Vavilovskii Zhurnal Genetiki i Selektsii
Vavilov Journal of Genetics and Breeding. 2024;28(2):228-238

DOI 10.18699/vjgb-24-27

Involvement of transposable elements in Alzheimer's disease pathogenesis

R.N. Mustafin [1] ✉, E.K. Khusnutdinova [1, 2]

[1] Bashkir State Medical University, Ufa, Russia
[2] Institute of Biochemistry and Genetics – Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences, Ufa, Russia
✉ ruji79@mail.ru

Abstract. Alzheimer's disease affects an average of 5 % of the population with a significant increase in prevalence with age, suggesting that the same mechanisms that underlie aging may influence this pathology. Investigation of these mechanisms is promising for effective methods of treatment and prevention of the disease. Possible participants in these mechanisms are transposons, which serve as drivers of epigenetic regulation, since they form species-specific distributions of non-coding RNA genes in genomes in evolution. Study of miRNA involvement in Alzheimer's disease pathogenesis is relevant, since the associations of protein-coding genes (*APOE4*, *ABCA7*, *BIN1*, *CLU*, *CR1*, *PICALM*, *TREM2*) with the disease revealed as a result of GWAS make it difficult to explain its complex pathogenesis. Specific expression changes of many genes were found in different brain parts of Alzheimer's patients, which may be due to global regulatory changes under the influence of transposons. Experimental and clinical studies have shown pathological activation of retroelements in Alzheimer's disease. Our analysis of scientific literature in accordance with MDTE DB revealed 28 miRNAs derived from transposons (17 from LINE, 5 from SINE, 4 from HERV, 2 from DNA transposons), the expression of which specifically changes in this disease (decreases in 17 and increases in 11 microRNA). Expression of 13 out of 28 miRNAs (miR-151a, -192, -211, -28, -31, -320c, -335, -340, -378a, -511, -576, -708, -885) also changes with aging and cancer development, which indicates the presence of possible common pathogenetic mechanisms. Most of these miRNAs originated from LINE retroelements, the pathological activation of which is associated with aging, carcinogenesis, and Alzheimer's disease, which supports the hypothesis that these three processes are based on the primary dysregulation of transposons that serve as drivers of epigenetic regulation of gene expression in ontogeny.
Key words: Alzheimer's disease; carcinogenesis; miRNA; aging; transposons; retroelements.

For citation: Mustafin R.N., Khusnutdinova E.K. Involvement of transposable elements in Alzheimer's disease pathogenesis. *Vavilovskii Zhurnal Genetiki i Selektsii = Vavilov Journal of Genetics and Breeding*. 2024;28(2):228-238. DOI 10.18699/vjgb-24-27

Влияние транспозонов на развитие болезни Альцгеймера

Р.Н. Мустафин [1] ✉, Э.К. Хуснутдинова [1, 2]

[1] Башкирский государственный медицинский университет, Уфа, Россия
[2] Институт биохимии и генетики – обособленное структурное подразделение Уфимского федерального исследовательского центра Российской академии наук, Уфа, Россия
✉ ruji79@mail.ru

Аннотация. Болезнь Альцгеймера поражает в среднем 5 % населения со значительным увеличением распространенности с возрастом, что свидетельствует о возможном влиянии на данную патологию тех же механизмов, которые лежат в основе старения человека. Исследование этих механизмов перспективно для разработки эффективных методов лечения и профилактики заболевания. Возможными участниками этих механизмов являются транспозоны, которые служат драйверами эпигенетической регуляции, поскольку формируют в эволюции видоспецифические распределения генов некодирующих РНК в геноме человека. Изучение роли микроРНК в развитии болезни Альцгеймера актуально, поскольку по результатам проведенных GWAS ассоциаций белок-кодирующих генов (*APOE4*, *ABCA7*, *BIN1*, *CLU*, *CR1*, *PICALM*, *TREM2*) трудно объяснить сложный патогенез заболевания. Кроме того, в различных долях головного мозга при болезни Альцгеймера были обнаружены специфические изменения экспрессии множества генов, что может быть обусловлено глобальными регуляторными изменениями под влиянием транспозонов. Действительно, экспериментальные и клинические исследования показали патологическую активацию ретроэлементов при болезни Альцгеймера. Проведенный нами анализ научной литературы в соответствии с базой данных MDTE DB (microRNAs derived from transposable elements) позволил выявить 28 различных микроРНК, происходящих от мобильных элементов (17 – от LINE, 5 – от SINE, 4 – от HERV, 2 – от ДНК-транспозонов), экспрессия которых специфически изменяется при данном заболевании (снижается у 17 и повышается у 11 микроРНК). Экспрес-

сия 13 из 28 микроРНК (miR-151a, -192, -211, -28, -31, -320c, -335, -340, -378a, -511, -576, -708, -885) меняется также при старении и развитии злокачественных новообразований, что подтверждает возможное наличие общих патогенетических механизмов. Большинство из этих микроРНК произошли от LINE-ретроэлементов, патологическая активация которых ассоциирована со старением, канцерогенезом и болезнью Альцгеймера, что свидетельствует в пользу гипотезы о том, что в основе этих трех процессов лежит первичная дисрегуляция транспозонов, которые служат драйверами эпигенетической регуляции экспрессии генов в онтогенезе.
Ключевые слова: болезнь Альцгеймера; канцерогенез; микроРНК; старение; транспозоны; ретроэлементы.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease. Disease pathogenesis is caused by extracellular deposition of beta-amyloid plaques and intracellular accumulation of tau protein tangles with cell death in the brain (Barak et al., 2013). AD is detected in 62 % of patients with dementia (Swarbrick et al., 2019). In 2017, a meta-analysis revealed a 5 % prevalence of AD in Europe (3.31 % in men and 7.13 % in women) and an increase in these rates with age (7.66 % in 75–84-year-olds, 22.53 % in 85-year-olds and older). In Japan, AD occurs in 7 % of people over 65 years of age, in the USA – in 9.51 % of people over 70 years of age. In Chinese residents, the incidence of AD is 1.27 % in people 65–69 years old and 18.54 % in people 85–89 years old (Niu et al., 2017). Twin studies showed the heritability of AD to be 58 %, regardless of gender (Gatz et al., 2006).

In 2018, a genome-wide association study (GWAS) of DNA samples from 314,278 patients showed an association of the *ACE*, *ADAM10*, *BCKDK/KAT8*, *TOMM40*, *VKORC1* genes with AD (Marioni et al., 2018). In 2019, a meta-analysis of GWAS results (53,042 AD patients and 355,900 healthy controls) identified 37 specific loci associated with AD in the human genome. Among them, the *APH1B*, *BIN1*, *CASS4*, *CCDC6*, *NCK2*, *PILRA*, *PTK2B*, *SPRED2*, *TSPAN14* genes showed the greatest significance. However, it is difficult to explain the role of allelic variants of these genes in the pathogenesis of AD of these genes.

Possible mechanisms of other AD-associated genes are shown for *LILRB2* (encodes a receptor that recognizes multiple HLA alleles and may be involved in the growth of beta-amyloid fibrils), *ABCA1* (involved in the transfer of phospholipids to apolipoproteins), *AGRN* (involved in the formation of synapses of mature hippocampal neurons) (Schwartzentruber et al., 2021). In 2021, a meta-analysis showed an association of 23 different SNPs with AD, among which the highest significance was determined for rs3865444 (in the *CD33* transmembrane receptor gene), rs7561528 (in the nucleocytoplasmic adapter protein gene (*BIN1*)) and rs1801133 (in the methylenetetrahydrofolate reductase gene (*MTHFR*)) (GNS et al., 2021).

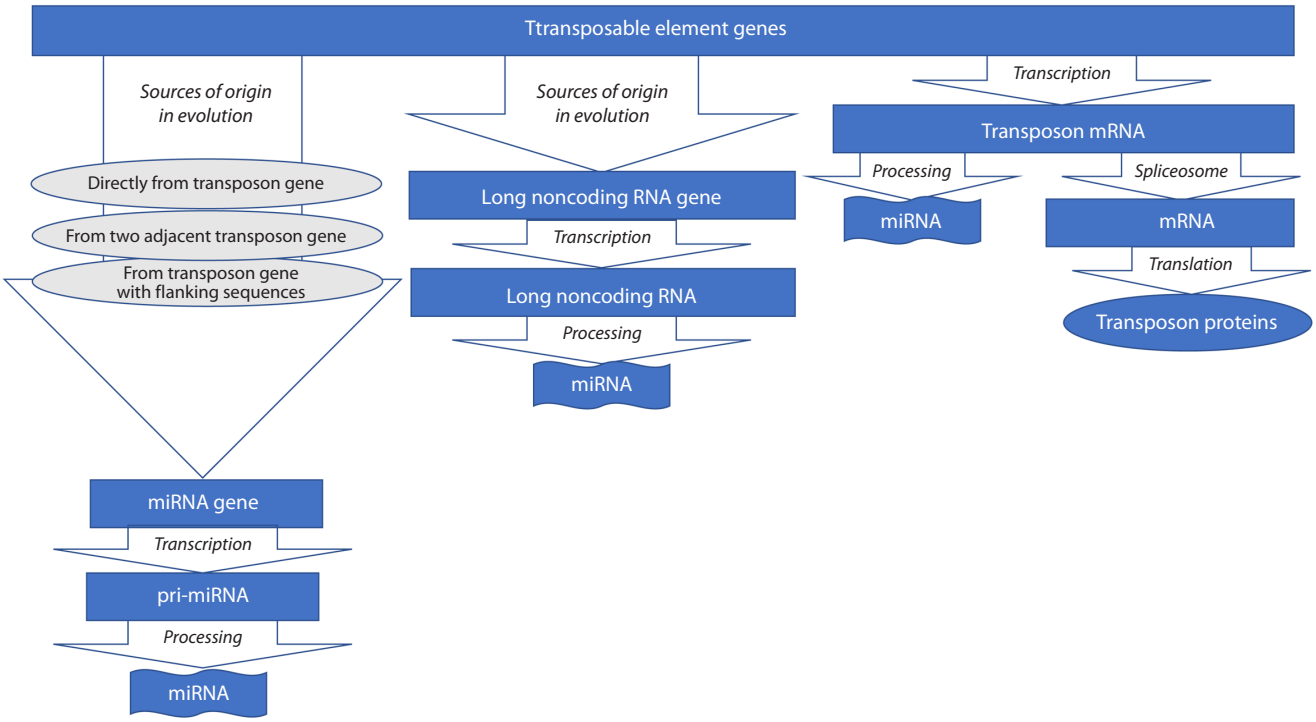
In GWASs, a significant association with AD was also shown for the *CLU* (*APOJ*, encodes apolipoprotein J), *CR1* (encodes complement component 3b/4b) (Lambert et al., 2009), *APOE* (encodes apolipoprotein E), *PICALM* (encodes protein phosphatidlinositol-binding clathrin assembly) (Harold et al., 2009; Ando et al., 2022), *BIN1* (Ando et al., 2022) genes. Meta-analyses of GWAS results with Alzheimer's disease showed a significant association of allelic variants of the *TREM2* (encodes the trigger receptor expressed on protein 2 myeloid cells) (Guerreiro et al., 2013) and *ABCA7* (Ma et al., 2018) genes.

According to numerous genome-wide association meta-analyses and large-scale genome-wide association studies, the strongest genetic risk factor for sporadic AD is the *APOE* ε4 allele, while the most powerful protective genetic factor is the *APOE* ε2 allele. This is due to the effects of APOE on β-amyloid peptide aggregation and clearance, neurofibrillary tau degeneration, microglial and astrocyte responses, and the blood-brain barrier (Serrano-Pozo et al., 2021). The production and breakdown of amyloid are also directly influenced by the *AβPP*, *PSEN1* and *PSEN2* genes, the allelic variants of which contribute to increased toxic amyloid types aggregation (Robinson et al., 2017).

The key role of genetic factors in the development of AD is evidenced by the presence of monogenic hereditary forms of the disease with an autosomal dominant type of inheritance. These forms of the disease are caused by germline mutations in the *APP* (amyloid precursor protein) (Rogaev et al., 1994; Goate et al., 2006), *PSEN1* (presenilin-1) (Sherrington et al., 1995), *PSEN2* (presenilin-2) (Levy-Lahad et al., 1995) genes. Genomic instability is important in the pathogenesis of AD, as evidenced by the pronounced association of AD with age (which is characterized by genomic instability) (Hou et al., 2017). A genomic instability component in AD may be expression changes of long non-coding RNAs, such as XIST (X-inactive specific transcript), which is considered as a potential target for AD therapy (Chanda, Mukhopadhyay, 2020).

In addition to the association of allelic variants of specific genes from DNA samples of peripheral blood leukocytes of patients with AD, a number of studies have analyzed the expression of specific genes in the brain cells of patients. The data obtained could better explain the possible mechanisms of AD pathogenesis. In 2022, a meta-analysis identified 1915 differentially expressed genes in the entorhinal cortex (the hippocampus-related part of the temporal lobe) in AD patients compared to healthy controls (Fagone et al., 2022). Earlier, in 2019, a meta-analysis of the transcriptome in AD had showed differential expression of a large number of genes in different lobes of the brain: in the temporal lobe – 323, in the frontal – 435, parietal – 1023, cerebellar – 828 genes (Patel et al., 2019). This indicates a pronounced deregulation of gene expression in the brain in AD on a genome-wide scale, a possible cause of which is the pathological activation of transposable elements (TEs), which occupy 45 % of the human genome. TEs have a global regulatory effect on the expression of all genes (as drivers of epigenetic regulation (Mustafin, Khusnutdinova, 2017)) and binding sites for transcription factors (Mustafin, 2019).

The cause of genomic instability in neurons in AD may be somatic recombinations between TEs, such as Alus and LINE1s (Pascarella et al., 2022). This is evidenced by recent



Mechanisms of origin of microRNAs from transposable elements.

results obtained from fluorescent *in situ* hybridization (FISH) in individual neurons of AD patients' brain (Yurov et al., 2023), as well as experimental studies on mice with knockdown of one allele of the *BMI1* gene (encodes a protein of the Polycomb group and regulates compaction of heterochromatin). In adults, *BMI1* is normally expressed ubiquitously in brain neurons, but is reduced in AD. *Bmi1*+/– mice are characterized by neurodegenerative changes similar to AD. In this case, the loss of heterochromatin is determined mainly in the regions with repeating sequences, which include TEs or originated from them in evolution (El Hajjar et al., 2019).

TEs carry out epigenetic regulation due to their interaction with microRNAs, which evolved from TEs by various mechanisms (see the Figure), as well as by processing their transcripts to form microRNAs (Wei et al., 2016). MicroRNAs have a post-transcriptional regulatory effect on gene expression (Barak et al., 2013) and are guides for binding to DNA methyltransferases (RdDM, RNA-directed DNA methylation) with specific genomic loci, regulating expression at the transcription level (Watcharanurak, Mutirangura, 2022). Therefore, it can be assumed that the observed hypermethylation of 236 specific CpG location loci in the cerebral cortex of AD patients occurs under the influence of microRNAs upon activation of TEs (Smith et al., 2021).

TEs are divided into classes of DNA transposons (moving by a cut-and-paste mechanism) and retroelements (REs). Transposition of REs occurs by "copy-and-paste" with an intermediate RNA, from which cDNA is formed by reverse transcription. Based on the presence of long terminal repeats (LTRs), REs are classified into LTR-containing REs and non-LTR-REs. The latter include autonomous LINEs (long interspersed elements) and non-autonomous SINEs (short interspersed elements) and SVEs (SINE-VNTR-Alus). LTR-REs are endogenous retroviruses (ERVs), occupying 8 % of the human genome, while LINEs (L1 and L2) occupy 21 % (Ravel-Godreuil et al., 2021).

Role of transposable elements in Alzheimer's disease development

The activity of TEs is under the control of epigenetic modifiers (DNA and histone methylation), as well as specific molecules, such as PRC2 (Polycomb repressive complex 2, which forms the H3K27me3 mark), DNMT1 (promotes the formation of H4K20me3), KAP1 protein (Kruppel-associated box associated protein 1, promotes the formation of H3K9me3 marks), sirtuin 6 (SIRT6, causes repression of L1 through ribosylation of KAP1, facilitating the interaction of KAP1 with its partners and the formation of heterochromatin in the L1 promoter region) (Ravel-Godreuil et al., 2021). According to recent data, TEs themselves are drivers of epigenetic regulation of genes through the formation of long non-coding RNAs and microRNAs from their transcripts (Mustafin, Khusnutdinova, 2017). That is, TEs are under the control of regulatory mechanisms that they drive, which indicates the presence of evolutionarily programmed self-control. Failure in this system is one of the factors of human aging (Wood, Helfand, 2013; Van Meter et al., 2014).

It is possible that the relationship between TEs and tau proteins reflects the system of mutual regulation of TEs and genes in the human genome. Indeed, inhibition of the *BMI1* gene (component of the Polycomb repressive complex 1, which promotes chromatin compaction and gene silencing through E3-mono-ubiquitin ligation activity mediated by Ring1a/b on histone H2A at lysine 19 ($H2A^{ub}$)) expression was found in

the brain of AD patients. *BMI1* gene knockout in postmitotic human neurons resulted in beta-amyloid deposition and accumulation of tau protein (because BMI1 suppresses tau protein transcription) (Flamier et al., 2018).

Modeling AD in mice by knocking out one allele of the *Bmi1* gene showed the development of neurodegeneration due to derepression of TEs (El Hajjar et al., 2019). Experiments in mice show enhanced processing of non-coding RNAs from SINE B2 transcripts in the hippocampus under the influence of amyloid deposition (Cheng et al., 2020). Transcriptomic analysis showed activation of TEs (mainly ERVs) induced by aging and tau in mouse brain. Transgenic mice expressing tau protein in the brain showed an increased number of TEs' DNA copies (Ramirez et al., 2022). G-quadruplex derived from evolutionarily conserved L1 suppresses gene expression in AD neurons (Hanna et al., 2021).

In 2018, an analysis of postmortem brain tissue samples showed that in tauopathies, decondensation of heterochromatin and decreased levels of piwi and piRNA cause deregulation of TEs. A significant increase in HERVs transcripts was also found in AD brains (Sun et al., 2018). In the same year, a study of postmortem brain tissue from AD patients (636 people) and a Drosophila model of the disease showed differential expression of several specific REs in association with the load of neurofibrillary tau tangles. In this case, global transcriptional activation of LINE1s and ERVs occurred. Tau protein-associated chromatin marks were detected at HERV-Fc1 location loci. Profiling of TEs in Drosophila throughout the brain showed heterogeneous response profiles, including those depending on age and genotype, activation of TEs under the influence of tau proteins (Guo C. et al., 2018).

Further studies of post-mortem brain tissue from patients with AD (60 individuals) confirmed the data on the activation of specific TEs (L1s and Alus) in AD compared with controls (Grundman et al., 2021). Analysis of blood samples from 25 late-onset AD patients revealed a significant increase in the expression of 1790 RE transcripts (LINE, LTR, SVA) before clinical phenoconversion (from normal cognitive indicators to the manifestation of AD), which the authors called a retrotransposon storm (Macciardi et al., 2022). It is possible that the data obtained by the researchers indicate the effect of a feedback relationship between TEs activated during aging and the influence of the resulting tau proteins on them, which triggers the cascade mechanism of the TEs > tau proteins > TEs relationship.

Activation of REs in AD depends on the transmission of redox signals (such as complex I of the mitochondrial respiratory chain) from mitochondria to the nucleus. It is believed that this phenomenon is a side effect of general signaling from mitochondria to the nucleus, aimed at facilitating the transcription of mitochondrial genes to restore mitochondrial function (Baeken et al., 2020). As a result, DNA hypomethylation and increased expression of REs, such as LINE1s, occur (Protasova et al., 2021). In this case, a vicious circle may develop when activated REs aggravate mitochondrial pathology due to insertions into genes involved in their functioning. Thus, frequent primate-specific retrotranspositions of Alu elements into the introns of the *TOMM40* gene, encoding the β-barrel protein necessary for mitochondrial transport of preproteins and associated with AD, were identified (Larsen et al., 2017).

Association of microRNAs derived from transposable elements with Alzheimer's disease

In 2016, G. Wei et al. created a database of microRNAs derived from TEs (MDTE DB: a database for microRNAs derived from Transposable element) (Wei et al., 2016). Due to the presence of data on the role of dysregulation of TEs in AD (Guo C. et al., 2018; Sun et al., 2018; Grudman et al., 2021; Macciardi et al., 2022), analysis of specific microRNAs presented in the MDTE DB may reveal one of the mechanisms of AD pathogenesis upon activation of TEs. In 2019, S. Swarbrick et al. conducted a systematic review of the accumulated data in the scientific literature on microRNAs associated with Alzheimer's disease. A significant role was identified for 44 microRNAs in blood plasma, 250 microRNAs in the brain, 153 microRNAs in cerebrospinal fluid (Swarbrick et al., 2019).

Our analysis of the scientific literature allowed us to determine the association of a number of microRNAs derived from TEs that are associated with AD. In 2014, a study of the brains of rabbits modeled for AD found decreased expression of miR-576-3p (Liu et al., 2014), which was derived from L1 (Wei et al., 2016). In 2022, a reduced level of miR-576-3p was detected in the serum of people with AD (Xu et al., 2022). In 2014, a GWAS of blood samples from 158 AD patients and 155 healthy controls showed a significant difference in the expression of miR-885-5p (derived from SINE/MIR (Wei et al., 2016)) in AD (Tan et al., 2014). Further studies showed that overexpression of miR-885-5p attenuates beta-amyloid-induced neuronal damage by suppressing KREMEN1 synthesis (Pan et al., 2022).

In 2015, a comparative analysis of microRNA levels in blood samples of 48 patients with AD and 22 controls showed an increase in the expression of miR-151a (Satoh et al., 2015), derived from L2 (Wei et al., 2016), miR-3200 (Satoh et al., 2015), derived from ERVL (Wei et al., 2016), and a decrease in the expression of miR-502 (derived from L2 (Wei et al., 2016)) (Satoh et al., 2015). In the same year, a study of 127 AD patients and 123 controls revealed a decrease in the level of miR-31 in AD (Dong H. et al., 2015), which originated from L2 (Wei et al., 2016). Experiments on AD mouse models showed significant improvement in neurological parameters with lentiviral-mediated expression of miR-31 due to a decrease of beta-amyloid in the hippocampus (Barros-Viegas et al., 2020).

In 2016, an experiment in mice modeled for AD demonstrated the role of miR-211 (derived from L2 (Wei et al., 2016)), affecting NUAK1, causing the accumulation of beta-amyloid and reducing neuronal survival (Fan et al., 2016). Elevated levels of miR-211 were found in another study in AD mouse models and beta-amyloid accumulation (Sierksma et al., 2018). A decrease in the expression of miR-511 (derived from L1 (Wei et al., 2016)) was found in AD, resulting in increased synthesis of the FKBP5 protein (Zheng et al., 2016). Treatment of AD mouse models with cauterization at acupuncture points of the control vessel contributed to the improvement of cognitive functions by increasing the expression of miR-511-3p (Jia et al., 2022).

In 2017, mouse models of AD showed increased levels of miR-28-3p (the miR-28 family is derived from L2 (Wei et al.,

2016)) in the cerebrospinal fluid (Hong et al., 2017). In the blood serum of people with asthma, an increased concentration of miR-28-3p was also determined, compared to healthy controls. The level of this microRNA decreased with effective donepizil therapy (Zhao et al., 2020).

ERVL-derived miR-1246 (Wei et al., 2016) has been proposed as a biomarker of AD to determine its level in the blood serum of patients (Guo R. et al., 2017). A decreased miR-545-3p level was determined in the blood plasma of patients with AD compared to controls (Cosin-Tomas et al., 2017). The miR-545 family originated from L2 (Wei et al., 2016). In AD, reduced expression of miR-325 (derived from L2 (Wei et al., 2016)) is determined, which has a post-transcriptional regulatory effect on tomosyn synthesis (impairs synaptic transmission in the brain) in the hippocampus (Barak et al., 2013). The pro-inflammatory microRNA miR-326, derived from the DNA transposon hAT-Tip100 (Wei et al., 2016), was characterized by increased expression in AD (Cai et al., 2017). Low levels of miR-342-5p (derived from SINE (Wei et al., 2016)) were detected in the worst course of AD (Dakterzada et al., 2021). SINE-derived miR-3646 was overexpressed in AD patients (Lu et al., 2021).

In 2018, increased expression of miR-320c (derived from L1 (Wei et al., 2016)) was determined in patients with AD compared to patients with amyotrophic lateral sclerosis (Raheja et al., 2018). Previously, significant association of miR-320 gene locus was determined in a genome-wide linkage analysis in patients with late-onset familial AD (Kunkle et al., 2016).

In mouse models of AD, increased expression of miR-320 in brain neurons was determined (Boese et al., 2016). Reduced level of miR-4487 (derived from L1 (Wei et al., 2016)) was detected in neurons of the brain of AD patients (Hu et al., 2018). In AD, miR-384 (derived from LINE/Dong-R4 (Wei et al., 2016)) is overexpressed. This microRNA interacts with mRNA of BACE1 protein (beta-secretase, which catalyzes the conversion of amyloid precursor to beta-amyloid (Samadian et al., 2021)). In the blood serum of AD patients, a reduced level of miR-4286 (Henriques et al., 2020), derived from ERVL (Wei et al., 2016), and miR-4422-5p (derived from LTR/Gypsy (Wei et al., 2016)) was detected (Hajjari et al., 2021).

In 2019, in the search for potential biomarkers and therapeutic agents for AD, integration of transcriptomic data with protein-protein and transcriptional regulatory interactions revealed the role of miR-192-5p (derived from L2) and miR-335-5p (derived from SINE/MIR) (Wei et al., 2016) as key signaling and regulatory molecules associated with transcriptional changes in AD. Their levels decrease both in the blood of people with AD (Rahman et al., 2019) and in relation to miR-192-5p in the hippocampus of experimental mice. Further studies showed the potential protective efficacy of miR-192-5p in AD. The level of this microRNA decreased with exercise and contributed to a decrease in the expression of TNF-α, IL-6 and IL-1β, which are involved in inflammation in AD (Qin et al., 2022). Similar results were obtained in experiments on cell cultures and AD mouse models regarding miR-335-5p, which can be used for targeted therapy of the disease (Wang et al., 2020).

In 2020, reduced expression of miR-340 (derived from TcMar-Mariner DNA TE (Wei et al., 2016)) was detected in mouse AD models (Tan et al., 2020). A low level of miR-708-5p (derived from L2 (Wei et al., 2016)) was detected in blood samples of 28 patients with AD (Rahman et al., 2020). The data obtained were confirmed by studying the brain neurons of AD patients (Di Palo et al., 2022). Analysis of brain samples from patients who died from AD showed increased levels of miR-1202 (Henriques et al., 2020), derived from L1 (Wei et al., 2016).

In 2021, an analysis of DNA blood samples from 48 AD patients and 48 healthy controls showed a significant increase in the level of miR-378a (Dong Z. et al., 2021), which was derived from SINE/MIR (Wei et al., 2016). This microRNA has been proposed as a biomarker for AD. The brains of deceased AD patients showed reduced levels of miR-1271 (Majumder et al., 2021), which was derived from L2 (Wei et al., 2016). An increase in the expression of miR-4504 (derived from L1) in the brain of patients with AD was determined (Eysert et al., 2021). Our data on changes in the expression of specific microRNAs derived from TEs in AD are shown in Table 1.

Association of transposable element-derived microRNAs with aging, carcinogenesis and Alzheimer disease

Epidemiological studies indicate a significant increase in the risk of developing AD with age (Niu et al., 2017). In both aging and neurodegenerative diseases, genomic instability is observed in neurons, with activation of TEs by various mechanisms (Wood, Helfand, 2013; Guo C. et al., 2018), including loss of SIRT6 marks (Van Meter et al., 2014). Although AD and cancer are diseases associated with aging, an analysis of scientific literature has identified an inverse correlation between cancer and AD, which may be due to the influence of the proteins p53 and PIN1 (Peptidyl-prolyl cis-trans isomerase) (Lanni et al., 2021). At the same time, mortality from AD in people who survived cancer for 10 years or more was higher than in the general population (Abdel-Rahman, 2020), which may indicate the presence of common pathogenetic pathways of these diseases, possibly associated with TEs deregulation.

Changes in TEs activity during aging contribute to changes in the expression of microRNAs, which can contribute to the development of AD and suppress the growth of cancer (acting as tumor suppressors). To test this assumption, we analyzed an online resource created in 2018 by N.W. Wong et al. concerning changes in specific microRNAs in certain cancer types (Wong et al., 2018), as well as searched for scientific data on microRNAs associated with AD and aging. As a result, we identified 13 specific microRNAs derived from TEs associated with aging and simultaneously involved in the pathogenesis of AD and cancer (Table 2).

MiR-151a is associated with Alzheimer's disease (Satoh et al., 2015); expression changes of this microRNA are also characteristic of various cancers (Wong et al., 2018) and aging (Noren Hooten et al., 2013). LINE2-derived miR-192 (Wei et al., 2016), the level of which decreases in AD (Rahman et al., 2019; Qin et al., 2022), is associated with various cancers (Wong et al., 2018). miR-192 expression is significantly reduced in aging kidney tissue (Sataranatarajan et al., 2012). LINE/L2-derived miR-211 (Wei et al., 2016), the level of which increases in AD (Fan et al., 2016; Sierksma et al., 2018), is also associated with cancer (Wong et al., 2018). miR-211

Table 1. Association of transposon-derived microRNAs with Alzheimer's disease

miRNA	Transposon, source of microRNA	Expression change	Reference
miR-1202	L1	Increased	Henriques et al., 2020
miR-1246	ERVL	Increased	Guo R. et al., 2017
miR-1271	L2	Decreased	Majumder et al., 2021
miR-151a	L2	Increased	Satoh et al., 2015
miR-192	L2	Decreased	Rahman et al., 2019; Qin et al., 2022
miR-211	L2	Increased	Fan et al., 2016; Sierksma et al., 2018
miR-28	L2	Increased	Hong et al., 2017; Zhao et al., 2020
miR-31	L2	Decreased	Dong H. et al., 2015; Barros-Viegas et al., 2020
miR-320	L1	Increased	Boese et al., 2016; Raheja et al., 2018
miR-3200	ERVL	Decreased	Satoh et al., 2015
miR-325	L2	Decreased	Barak et al., 2013
miR-326	DNA/hAT-Tip100	Increased	Cai et al., 2017
miR-335	SINE/MIR	Decreased	Rahman et al., 2019; Wang et al., 2020
miR-340	DNA/TcMar-Mariner	Decreased	Tan et al., 2020
miR-342	SINE	Decreased	Dakterzada et al., 2021
miR-3646	SINE/MIR	Increased	Lu et al., 2021
miR-378a	SINE/MIR	Increased	Dong Z. et al., 2021
miR-384	LINE/Dong-R4	Increased	Samadian et al., 2021
miR-4286	ERVL	Decreased	Henriques et al., 2020
miR-4422	LTR-Gypsy	Decreased	Hajjari et al., 2021
miR-4487	L1	Decreased	Hu et al., 2018
miR-4504	L1	Increased	Eysert et al., 2021
miR-502	L2	Decreased	Satoh et al., 2015
miR-511	L1	Decreased	Zheng et al., 2016; Jia et al., 2022
miR-545	L2	Decreased	Cosin-Tomas et al., 2017
miR-576	L1	Decreased	Liu et al., 2014; Xu et al., 2022
miR-708	L2	Decreased	Rahman et al., 2020; Di Palo et al., 2022
miR-885	SINE/MIR	Decreased	Tan et al., 2014; Pan et al., 2022

expression is increased in centenarians and may serve as a biomarker of aging (Smith-Vikos et al., 2016).

LINE2-derived miR-28 (Wei et al., 2016), the level of which increases in AD (Hong et al., 2017; Zhao et al., 2020), is also associated with specific cancers (Wong et al., 2018). Physiological aging is associated with decreased miR-28 production (Zhang T. et al., 2017). LINE2-derived miR-31 (Wei et al., 2016), the level of which decreases in AD (Dong H. et al., 2015; Barros-Viegas et al., 2020), is associated with cancer (Wong et al., 2018). Expression of this microRNA is increased during replicative aging (Dellago et al., 2013). MiR-320c, derived from LINE2 (Wei et al., 2016), the level of which is increased in AD (Boese et al., 2016; Raheja et al., 2018), is also associated with specific cancers (Wong et al., 2018). MiR-320c levels decrease with aging (Ukai et al., 2012).

MiR-335, derived from SINE/MIR (Wei et al., 2016), which is reduced in AD (Rahman et al., 2019; Wang et al., 2020), is also associated with cancer (Wong et al., 2018) and aging (Raihan et al., 2018). MiR-340, derived from DNA-TE TcMar-Mariner (Wei et al., 2016), the expression of which is reduced in AD, is associated with cancer (Wong et al., 2018) and with aging (Zhang H. et al., 2015). SINE/MIR-derived miR-378a (Wei et al., 2016), the level of which is significantly increased in AD (Dong Z. et al., 2021), is associated with various cancers (Wong et al., 2018) and aging (Guo D. et al., 2017). The level of miR-511 (source: L1 (Wei et al., 2016)) decreases not only

Table 2. TE-derived miRNAs associated with aging, carcinogenesis and Alzheimer's disease

miRNA (TE-source)	Type of cancer (change in microRNA expression)	miRNA level change	
		in AD (reference)	in aging (reference)
miR-151a (LINE/L2)	BLCA, BRCA, CESC, COAD, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, UCEC (increased)	Increased Satoh et al., 2015	Decreased Noren Hooten et al., 2013
miR-192 (LINE/L2)	BLCA, BRCA, COAD, KIRC, LUAD, LUSC, PRAD, READ, STAD, UCEC (increased); CHOL, KICH, KIRP, LICH, THCA (decreased)	Decreased Rahman et al., 2019; Qin et al., 2022	Decreased Sataranatarajan et al., 2012
miR-211 (LINE/L2)	KIRC, KIRP, LIHC (increased); BRCA, HNSC, LUAD (decreased)	Increased Fan et al., 2016; Sierksma et al., 2018	Increased Smith-Vikos et al., 2016
miR-28 (LINE/L2)	HNSC, KIRC, LUAD, LUSC, PRAD (increased); BRCA, CHOL, COAD, ESCA, PCPG, READ, STAD, THCA (decreased)	Increased Hong et al., 2017; Zhao et al., 2020	Decreased Zhang T. et al., 2017
miR-31 (LINE/L2)	BLCA, CESC, HNSC, KIRP, LUAD, LUSC, STAD, THCA, UCEC (increased); KICH, KIRC, PRAD (decreased)	Decreased Dong H. et al., 2015; Barros-Viegas et al., 2020	Increased Cho et al., 2015; Dellago et al., 2013
miR-320c (LINE/L1, L2)	CHOL, KIRC, LUSC, STAD, UCEC (increased); COAD, READ (decreased)	Increased Boese et al., 2016; Raheja et al., 2018	Decreased Ukai et al., 2012
miR-335 (SINE/MIR)	BLCA, COAD, ESCA, HNSC, LUAD, LUSC, PRAD, STAD, THCA, UCEC (increased); BRCA, KICH, KIRC, LIHC (decreased)	Decreased Rahman et al., 2019; Wang et al., 2020	Increased Raihan et al., 2018
miR-340 (DNA/TcMar-Mariner)	BRCA, COAD, KICH, KIRC, KIRP, LUAD, LUSC, PRAD, UCEC (increased); CHOL, LIHC, PAAD (decreased)	Decreased Tan et al., 2020	Decreased Zhang H. et al., 2015
miR-378a (SINE/MIR)	PAAD (increased); BRCA, CHOL, COAD, HNSC, LIHC, LUAD, PAAD, PRAD, READ, STAD (decreased)	Increased Dong Z. et al., 2021	Increased Guo D. et al., 2017
miR-511 (LINE/L1)	HNSC, PRAD, READ, STAD (increased); BRCA, CHOL, KICH, KIRP, LIHC, LUSC, PCPG (decreased)	Decreased Zheng et al., 2016; Jia et al., 2022	Decreased Zheng et al., 2016
miR-576 (LINE/L1)	BLCA, BRCA, ESCA, HNSC, KICH, KIRC, KIRP, LUAD, LUSC, PRAD, READ, STAD, UCEC (increased); CHOL, LIHC, THCA (decreased)	Decreased Liu et al., 2014; Xu et al., 2022	Increased Ipson et al., 2018
miR-708 (LINE/L2)	BLCA, BRCA, CHOL, COAD, HNSC, KIRC, LUAD, LUSC, PRAD, READ, STAD (increased); KICH, THCA (decreased)	Decreased Rahman et al., 2020; Di Palo et al., 2022	Increased Lee et al., 2017
miR-885 (SINE/MIR)	KICH (increased); CHOL (decreased)	Decreased Tan et al., 2014; Pan et al., 2022	Increased Behbahanipour et al., 2019

Note. BLCA – bladder urothelial carcinoma; BRCA – breast invasive carcinoma; CESC – cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL – cholangiocarcinoma; COAD – colon adenocarcinoma; ESCA – esophageal carcinoma; HNSC – head and neck squamous cell carcinoma; KICH – kidney chromophobe carcinoma; KIRC – kidney renal clear cell carcinoma; KIRP – kidney renal palillary cell carcinoma; LIHC – liver hepatocellular carcinoma; LUAD – lung adenocarcinoma; LUSC – lung squamous cell carcinoma; PAAD – pancreatic adenocarcinoma; PRAD – prostate adenocarcinoma; PCPG – pheochromocytoma and paraganglioma; READ – rectal adenocarcinoma; STAD – stomach adenocarcinoma; THCA – thyroid carcinoma; UCEC – uterine corpus endometrial carcinoma.

in AD (Zheng et al., 2016; Jia et al., 2022), but also in aging. This microRNA is also associated with cancer (Wong et al., 2018). L1-derived miR-576 (Wei et al., 2016), the level of which is reduced in AD (Liu et al., 2014; Xu et al., 2022), is associated with cancer (Wong et al., 2018).

Increased expression of miR-576 is detected during aging (Ipson et al., 2018). MiR-708, derived from LINE2 (Wei et al., 2016), a reduced level of which is observed in AD (Rahman et al., 2020; Di Palo et al., 2022), is associated with specific cancers (Wong et al., 2018) and with aging (Lee et al., 2017). The SINE/MIR-derived microRNA miR-885, which is downregulated in AD (Tan et al., 2014), is associated with chromophobe kidney cancer and cholangiocarcinoma (Wong et al., 2018) and aging (Behbahanipour et al., 2019).

Conclusion

The role of microRNAs in the development of AD indicates the possible potential of targeted therapy for the disease, as well as the search for the most optimal treatment regimens for AD. Examples are the decrease in miR-192-5p levels during exercise, which contributes to suppression of pro-inflammatory cytokines TNF-α, IL-6 and IL-1β production (Qin et al., 2022); the decrease in miR-28-3p levels after donepizil therapy (which can be used as a diagnostic criterion for the effectiveness of treatment) (Zhao et al., 2020).

MicroRNAs can become not only therapeutic agents, but also highly accurate diagnostic markers, since changes in their levels are accompanied by regression in AD clinical picture, as was shown for miR-511 when exposed to acupuncture moxibustion in AD (Jia et al., 2022). The experimental effectiveness of miR-31 (Barros-Viegas et al., 2020) and miR-335-5p (Wang et al., 2020) in significantly reducing beta-amyloid accumulation in the hippocampus and its base indicates the potential of using this microRNA for targeting AD therapy (Barros-Viegas et al., 2020; Wang et al., 2020).

The association of TE-derived miRNAs with Alzheimer's disease indicates both the promise of their use in the treatment of AD and the need for a more detailed study of the mechanisms of action of these miRNAs, since the complementarity of their sequences with various TEs may become a likely basis for global changes in the expression of genes under TEs regulatory control.

References

Abdel-Rahman O. Death from Alzheimer's disease among cancer survivors: a population-based study. *Curr. Med. Res. Opin*. 2020;36(5):835-841. DOI 10.1080/03007995.2020.1734921

Ando K., Nagaraj S., Kucukali F., de Fisenne M.A., Kosa A.C., Doeraene E., Gutierrez L.L., Brion J.P., Leroy K. PICALM and Alzheimer's disease: An update and perspectives. *Nutrients.* 2022;14(3):539. DOI 10.3390/nu14030539

Baeken M.W., Moosmann B., Hajieva P. Retrotransposon activation by distressed mitochondria in neurons. *Biochem. Biophys. Res. Commun.* 2020;525(3):570-575. DOI 10.1016/j.bbrc.2020.02.106

Barak B., Shvarts-Serebro I., Modai S., Gilam A., Okun E., Michaelson D.M., Mattson M.P., Shomron N., Ashery U. Opposing actions of environmental enrichment and Alzheimer's disease on the expression of hippocampal microRNA in mouse models. *Transl. Psychiatry*. 2013;3(9):e304. DOI 10.1038/tp.2013.77

Barros-Viegas A.T., Carmona V., Ferreiro E., Guedes J., Cardoso A.M., Cunha P., de Almeida L.P., de Oliveira C.R., de Magalhães J.P., Peça J., Cardoso A.L. miRNA-31 improves cognition and abolishes amyloid-β pathology by targeting APP and BACE1 in an animal model of Alzheimer's disease. *Mol. Ther. Nucleic. Acids*. 2020;19:1219-1236. DOI 10.1016/j.omtn.2020.01.010

Behbahanipour M., Peymani M., Salari M., Hashemi M.S., Nasr-Esfahani M.H., Ghaedi K. Expression profiling of blood microRNAs 885, 361, and 17 in the patients with the Parkinson's disease: integrating interatction data to uncover the possible triggering age-related mechanisms. *Sci. Rep.* 2019;9:13759. DOI 10.1038/s41598-019-50256-3

Boese A.S., Saba R., Campbell K., Majer A., Medina S., Burton L., Booth T.F., Chong P., Westmacott G., Dutta S.M., Saba J.A., Booth S.A. MicroRNA abundance is altered in synaptoneurosomes during prion disease. *Mol. Cell. Neurosci*. 2016;71:13-24. DOI 10.1016/j.mcn.2015.12.001

Cai Y., Sun Z., Jia H., Luo H., Ye X., Wu Q., Xiong Y., Zhang W., Wan J. *Rpph1* upregulates CDC42 expression and promotes hippocampal neuron dendritic spine formation by competing with miR-330-5p. *Front. Mol. Neurosci*. 2017;10:27. DOI 10.3389/fnmol.2017.00027

Chanda K., Mukhopadhyay D. LncRNA Xist, X-chromosome instability and Alzheimer's disease. *Curr. Alzheimer Res.* 2020;17(6):499-507. DOI 10.2174/1567205017666200807185624

Cheng Y., Saville L., Gollen B., Isaac C., Belay A., Mehla J., Patel K., Thakor N., Mohajerani M.H., Zovoilis A. Increased processing of SINE B2 ncRNAs unveils a novel type of transcriptome deregulation in amyloid beta neuropathology. *eLife.* 2020;9:e61265. DOI 10.7554/eLife.61265

Cho J.H., Dimri M., Dimri G.P. MicroRNA-31 is a transcriptional target of histone deacetylase inhibitors and a regulator of cellular senescence. *J. Biol. Chem*. 2015;290(16):10555-10567. DOI 10.1074/jbc.M114.624361

Cosin-Tomas M., Antonell A., Llado A., Alcoelea D., Fortea J., Ezquerra M., Lleo A., Marti M.J., Pallas M., Sanchez-Valle R.S., Molinuevo J.L., Sanfeliu C., Kaliman P. Plasma miR-545-3p as early biomarkers of Alheimer's disease: potential and limitations. *Mol. Neurobiol*. 2017;54(7):5550-5562. DOI 10.1007/s12035-016-0088-8

Dakterzada F., Benítez I.D., Targa A., Lladó A., Torres G., Romero L., de Gonzalo-Calvo D., Moncusí-Moix A., Tort-Merino A., Huerto R., Sánchez-de-la-Torre M., Barbé F., Piñol-Ripoll G. Reduced levels of miR-342-5p in plasma are associated with worse cognitive evolution in patients with mild Alzheimer's disease. *Front. Aging Neurosci*. 2021;13:705989. DOI 10.3389/fnagi.2021.705989

Dellago H., Preschitz-Kammerhofer B., Terlecki-Zaniewicz L., Schreiner C., Fortschegger K., Chang M.W., Hackl M., Monteforte R., Kuhnel H., Schosserer M., Gruber F., Tschachler E., Scheideler M., Grillari-Voglauer R., Grillari J., Wieser M. High levels of oncomiR-21 contribute to the senescence-induced growth arrest in normal human cells and its knock-down increases the replicative lifespan. *Aging Cell*. 2013;12(3):446-458. DOI 10.1111/acel.12069

Di Palo A.D., Siniscalchi C., Crescente G., Leo I.D., Fiorentino A., Pacifico S., Russo A., Potenza N. Effect of cannabidiolic acid, *N-trans*-caffeoyltyramine and cannabisin B from hemp seeds on microRNA expression in human neural cells. *Curr. Issues Mol. Biol*. 2022;44(10):5106-5116. DOI 10.3390/cimb44100347

Dong H., Li J., Huang L., Chen X., Li D., Wang T., Hu C., Xu J., Zhang C., Zen K., Xiao S., Yan Q., Wang C., Zhang C.Y. Serum microRNA profiles serve as novel biomarkers for the diagnosis of Alzheimer's disease. *Dis. Markers*. 2015;2015:625659. DOI 10.1155/2015/625659

Dong Z., Gu H., Guo Q., Liang S., Xue J., Yao F., Liu X., Li F., Liu H., Sun L., Zhao K. Profiling of serum exosome miRNA reveals the potential of a miRNA panel as diagnostic biomarker for Alzheimer's disease. *Mol. Neurobiol*. 2021;58(7):3084-3094. DOI 10.1007/s12035-021-02323-y

El Hajjar J., Chatoo W., Hanna R., Nkanza P., Tétreault N., Tse Y.C., Wong T.P., Abdouh M., Bernier G. Heterochromatic genome instability and neurodegeneration sharing similarities with Alzheimer's disease in old *Bmi1*+/− mice. *Sci. Rep*. 2019;9(1):594. DOI 10.1038/s41598-018-37444-3

Eysert F., Coulon A., Boscher E., Vreulx A.C., Flaig A., Mendes T., Kilinc D., Lambert J., Chapuis J. Alzheimer's genetic risk factor FERMT2 (Kindlin-2) controls axonal growth and synaptic plasticity in an APP-dependent manner. *Mol. Psychiatry*. 2021;26(10):5592-5607. DOI 10.1038/s41380-020-00926-w

Fagone P., Mangano K., Martino G., Quattropani M.C., Pennisi M., Bella R., Fisicaro F., Nicoletti F., Petralia M.C. Characterization of altered molecular pathways in the entorhinal cortex of Alzheimer's disease patients and *in silico* prediction of potential repurposable drugs. *Genes* (*Basel*). 2022;13(4):703. DOI 10.3390/genes13040703

Fan C., Wu Q., Ye X., Luo H., Yan D., Xiong D., Xiong Y., Zhu H., Diao Y., Zhang W., Wan J. Role of miR-211 in neuronal differentiation and viability: implications to pathogenesis of Alzheimer's disease. *Front. Aging Neurosci*. 2016;8:166. DOI 10.3389/fnagi.2016.00166

Flamier A., El Hajjar J., Adjaye J., Fernandes K.J., Abdouh M., Bernier G. Modeling late-onset sporadic Alzheimer's disease through BMI1 deficiency. *Cell Rep*. 2018;23(9):2653-2666. DOI 10.1016/j.celrep.2018.04.097

Gatz M., Reynolds C.A., Fratiglioni L., Johansson B., Mortimer J.A., Berg S., Fiske A., Pedersen N.L. Role of genes and environments for explaining Alzheimer disease. *Arch. Gen. Psychiatry*. 2006;63(2):168-174. DOI 10.1001/archpsyc.63.2.168

GNS H.S., Marise V.L.P., Satish K.S., Yergolkar A.V., Krishnamurthy M., Rajalekshmi G.S., Radhika K., Burri R.R. Untangling huge literature to disinter genetic underpinnings of Alzheimer's disease: A systematic review and meta-analysis. *Ageing Res. Rev.* 2021;71:101421. DOI 10.1016/j.arr.2021.101421

Goate A. Segregation of a missense mutation in the amyloid beta-protein precursor gene with familial Alzheimer's disease. *J. Alzheimers Dis*. 2006;9(3 Suppl.):341-347. DOI 10.3233/jad-2006-9s338

Grundman J., Spencer B., Sarsoza F., Rissman R.A. Transcriptome analyses reveal tau isoform-driven changes in transposable element and gene expression. *PLoS One*. 2021;16(9):e0251611. DOI 10.1371/journal.pone.0251611

Guerreiro R., Wojtas A., Bras J., Carrasquillo M., Rogaeva E., Majounie E., Cruchaga C., Sassi C., Kauwe J.S., Younkin S., Hazrati L., Collinge J., Pocock J., Lashley T., Williams J., Lambert J.C., Amouyel P., Goate A., Rademakers R., Morgan K., Powell J., St. George-Hyslop P., Singleton A., Hardy J., Alzheimer Genetic Analysis Group. TREM2 variants in Alzheimer's disease. *N. Engl. J. Med*. 2013;368(2):117-127. DOI 10.1056/NEJMoa1211851

Guo C., Jeong H.H., Hsieh Y.C., Klein H.U., Bennett D.A., De Jager P.L., Liu Z., Shulman J.M. Tau activates transposable elements in Alzheimer's disease. *Cell Rep*. 2018;23(10):2874-2880. DOI 10.1016/j.celrep.2018.05.004

Guo D., Ye Y., Qi J., Tan X., Zhang Y., Ma Y., Li Y. Age and sex differences in microRNAs expression during the process of thymus aging. *Acta Biochim. Biophys. Sin.* (*Shanghai*). 2017;49(5):409-419. DOI 10.1093/abbs/gmx029

Guo R., Fan G., Zhang J., Wu C., Du Y., Ye H., Li Z., Wang L., Zhang Z., Zhang L., Zhao Y., Lu Z. A 9-microRNA signature in serum serves as a noninvasive biomarker in early diagnosis of Alzheimer's disease. *J. Alzheimers Dis*. 2017;60(4):1365-1377. DOI 10.3233/JAD-170343

Hajjari S.N., Sadigh-Eteghad S., Shanehbandi D., Teimourian S., Shahbazi A., Mehdizadeh M. MicroRNA-4422-5p as a negative regulator of amyloidogenic secretases: A potential biomarker for Alzheimer's disease. *Neuroscience*. 2021;463:108-115. DOI 10.1016/j.neuroscience.2021.03.028

Hanna R., Flamier A., Barabino A., Bernier G. G-quadruplexes originating from evolutionary conserved L1 elements interfere with neuronal gene expression in Alzheimer's disease. *Nat. Commun*. 2021;12(1):1828. DOI 10.1038/s41467-021-22129-9

Harold D., Abraham R., Hollingworth P., Sims R., Gerrish A., Hamshere M.L., Pahwa J.S., Moskvina V., Dowzell K., Williams A., Jones N., Thomas C., Stretton A., Morgan A.R., Lovestone S., Powell J., Proitsi P., Klopp N., Wichmann H.E., Carrasquillo M.M., Pankratz V.S., Yonkin S.G., Holmans P.A., O'Donovan M., Owen M.J., Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat. Genet*. 2009;41(10):1088-1093. DOI 10.1038/ng.440

Henriques A.D., Machado-Silva W., Leite R.E.P., Suemoto C.K., Leite K.R.M., Srougi M., Pereira A.C., Jacob-Filho W., Brazilian Aging Brain Study Group. Genome-wide profiling and predicted significance of post-mortem brain microRNA in Alzheimer's disease. *Mech. Ageing Dev*. 2020;191:111352. DOI 10.1016/j.mad.2020.111352

Hong H., Li Y., Su B. Identification of circulating miR-125b as a potential biomarker of Alzheimer's disease in APP/PS1 transgenic mouse. *J. Alzheimers Dis*. 2017;59(4):1449-1458. DOI 10.3233/JAD-170156

Hou Y., Song H., Croteau D.L., Akbari M., Bohr V.A. Genome instability in Alzheimer disease. *Mech. Ageing Dev*. 2017;161(Pt. A):83-94. DOI 10.1016/j.mad.2016.04.005

Hu L., Zhang R., Yuan Q., Gao Y., Yang M.Q., Zhang C., Huang J., Sun Y., Yang W., Yang J.Y., Min Z., Cheng J., Deng Y., Hu X. The emerging role of microRNA-4487/6845-3p in Alzherimer's disease pathologies is induced by Aβ25-35 triggered in SH-SY5Y cell. *BMC Syst. Biol*. 2018;12(Suppl. 7):119. DOI 10.1186/s12918-018-0633-3

Ipson B.R., Fletcher M.B., Espinoza S.E., Fisher A.L. Identifying exosome-derived microRNAs as candidate biomarkers of frailty. *J. Frailty Aging*. 2018;7(2):100-103. DOI 10.14283/jfa.2017.45

Jia Y.M., Zhu C.F., She Z.Y., Wu M.M., Wu Y.Y., Zhou B.Y., Zhang N. Effects on autophagy of moxibustion at governor vessel acupoints in APP/PS1double-Transgenic Alzheimer's Disease Mice through the lncRNA Six3os1/miR-511-3p/AKT3 Molecular Axis. *Evid. Based Complement. Alternat. Med*. 2022;2022:3881962. DOI 10.1155/2022/3881962

Kunkle B.W., Jaworski J., Barral S., Bardarajan B., Beecham G.W., Haines J.L., Pericak-Vance M. Genome-wide linkage analyses of non-Hispanic white families identify novel loci for familial late-onset Alzheimer's disease. *Alzheimer's Dement*. 2016;12(1):2-10. DOI 10.1016/j.jalz.2015.05.020

Lambert J.C., Heath S., Even G., Campion D., Sleegers K., Hiltunen M., Combarros O., Zelenika D., Bullido M.J., Tavernier B., Letenneur L., Bettens K., Berr C., Pasquier F., Fievet N., Barbeerger-Gateau P., Engelborghs S., Deyn P.D., Mateo I., Franck A., Helisalmi S., Tzourio C., Gut I., Van Broeckhoven C., Alperovitch A., Lathrop M., Amouyel P. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat. Genet*. 2009;41(10):1094-1099. DOI 10.1038/ng.439

Lanni C., Masi M., Racchi M., Govoni S. Cancer and Alzheimer's disease inverse relationship: an age-associated diverging derailment of shared pathways. *Mol. Psychiatry*. 2021;26(1):280-295. DOI 10.1038/s41380-020-0760-2

Larsen P.A., Lutz M.W., Hunnicutt K.E., Mihovilovic M., Saunders A.M., Yoder A.D., Roses A.D. The *Alu* neurodegeneration hypothesis: A primate-specific mechanism for neuronal transcription noise, mitochondrial dysfunction, and manifestation of neurodegenerative disease. *Alzheimer's Dement*. 2017;13(7):828-838. DOI 10.1016/j.jalz.2017.01.017

Lee B.P., Buric I., George-Pandeth A., Flurkey K., Harrison D.E., Yuan R., Peters L.L., Kuchel G.A., Melzer D., Harries L.W. MicroRNAs miR-203-3p, miR-664-3p and miR-708-5p are associated with median strain lifespan in mice. *Sci. Rep*. 2017;7:44620. DOI 10.1038/srep44620

Levy-Lahad E., Wasco W., Poorkaj P., Romano D.M., Oshima J., Pettingell W.H., Yu C.E., Jondro P.D., Schmidt S.D., Wang K. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science*. 1995;269(5226):973-977. DOI 10.1126/science.7638622

Liu Q.Y., Chang M.N.V., Lei J.X., Koukiekolo R., Smith B., Zhang D., Ghribi O. Identification of microRNAs involved in Alzheimer's progression using a rabbit model of the disease. *Am. J. Neurodegener. Dis*. 2014;3(1):33-44

Lu L., Dai W., Zhu X., Ma T. Analysis of serum miRNAs in Alzheimer's disease. *Am. J. Alzheimers Dis. Other Demen*. 2021;36:15333175211021712. DOI 10.1177/15333175211021712

Ma F.C., Wang H.F., Cao X.P., Tan C.C., Tan L., Yu J.T. Meta-analysis of the association between variants in ABCA7 and Alzheimer's disease. *J. Alzheimers Dis.* 2018;63(4):1261-1267. DOI 10.3233/JAD-180107

Macciardi F., Bacalini M.G., Miramontes R., Boattini A., Taccioli C., Modenini G., Malhas R., Anderlucci L., Gusev Y., Gross T.J., Padilla R.M., Fiandaca M.S., Head E., Guffanti G., Federoff H.J., Mapstone M. A retrotransposon storm marks clinical phenoconversion to late-onset Alzheimer's disease. *Geroscience*. 2022;44(3):1525-1550. DOI 10.1007/s11357-022-00580-w

Majumder P., Chanda K., Das D., Singh B.K., Charkrabarti P., Jana N.R., Mukhopadhyay D. A nexus of miR-1271, PAX4 and ALK/RYK influences the cytoskeletal architectures in Alzheimer's disease and type 2 diabetes. *Biochem. J*. 2021;478(17):3297-3317. DOI 10.1042/BCJ20210175

Marioni R.E., Harris S.E., Zhang Q., McRae A.F., Hagenaars S.P., Hill W.D., Davies G., Ritchie C.W., Gale C.R., Starr J.M., Goate A.M., Porteous D.J., Yang J., Evans K.L., Deary I.J., Wray N.R., Visscher P.M. GWAS on family history of Alzheimer's disease. *Transl. Psychiatry*. 2018;8(1):99. DOI 10.1038/s41398-018-0150-6

Mustafin R.N. The relationship between transposons and transcription factors in the evolution of eukaryotes. *Zhurnal Evolyutsionnoi Biokhimii i Fiziologii = Journal of Evolutionary Biochemistry and Physiology.* 2019;55(1):14-22. DOI 10.1134/S004445291901008X (in Russian)

Mustafin R.N., Khusnutdinova E.K. Non-coding parts of genomes as the basis of epigenetic heredity. *Vavilovskii Zhurnal Genetiki i Selektsii = Vavilov Journal of Genetics and Breeding.* 2017;21(6):742-749. DOI 10.18699/VJ17.30-o (in Russian)

Niu H., Alvarez-Alvarez I., Guillen-Grima F., Aguinaga-Ontoso I. Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis. *Neurologia*. 2017;32(8):523-532. DOI 10.1016/j.nrl.2016.02.016

Noren Hooten N., Fitzpatrick M., Wood W.H. 3rd, De S., Ejiogu N., Zhang Y., Mattison J.A., Becker K.G., Zonderman A.B., Evans M.K. Age-related changes in microRNA levels in serum. *Aging* (*Albany N. Y.*). 2013;5(10):725-740. DOI 10.18632/aging.100603

Pan W., Hu Y., Wang L., Li J. Circ_0003611 acts as a miR-885-5p sponge to aggravate the amyloid-β-induced neuronal injury in Alzheimer's disease. *Metab. Brain Dis*. 2022;37(4):961-971. DOI 10.1007/s11011-022-00912-x

Pascarella G., Hon C.C., Hashimoto K., Busch A., Luginbuhl J., Parr C., Yip W.H., Abe K., Kratz A., Bonetti A., Agostini F., Severin J., Murayama S., Suzuki Y., Gustincich S., Frith M., Carninci P. Recombination of repeat elements generates somatic complexity in human genomes. *Cell*. 2022;185(16):3025-3040.e6. DOI 10.1016/j.cell.2022.06.032

Patel H., Dobson R.J.B., Newhouse S.J. A meta-analysis of Alzheimer's disease brain transcriptomic data. *J. Alzheimers Dis*. 2019;68(4):1635-1656. DOI 10.3233/JAD-181085

Protasova M.S., Andreeva T.V., Rogaev E.I. Factors regulating the activity of LINE1 retrotransposons. *Genes* (*Basel*). 2021;12(10):1562. DOI 10.3390/genes12101562

Qin Z., Han X., Ran J., Guo S., Lv L. Exercise-mediated alteration of miR-192-5p is associated with cognitive improvement in Alzheimer's disease. *Neuroimmunomodulation.* 2022;29(1):36-43. DOI 10.1159/000516928

Raheja R., Regev K., Healy B.C., Mazzola M.A., Beynon V., Glehn F.V., Paul A., Diaz-Cruz C., Gholipour T., Glanz B.I., Kivisakk P., Chitnis T., Weiner H.L., Berry J.D., Gandhi R. Correlating serum microRNAs and clinical parameters in amyotrophic lateral sclerosis. *Muscle Nerve*. 2018;58(2):261-269. DOI 10.1002/mus.26106

Rahman M.R., Islam T., Turanli B., Zaman T., Faruquee H.M., Rahman M.M., Mollah M.N.H., Nanda R.K., Arga K.Y., Gov E., Moni M.A. Network-based approach to identify molecular signatures and therapeutic agents in Alzheimer's disease. *Comput. Biol. Chem.* 2019;78:431-439. DOI 10.1016/j.compbiolchem.2018.12.011

Rahman M.R., Islam T., Zaman T., Shahjaman M., Karim M.R., Huq F., Quinn J.M.W., Holsinger R.M.D., Gov E., Moni M.A. Identification of molecular signatures and pathways to identify novel therapeutic targets in Alzheimer's disease: Insights from a systems biomedicine perspective. *Genomics.* 2020;112(2):1290-1299. DOI 10.1016/j.ygeno.2019.07.018

Raihan O., Brishti A., Molla M.R., Li W., Zhang Q., Xu P., Khan M.I., Zhang J., Liu Q. The age-dependent elevation of miR-335-3p leads to reduced cholesterol and impaired memory in brain. *Neuroscience*. 2018;390:160-173. DOI 10.1016/j.neuroscience.2018.08.003

Ramirez P., Zuniga G., Sun W., Beckmann A., Ochoa E., DeVos S., Hyman B., Chiu G., Roy E.R., Cao W., Orr M., Buggia-Prevot V., Ray W.J., Frost B. Pathogenic tau accelerates aging-associated activation of transposable elements in the mouse central nervous system. *Prog. Neurobiol*. 2022;208:102181. DOI 10.1016/j.pneurobio.2021.102181

Ravel-Godreuil C., Zhaidi R., Bonnifet T., Joshi R.L., Fuchs J. Transposable elements as new players in neurodegenerative diseases. *FEBS Lett.* 2021;595(22):2733-2755. DOI 10.1002/1873-3468.14205

Robinson M., Lee B.Y., Hane F.T. Recent progress in Alzheimer's disease research. Part 2: genetics and epidemiology. *J. Alzheimers Dis*. 2017;57(2):317-330. DOI 10.3233/JAD-161149

Rogaev E.I., Lukiw W.J., Lavrushina O., Rogaeva E.A., St. George-Hyslop P.H. The upstream promoter of the β-amyloid precursor protein gene (*APP*) shows differential patterns of methylation in human brain. *Genomics.* 1994;22(2):340-347. DOI 10.1006/geno.1994.1393

Samadian M., Gholipour M., Hajiesmaeili M., Taheri M., Ghafouri-Fard S. The eminent role of microRNAs in the pathogenesis of Alzheimer's disease. *Front. Aging Neurosci.* 2021;13:641080. DOI 10.3389/fnagi.2021.641080

Sataranatarajan K., Feliers D., Mariappan M.M., Lee H.J., Lee M.J., Day R.T., Bindu H., Yalamanchili H.B., Choudhury G.G., Barnes J.L., Remmen H.V., Richardson A., Kasinath B.S. Molecular events in matrix protein metabolism in the aging kidney. *Aging Cell.* 2012;11(6):1065-1073. DOI 10.1111/acel.12008

Satoh J.I., Kino Y., Niida S. MicroRNA-seq data analysis pipeline to identify blood biomarkes for Alzheimer's disease from public data. *Biomark. Insights*. 2015;10:21-31. DOI 10.4137/BMI.S25132

Schwartzentruber J., Cooper S., Liu J.Z., Barrio-Hernandez I., Bello E., Kumasaka N., Young A.M.H., Franklin R.J.M., Johnson T., Estrada K., Gaffney D.J., Beltrao P., Bassett A. Genome-wide meta-analysis, fine-mapping and integrative prioritization implicate new Alzheimer's disease risk genes. *Nat. Genet*. 2021;53(3):392-402. DOI 10.1038/s41588-020-00776-w

Serrano-Pozo A., Das S., Hyman B.T. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol*. 2021;20(1):68-80. DOI 10.1016/S1474-4422(20)30412-9

Sherrington R., Rogaev E.I., Liang Y., Rogaeva E.A., Levesque G., Ikeda M., Chi H., Lin C., Li G., Holman K., Tsuda T., Mar L., Foncin J.F., Bruni A.C., Montesi M.P., Sorbi S., Rainero I., Pinessi L., Nee L., Chumakov I., Pollen D., Brookes A., Sanseau P., Polinsky R.J., Wasco W., Da Silva H.A., Haines J.L., Perkicak-Vance M.A., Tanzi R.E., Roses A.D., Fraser P.E., Rommens J.M., St. George-Hyslop P.H. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature*. 1995;375(6534):754-760. DOI 10.1038/375754a0

Sierksma A., Lu A., Salta E., Eynden E.V., Callaerts-Vegh Z., D'Hooge R., Blum D., Buee L., Fiers M., Stooper B.D. Deregulation of neuronal miRNAs induced by amyloid-β or TAU pathology. *Mol. Neurodegener*. 2018;13(1):54. DOI 10.1186/s13024-018-0285-1

Smith R.G., Pishva E., Shireby G., Smith A.R., Roubroeks J.A.Y., Hannon E., Wheildon G., Mastroeni D., Gasparoni G., Riemenschneider M., Giese A., Sharp A.J., Schalkwyk L., Haroutunian V., Viechtbauer W., van den Hove D.L.A., Weedon M., Brokaw D., Francis P.T., Thomas A.J., Love S., Morgan K., Walter J., Coleman P.D., Bennett D.A., De Jager P.L., Mill J., Lunnon K. A meta-analysis of epigenome-wide association studies in Alzheimer's disease highlights novel differentially methylated loci across cortex. *Nat. Commun*. 2021;12(1):3517. DOI 10.1038/s41467-021-23243-4

Smith-Vikos T., Liu Z., Parsons C., Gorospe M., Ferrucci L., Gill T.M., Slack F.J. A serum miRNA profile of human longevity: findings from the Baltimore Longitudinal Study of Aging (BLSA). *Aging* (*Albany N.Y.*). 2016;8(11):2971-2987. DOI 10.18632/aging.101106

Sun W., Samimi H., Gamez M., Zare H., Frost B. Pathogenic tau-induced piRNA depletion promotes neuronal death through transposable element dysregulation in neurodegenerative tauopathies. *Nat. Neurosci.* 2018;21(8):1038-1048. DOI 10.1038/s41593-018-0194-1

Swarbrick S., Wragg N., Ghosh S., Stolzing A. Systematic review of miRNA as biomarkers in Alzheimer's disease. *Mol. Neurobiol*. 2019;56(9):6156-6167. DOI 10.1007/s12035-019-1500-y

Tan L., Yu J.T., Tan M.S., Liu Q.Y., Wang H.F., Zhang W., Jiang T., Tan L. Genome-wide serum microRNA expression profiling identifies serum biomarkers for Alzheimer's disease. *J. Alzheimers Dis.* 2014;40(4):1017-1027. DOI 10.3233/JAD-132144

Tan X., Luo Y., Pi D., Xia L., Li Z., Tu Q. MiR-340 reduces the accumulation of amyloid-β through targeting BACE1 (β-site amyloid precursor protein cleaving enzyme 1) in Alzheimer's disease. *Curr. Neurovasc. Res*. 2020;17(1):86-92. DOI 10.2174/1567202617666200117103931

Ukai T., Sato M., Akutsu H., Umezawa A., Mochida J. MicroRNA-199a-3p, microRNA-193b, and microRNA-320c are correlated to aging and regulate human cartilage metabolism. *J. Orthop. Res*. 2012;30(12):1915-1922. DOI 10.1002/jor.22157

Van Meter M., Kashyap M., Rezazadeh S., Geneva A.J., Morello T.D., Seluanov A., Gorbunova V. SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nat. Commun*. 2014;5:5011. DOI 10.1038/ncomms6011

Wang D., Fei Z., Wang H. MiR-335-5p inhibits β-amyloid (Aβ) accumulation to attenuate cognitive deficits through targeting c-jun-N-terminal kinase 3 in Alzheimer's disease. *Curr. Neurovasc. Res*. 2020;17(1):93-101. DOI 10.2174/1567202617666200128141938

Watcharanurak P., Mutirangura A. Human RNA-directed DNA-methylation methylates high-mobility group box 1 protein-produced DNA gaps. *Epigenomics*. 2022;14(12):741-756. DOI 10.2217/epi-2022-0022

Wei G., Qin S., Li W., Chen L., Ma F. MDTE DB: a database for microRNAs derived from Transposable element. *IEEE/ACM Trans. Comput. Biol. Bioinform*. 2016;13:1155-1160. DOI 10.1109/TCBB.2015.2511767

Wong N.W., Chen Y., Chen S., Wang X. OncomiR: and online resource for exploring pan-cancer microRNA dysregulation. *Bioinformatics.* 2018;34(4):713-715. DOI 10.1093/bioinformatics/btx627

Wood J.G., Helfand S.L. Chromatin structure and transposable elements in organismal aging. *Front. Genet.* 2013;4:274. DOI 10.3389/fgene.2013.00274

Xu X., Gu D., Xu B., Yang C., Wang L. Circular RNA circ_0005835 promotes neural stem cells proliferation and differentiate to neuron and inhibits inflammatory cytokines levels through miR-576-ep in Alzheimer's disease. *Environ. Sci. Pollut. Res. Int*. 2022;29(24):35934-35943. DOI 10.1007/s11356-021-17478-3

Yurov Y.B., Vorsanova S.G., Iourov I.Y. FISHing for crhomosome instability and aneuploidy in the Alzheimer's disease brain. *Methods Mol. Biol*. 2023;2561:191-204. DOI 10.1007/978-1-0716-2655-9_10

Zhang H., Yang H., Zhang C., Jing Y., Wang C., Liu C., Zhang R., Wang J., Zhang J., Zen K., Zhang C., Li D. Investigation of microRNA expression in human serum during the aging process. *J. Gerontol. A Biol. Sci. Med. Sci*. 2015;70(1):102-109. DOI 10.1093/Gerona/glu145

Zhang T., Brinkley T.E., Liu K., Feng X., Marsh A.P., Kritchevsky S., Zhou X., Nicklas B.J. Circulating miRNAs as biomarkers of gait speed responses to aerobic exercise training in obese older adults. *Aging* (*Albany N.Y.*). 2017;9(3):900-913. DOI 10.18632/aging.101199

Zhao X., Wang S., Sun W. Expression of miR-28-3p in patients with Alzheimer's disease before and after treatment and its clinical value. *Exp. Ther. Med*. 2020;20(3):2218-2226. DOI 10.3892/etm.2020.8920

Zheng D., Sabbagh J.J., Blair L.J., Darling A.L., Wen X., Dickey C.A. MicroRNA-511 binds to FKBP5 mRNA, which encodes a chaperone protein, and regulates neuronal differentiation. *J. Biol. Chem*. 2016;291(34):17897-17906. DOI 10.1074/jbc.M116.727941

Conflict of interest. The authors declare no conflict of interest.
Received November 9, 2022. Revised October 30, 2023. Accepted November 2, 2023.