underway in AD (NCT02820896; Marshall, 2017). These approaches could potentially be used to treat FTD due to *C9orf72* or *MAPT* mutations. An FTLD marmoset model has recently been produced by silencing *FUS* gene using an adeno-associated virus encoding shRNA against the marmoset FUS gene. The adeno-associated virus encoding shRNA against the marmoset *FUS* gene was introduced into the frontal cortex of young adult female marmoset monkeys by stereotactic injection and caused FUS expressions to be decreased by 70–80%, with an increase in astrocytes and microglia (Endo et al., 2018). This model may provide important information on potential biomarkers, disease progression, and testing of possible therapeutic strategies.

To summarize, there has been progress made in the recent studies for distinguishing FTD from healthy controls, AD, and ALS by analyzing miRNAs in blood plasma, blood serum, CSF, exosomes from CSF, frontal and temporal cortical tissue, and have included single and combinations of miRNAs as well as ratios of two miRNAs that were subjected to ROC analysis. Limitations identified in many of the studies included small group sizes, disproportion in ages and gender, heterogeneity of FTD, AD and HC groups, normalization and statistical analysis of data. By continuing to address these concerns in future studies it is hoped that a sensitive and specific, minimally invasive test can be developed to identify patients with FTD 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 FTD subtypes to be accurately distinguished.

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References

Alexandrov PN, Zhao Y, Pogue AI, Tarr MA, Kruck TP, Percy ME, Cui JG, Lukiw WJ (2012) microRNA (miRNA) speciation in Alzheimer’s disease cerebrospinal fluid (CSF) and extracellular fluid (ECF). In J Biochem Mol Biol 3:365-373.

Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, Mann D, Tsuchiya K, Yoshida M, Hashizume Y, Oda T (2006) TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun 351:602-611.

Arrant AE, Roberson ED (2014) MicroRNA-124 modulates social behavior in frontotemporal dementia. Nat Med 20:1381-1383.

Bagga S, Bracht J, Hunter S, Massirer K, Holtz J, Eachus R, Pasquinelli AE (2005) Regulation by let-7 and lin-4 miRNAs results in target mRNA degradation. Cell 122:553-563

Bang J, Spina S, Miller BL (2015) Frontotemporal dementia. Lancet 386:1672-1682.

Bertrand A, Wen J, Rinaldi D, Houot M, Sayah S, Camuzat A, Fournier C, Fontanella S, Routier A, Couratier P, Pasquier F, Habert MO, Hannequin D, Martinaud O, Caroppo P, Levy R, Dubois B, Brice A, Durrleman S, Colliot O, Le Ber I (2018) Early cognitive, structural, and microstructural changes in presymptomatic C9orf72 carriers younger than 40 years. JAMA Neurol 75:236-245.

Blauwendraat C, Wilke C, Simón-Sánchez J, Jansen IE, Reifschneider A, Capell A, Haass C, Castillo-Lizardo M, Biskup S, Maetzler W, Rizzu P, Heutink P, Synofzik M (2018) The wide genetic landscape of clinical frontotemporal dementia: systematic combined sequencing of 121 consecutive subjects. Genet Med 20:240-249.

Bruun M, Koikkalainen J, Rhodius-Meester HF, Baroni M, Gjerum L, van Gils M, Soininen H, Remes AM, Hartikainen P, Waldemar G, Mecocci P, Barkhof F, Pijnenburg Y, van der Flier WM, Hasselbalch SG, Lötjönen J, Frederiksen KS (2019) Detecting frontotemporal dementia syndromes using MRI biomarkers. Neuroimage Clin 22:101711.

Buratti E, Baralle FE (2010) The multiple roles of TDP-43 in pre-mRNA processing and gene expression regulation. RNA Biol 7:420-429.

Casoli T, Paolini S, Fabbietti P, Fattoretti P, Paciaroni L, Fabi K, Gobbi B, Galeazzi R, Rossi R, Lattanzio F, Pelliccioni G (2019) Cerebrospinal fluid biomarkers and cognitive status in differential diagnosis of frontotemporal dementia and Alzheimer’s disease. J Int Med Res 42:4968-4980.

Chen-Plotkin AS, Unger TL, Gallagher MD, Bill E, Kwong LK, Volpicelli-Daley L, Busch JI, Akle S, Grossman M, Van Deerlin V, Trojanowski JQ, Lee VM (2012) TMEM106B, the risk factor for frontotemporal dementia, is regulated by microRNA-132/212 cluster and affects progranulin pathways. J Neurosci 32:11213-11227.

Cogswell JP, Ward J, Taylor IA, Waters M, Shi Y, Cannon B, Kelnar K, Kemppainen J, Brown D, Chen C, Prinjha RK, Richardson JC, Saunders AM, Roses AD, Richards CA (2008) Identification of miRNA changes in Alzheimer’s disease brain and CSF yields putative biomarkers and insights into disease pathways. J Alzheimers Dis 14:27-41.

Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, Suciu N, Cretoiu SM, Voinea SC (2020) miRNAs as biomarkers in disease: latest findings regarding their role in diagnosis and prognosis. Cells 9:276.

Dantham S, Srivastava AK, Gulati S, Rajeswari MR (2018) Differentially regulated cell-free microRNAs in the plasma of Friedreich’s ataxia patients and their association with disease pathology. Neuropediatrics 49:35-43.

de Mendonça A, Ribeiro F, Guerreiro M, Garcia C (2004) Frontotemporal mild cognitive impairment. J Alzheimers Dis 6:1-9.
DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, et al. (2011) Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 72:245-256.
Denk J, Oberhauser F, Kornhuber J, Wiltfang J, Fassbender K, Schroeter ML, Volk AE, Diehl-Schmid J, Prudlo J, Danek A, Landwehrmeyer B, Lauer M, Otto M, Jahn H (2018) Specific serum and CSF microRNA profiles distinguish sporadic behavioural variant of frontotemporal dementia compared with Alzheimer patients and cognitively healthy controls. PLoS One 13:e0197329.
Derkow K, Rössling R, Schipke C, Krüger C, Bauer J, Fähling M, Stroux A, Schott E, Ruprecht K, Peters O, Lehnardt S (2018) Distinct expression of the neurotoxic microRNA family let-7 in the cerebrospinal fluid of patients with Alzheimer's disease. PLoS One 13:e0200602.
Di Carlo V, Grossi E, Laneve P, Morlando M, Dini Modigliani S, Ballarino M, Bozzoni I, Caffarelli E (2013) TDP-43 regulates the microprocessor complex during in vitro neuronal differentiation. Mol Neurobiol 48:952-963.
Edwards-Lee T, Miller BL, Benson DF, Cummings JL, Russell GL, Boone K, Mena I (1997) The temporal variant of frontotemporal dementia. Brain 120:1027-1040.
Eisen A, Kiernan M, Mitsumoto H, Swash M (2014) Amyotrophic lateral sclerosis: a long preclinical period? J Neurol Neurosurg Psychiatry 85:1232-1238.
Elderkin-Thompson V, Boone KB, Hwang S, Kumar A (2004) Neurocognitive profiles in elderly patients with frontotemporal dementia or major depressive disorder. J Int Neuropsychol Soc 10:753-771.
Elfgren C, Passant U, Risberg J (1993) Neuropsychological findings in frontal lobe dementia. Dementia 4:214-219.
Endo K, Ishigaki S, Masamizu Y, Fujioka Y, Watakabe A, Yamamori T, Hatanaka N, Nambu A, Okado H, Katsuno M, Watanabe H, Matsuzaki M, Sobue G (2018) Silencing of FUS in the common marmoset (Callithrix jacchus) brain via stereotactic injection of an adeno-associated virus encoding shRNA. Neurosci Res 130:56-64.
Ferrari R, Kapogiannis D, Huey ED, Momeni P (2011) FTD and ALS: a tale of two diseases. Curr Alzheimer Res 8:273-294.
Fontana F, Siva K, Denti MA (2015) A network of RNA and protein interactions in fronto temporal dementia. Front Mol Neurosci 8:9.
Galimberti D, Villa C, Fenoglio C, Serpente M, Ghezzi L, Cioffi SM, Arighi A, Fumagalli G, Scarpini E (2014) Circulating miRNAs as potential biomarkers in Alzheimer's disease. J Alzheimers Dis 42:1261-1267.
Gascon E, Gao FB (2014) The emerging roles of microRNAs in the pathogenesis of frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) spectrum disorders. J Neurogenet 28:30-40.
Gascon E, Lynch K, Ruan H, Almeida S, Verheyden JM, Seeley WW, Dickson DW, Petrucelli L, Sun D, Jiao J, Zhou H, Jakovcevski M, Akbarian S, Yao WD, Gao FB. (2014) Alterations in microRNA-124 and AMPA receptors contribute to social behavior deficits in frontotemporal dementia. Nat Med 20:1444-1451.
Graff-Radford NR, Woodruff BK (2007) Frontotemporal dementia. Semin Neurol 27:48-57.
Grasso M, Piscopo P, Talarico G, Ricci L, Crestini A, Tosto G, Gasparini M, Bruno G, Denti MA, Confaloni A (2019) Plasma microRNA profiling distinguishes patients with frontotemporal dementia from healthy subjects. Neurobiol Aging 84:240.e1-240.
He L, Hannon GJ (2004) MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 5:522-531.
Hébert SS, Horré K, Nicolaï L, Papadopoulou AS, Mandemakers W, Silahtaroglu AN, Kauppinen S, Delacourte A, De Strooper B (2008) Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. Proc Nat Acad Sci U S A 105: 6415-6420.
Hébert SS, Wang WX, Zhu Q, Nelson PT (2013) A study of small RNAs from cerebral neocortex of pathology-verified Alzheimer's disease, dementia with lewy bodies, hippocampal sclerosis, frontotemporal lobar dementia, and non-demented human controls. J Alzheimers Dis 35:335-348.
Hodges JR (2001) Frontotemporal dementia (Pick's disease): clinical features and assessment. Neurology 56:S6-10.
Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, Kril JJ, Halliday GM (2004) Clinicopathological correlates in frontotemporal dementia. Ann Neurol 56:399-406.
Holm IE, Englund E, Mackenzie IR, Johannsen P, Isaacs AM (2007) A reassessment of the neuropathology of frontotemporal dementia linked to chromosome 3. J Neuropathol Exp Neurol 66:884-891.
Holm IE, Isaacs AM, Mackenzie IR (2009) Absence of FUS-immunoreactive pathology in frontotemporal dementia linked to chromosome 3 (FTD-3) caused by mutation in the CHMP2B gene. Acta Neuropathol 118:719-720.
Huey ED, Putnam KT, Grafman J (2006) A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. Neurology 66:17-22.
Iwamoto N, Butler DCD, Svrzikapa N, Mohapatra S, Zlatev I, Sah DWY, Meena, Standley SM, Lu G, Apponi LH, Frank-Kamenetsky M, Zhang JJ, Vargeese C, Verdine GL (2017) Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. Nat Biotechnol 35:845-851.
Jawaid A, Woldemichael BT, Kremer EA, Laferriere F, Gaur N, Afroz T, Polymenidou M, Mansuy IM (2019) Memory decline and its reversal in aging and neurodegeneration involve miR-183/96/182 biogenesis. Mol Neurobiol 56:3451-3462.
Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, Petersen RC (2006) Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Arch Neurol 63:674-681.
Kawahara Y, Mieda-Sato A (2012) TD-43 promotes microRNA biogenesis as a component of the Drosha and Dicer complexes. Proc Natl Acad Sci U S A 109:3347-3352.
Kertesz A, Davidson W, McCabe P, Munoz D (2003) Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia. Alzheimer Dis Assoc Disord 17:223-229.
Kiko T, Nakagawa K, Tsuduki T, Furukawa K, Arai H, Miyazawa T (2014) MicroRNAs in plasma and cerebrospinal fluid as potential markers for Alzheimer's disease. J Alzheimers Dis 39:253-259.
Kmetsch V, Anquetil V, Saracino D, Rinaldi D, Camuzat A, Gareau T, Jornea L, Forlani S, Couratier P, Wallon D, Pasquier F, Robil N, de la Grange P, Moszer I, Le Ber I, Colliot O, Becker E (2021) Plasma microRNA signature in presymptomatic and symptomatic subjects with C9orf 72-associated frontotemporal dementia and amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 92:485-493.
Kovanda A, Leonardis L, Zidar J, Koritnik B, Dolenc-Groselj L, Kovacic SR, Curk T, Rogelj B (2018) Differential expression of microRNAs and other small RNAs in muscle tissue of patients with ALS and healthy age-matched controls. Sci Rep 8:5609.
Lauretti E, Dincer O, Praticò D (2020) Regional and temporal miRNAs expression profile in a transgenic mouse model of tauopathy: implication for its pathogenesis. Mol Psychiatry doi: 10.1038/s41380-020-0655-2.
Lee G, Leugers CJ (2012) Tau and taupathies. Prog Mol Biol Transl Sci 107:263-293.
Lee ST, Chu K, Jung KH, Kim JH, Huh JY, Yoon H, Park DK, Lim JY, Kim JM, Jeon D, Ryu H, Lee SK, Kim M, Roh JK (2012) miR-206 regulates brain-derived neurotrophic factor in Alzheimer disease model. Ann Neurol 72:269-277.
Lee VM, Goedert M, Trojanowski JQ (2001) Neurodegenerative taupathies. Annu Rev Neurosci 24:1121-1159.
Lehmann SM, Krüger C, Park B, Derkow K, Rosenberger K, Baumgart J, Trimbuch T, Eom G, Hinz M, Kaul D, Habbel P, Kälin R, Franzoni E, Rybak A, Nguyen D, Veh R, Ninnemann O, Peters O, Nitsch R, Heppner FL, et al. (2012) An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. Nat Neurosci 15:827-835.
Li J, Liu Y, Kim T, Min R, Zhang Z (2010) Gene expression variability within and between human populations and implications toward disease susceptibility. PLoS One Comput Biol 6:e1000910.
Liu CG, Wang JL, Li L, Xue LX, Zhang YQ, Wang PC (2014) MicroRNA-135a and -200b, potential biomarkers for Alzheimer's disease, regulate β secretase and amyloid precursor protein. Brain Res 1583:55-64.
Liu K, Tong H, Li T, Wang X, Chen Y (2020) Research progress in molecular biology related to quantitated methods of microRNA. Am J Transl Res 12:3198-3211.
Ly CV, Miller TM (2018) Emerging antisense oligonucleotide and viral therapies for amyotrophic lateral sclerosis. Curr Opin Neurol 31:648-654.
Mackenzie IR, Rademakers R, Neumann M (2010) TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. Lancet Neurol 9:995-1007.
Maloney B, Lahiri DK (2016) Epigenetics of dementia: understanding the disease as a transformation rather than a state. Lancet Neurol 15:760-774.
Marshall A (2017) Can anti-tau therapies treat neurodegenerative disorders? Neurology Rev 25:26-29.
Mayo Clinic 2021. Frontotemporal dementia. https://www.mayoclinic.org/diseases-conditions/frontotemporal-dementia/diagnosis-treatment/drc-20354741; accessed 22 March 2021.
McMurtay AM, Chen AK, Shapira JS, Chow TW, Mishkin F, Miller BL, Mendez MF (2006) Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. Neurology 66:517-522.
Meister G (2007) miRNAs get an early start on translational silencing. Cell 131:25-28.
Mendez MF, McMurtay A, Chen AK, Shapira JS, Mishkin F, Miller BL (2006a) Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. J Neurol Neurosurg Psychiatry 77:4-7.
Mendez MF, McMurtray A, Licht E, Saul RE (2006b) Patients with possible frontotemporal dementia: eventual clinical diagnoses after longitudinal follow-up. Am Acad Neurol 66:A120.
Mendez MF, Perryman KM (2002) Neuropsychiatric features of frontotemporal dementia: evaluation of consensus criteria and review. J Neuropsychiatry Clin Neurosci 14:424-429.

Meng F, Dai E, Yu X, Zhang Y, Chen X, Liu X, Wang S, Wang L, Jiang W (2013) Constructing and characterizing a bioactive small molecule and microRNA association network for Alzheimer's disease. J R Soc Interface 11:20131057.
Miller BL, Cummings JL, Villanueva-Meyer J, Boone K, Mehringer CM, Lesser IM, Mena I (1991) Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. Neurology 41:1374-1382.
Moon J, Lee ST, Kong IG, Byun JI, Sunwoo JS, Shin JW, Shim JY, Park JH, Jeon D, Jung KH, Jung KY, Kim DY, Lee SK, Kim M, Chu K (2016) Early diagnosis of Alzheimer's disease from elevated olfactory mucosal miR-206 level. Sci Rep 6:20364.
Morquette B, Juźwik CA, Drake SS, Charabati M, Zhang Y, Lécuyer MA, Galloway DA, Dumas A, de Faria Junior O, Paradis-Isler N, Bueno M, Rambaldi I, Zandee S, Moore C, Bar-Or A, Vallières L, Prat A, Fournier AE (2019) MicroRNA-223 protects neurons from degeneration in experimental autoimmune encephalomyelitis. Brain 142:2979-2995.
Müller M, Kuiperij HB, Claassen JA, Küsters B, Verbeek MM (2014) MicroRNAs in Alzheimer's disease: differential expression in hippocampus and cell-free cerebrospinal fluid. Neurobiol Aging 35:152-158.
Müller M, Kuiperij HB, Versleijen AA, Chiasserini D, Farotti L, Baschieri F, Parnetti L, Struyfs H, De Roeck N, Luyckx J, Engelborghs S, Claassen JA, Verbeek MM (2016) Validation of microRNAs in cerebrospinal fluid as biomarkers for different forms of dementia in a multicenter study. J Alzheimers Dis 52:13210-1333.
Munoz DG, Neumann M, Kusaka H, Yokota O, Ishihara K, Terada S, Kuroda S, Mackenzie IR (2009) FUS pathology in basophilic inclusion body disease. Acta Neuropathol 118:617-627.
Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51:1546-1554.
Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM (2006) Ubiquitinated TDP-43 in frontotemporal dementia and amyotrophic lateral sclerosis. Science 314:130-133.
Neumann M, Rademakers R, Roeber S, Baker M, Kretzschmar HA, Mackenzie IR (2009a) A new subtype of frontotemporal lobar degeneration with FUS pathology. Brain 132:2922-2931.
Neumann M, Roeber S, Kretzschmar HA, Rademakers R, Baker M, Mackenzie IR (2009b) Abundant FUS-immunoreactive pathology in neuronal intermediate filament inclusion disease. Acta Neuropathol 118:605-616.
Noren Hooten N, Abdelmohsen K, Gorospe M, Ejiogu N, Zonderman AB, Evans MK (2010) microRNA expression patterns reveal differential expression of target genes with age. PLoS One 5:e10724.
Olszewska DA, Lonergan R, Fallon EM, Lynch T (2016) Genetics of frontotemporal dementia. Curr Neurol Neurosci Rep 16:107.
Pasquier F, Petit H (1997) Frontotemporal dementia: its rediscovery. Eur Neurol 38:1-6.
Paul S, Bravo Vázquez LA, Pérez Uribe S, Roxana Reyes-Pérez P, Sharma A (2020) Current status of microRNA-based therapeutic approaches in neurodegenerative disorders. Cells 9:1698.
Piscopo P, Albani D, Castellano AE, Forloni G, Confaloni A (2016a) Frontotemporal lobar degeneration and microRNAs. Front Aging Neurosci 8:17.
Piscopo P, Grasso M, Fontana F, Crestini A, Puopolo M, Del Vescovo V, Venerosi A, Calamandrei G, Vencken SF, Greene CM, Confaloni A, Denti MA (2016b) Reduced miR-659-3p levels correlate with progranulin increase in hypoxic conditions: implications for frontotemporal dementia. Front Mol Neurosci 9:31.
Piscopo P, Grasso M, Puopolo M, D'Acunto E, Talarico G, Crestini A, Gasparini M, Campopiano R, Gambardella S, Castellano AE, Bruno G, Denti MA, Confaloni A (2018) Circulating miR-127-3p as a potential biomarker for differential diagnosis in frontotemporal dementia. J Alzheimers Dis 65:455-464.
Rabinovici GD, Miller BL (2010) Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. CNS Drugs 24:375-398.
Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, et al. (2011) Sensitivity of revised diagnostic criteria for the behavioral variant of frontotemporal dementia. Brain 134:2456-2477.
Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes AM, Kaganovich A, Scholz SW, Duckworth J, Ding J, Harmer DW, Hernandez DG, et al. (2011) A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 72:257-268.
Rosso SM, Donker Kaat L, Baks T, Joosse M, de Koning I, Pijnenburg Y, de Jong D, van Duijn CM, Heutink P, van Swieten JC (2003) Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. Brain 126:2016-2022.
Sala Frigerio C, Lau P, Salta E, Tournoy J, Bossers K, Vandenberghe R, Wallin A, Bjerke M, Zetterberg H, Blennow K, De Strooper B (2013) Reduced expression of hsa-miR-27a-3p in CSF of patients with Alzheimer disease. Neurology 81:2103-2106.
Santos-Santos MA, Mandelli ML, Binney RJ, Ogar J, Wilson SM, Henry ML, Hubbard HI, Meese M, Attygalle S, Rosenberg L, Pakvasa M, Trojanowski JQ, Grinberg LT, Rosen H, Boxer AL, Miller BL, Seeley WW, Gorno-Tempini ML (2016) Features of patients with nonfluent/agrammatic primary progressive aphasia with underlying progressive supranuclear palsy pathology or corticobasal degeneration. JAMA Neurol 73:733-742.
Schneider R, McKeever P, Kim T, Graff C, van Swieten JC, Karydas A, Boxer A, Rosen H, Miller BL, Laforce R Jr, Galimberti D, Masellis M, Borroni B, Zhang Z, Zinman L, Rohrer JD, Tartaglia MC, Robertson J (2018) Downregulation of exosomal miR-204-5p and miR-632 as a biomarker for FTD: a GENFI study. J Neurol Neurosurg Psychiatry 89:851-858.
Sheinerman KS, Toledo JB, Tsivinsky VG, Irwin D, Grossman M, Weintraub D, Hurtig HI, Chen-Plotkin A, Wolk DA, McCluskey LF, Elman LB, Trojanowski JQ, Umansky SR (2017) Circulating brain-enriched microRNAs as novel biomarkers for detection and differentiation of neurodegenerative diseases. Alzheimers Res Ther 9:89.
Sheinerman KS, Tsivinsky VG, Abdullah L, Crawford F, Umansky SR (2013) Plasma microRNA biomarkers for detection of mild cognitive impairment: biomarker validation study. Aging (Albany NY) 5:925-938.
Sheinerman KS, Tsivinsky VG, Crawford F, Mullan MJ, Abdullah L, Umansky SR (2012) Plasma microRNA biomarkers for detection of mild cognitive impairment. Aging (Albany NY) 4:590-605.
Sheinerman KS, Umansky SR (2013) Circulating cell-free microRNA as biomarkers for screening, diagnosis and monitoring of neurodegenerative diseases and other neurologic pathologies. Front Cell Neurosci 7:150.
Sieben A, Van Langenhove T, Engelborghs S, Martin JJ, Boon P, Cras P, De Deyn PP, Santens P, Van Broeckhoven C, Cruts M (2012) The genetics and neuropathology of frontotemporal lobar degeneration. Acta Neuropathol 124:353-372.
Siedlecki-Wullich D, Català-Solsona J, Fábregas C, Hernández I, Clarimon J, Lleó A, Boada M, Saura CA, Rodríguez-Álvarez J, Miñano-Molina AJ (2019) Altered microRNAs related to synaptic function as potential plasma biomarkers for Alzheimer's disease. Alzheimers Res Ther 11:46.
Sørensen SS, Nygaard AB, Christensen T (2016) miRNA expression profiles in cerebrospinal fluid and blood of patients with Alzheimer's disease and other types of dementia–an exploratory study. Transl Neurodegener 5:6.
Stephan BC, Matthews FE, Khaw KT, Dufouil C, Brayne C (2009) Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND). Alzheimers Res Therapy 1:4-12.
The Lund and Manchester Groups (1994) Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 57:416-418.
Tian N, Cao Z, Zhang Y (2014) MiR-206 decreases brain-derived neurotrophic factor levels in a transgenic mouse model of Alzheimer's disease. Neurosci Bull 30:191-197.
Toivonen JM, Manzano R, Oliván S, Zaragoza P, García-Redondo A, Osta R (2014) MicroRNA-206: a potential circulating biomarker candidate for amyotrophic lateral sclerosis. PLoS One 9:e89065.
UCSF Weill Institute for Neurosciences. Familial FTD. https://memory.ucsf.edu/genetics/familial-ftd. accessed 11 April 2021.
Vijverberg EG, Dols A, Krudop WA, Peters A, Kerssens CJ, van Berckel BN, Wattjes MP, Barkhof F, Gossink F, Prins ND, Stek ML, Scheltens P, Pijnenburg YA (2016) Diagnostic accuracy of the frontotemporal dementia consensus criteria in the late-onset frontal lobe syndrome. Dement Geriatr Cogn Disord 41:210-219.
Waller R, Goodall EF, Milo M, Cooper-Knock J, Da Costa M, Hobson E, Kazoka M, Wollff H, Heath PR, Shaw PJ, Kirby J (2017) Serum miRNAs miR-206, 143-3p, and 374b-5p as potential biomarkers for amyotrophic lateral sclerosis (ALS). Neurobiol Aging 55:123-131.
Warren JD, Rohrer JD, Rossor MN (2013) Clinical review. Frontotemporal dementia. BMJ 347:f4827.
Wood MJ, Talbot K, Bowerman M (2017) Spinal muscular atrophy: antisense oligonucleotide therapy opens the door to an integrated therapeutic landscape. Hum Mol Genet 26:R151-159.
Zanardini R, Ciani M, Benussi L, Ghidoni R (2016) Molecular pathways bridging frontotemporal lobar degeneration and psychiatric disorders. Front Aging 8:10.

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