



Review

What we have learned to date from the omics approach to non-Alzheimer's dementias

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Abstract

Worldwide, more than 50 million people live with dementia, and due to the rapidly aging population, dementia cases are expected to increase at least five times in 2050. 30%–40% of dementia cases are diagnosed as non-Alzheimer's dementia. Common subtypes of non-Alzheimer's dementia are known as vascular, Lewy body, and frontotemporal dementia. Despite advances in modern medicine, the mechanism of dementia is still not fully understood. The term “omics” is a general term and is used to comprehensively characterize molecules by functional and biological similarities, focusing on the basic biological processes of a living organism and these techniques have enabled us to examine the unknown areas of biology, such as the genome, transcriptome, proteome, microbiome, and metabolome. This review highlights the progress that has been made in omics research while noting the gaps in our knowledge.

Keywords: Omics; Non-Alzheimer's dementia; Host; Microorganism; Cognitive impairment

1. Introduction

More than 50 million people live with dementia in worldwide, and due to the rapidly aging population, dementia cases are expected to increase at least five times in 2050 [1]. The term memory is defined as the ability to reproduce or remember experienced or learned information. Different types of memory structures and their classifications are still a matter of debate. Dementia refers to a clinical syndrome characterized by the deterioration of this memory ability and, progressive cognitive decline that hinders an individual's ability to function. Dementia symptoms are persistent and progressive [2]. Although 60%–70% of dementia cases that develop related are to Alzheimer's disease (AD), the remaining 30%–40% are diagnosed as non-Alzheimer's (non-AD) dementia. The non-AD pathogenesis is still unknown [3]. Despite advances in modern medicine, the developmental process of dementia is still not fully understood. Although some mechanisms have been defined, they still cannot fully explain the process that develops in all patients [4]. In recent years, new molecular techniques that enable high throughput data to be obtained in laboratories, have created hope for many neurological diseases, such as AD [5]. Thanks to the “omics” concept has become part of neurological research, these techniques have enabled us to examine the unknown areas of biology, such as the genome, transcriptome, proteome, microbiome, and metabolome, thus providing a new perspective of the interactions between host and microorganisms [6]. From this point of view, pre-clinical and clinical data has demonstrated a bidirectional interaction between the host and the microorganism and led to the formation of the term “gut-brain axis” between the

gastrointestinal system and the brain. This interaction is very important for the regulation of the neural, hormonal, and immunological balance of human beings [7]. Our gut is therefore named our second brain [8]. Indeed, based on this concept, new relationships between the gut microbiome and dementia have been identified. Alterations in the composition of the gut microbiome have also been shown to independently cause an increase in risk of dementia, along with other traditional risk factors [9]. The presence of microbiome-associated metabolites and bacterial products in the systemic circulation may increase, especially with the inflammatory process that can lead to dementia [10]. Despite this information, it is not yet known how changes in the gut microbiome and microbiota-related metabolites affect cognitive functions. Confusion due to conflicting findings regarding this relationship between the gut microbiome and dementia also exist [10,11]. Understanding this bidirectional interaction is essential for discovering the underlying molecular pathogenic mechanisms of many disorders, especially in the neuroscience field. Studies in this field will provide the means to develop personalized treatments and will reveal different biomarkers and help us consider new treatment options [12]. This review highlights the progress that has been made in omics research while noting the gaps in our knowledge.

2. Dementia and omics approach

The term “omics” is a general term and is used to comprehensively characterize molecules by functional and biological similarities, focusing on the basic biological processes of a living organism. According to the target molecule, many fields of study can be defined with the



use of this term in medicine [6,13,14]. For example, examining the genome role in drug response is called pharmacogenomics, changes in histone structure on genome or genome methylation are called epigenomics, the protein set characterization is called proteomics, the identification of RNA transcripts is called transcriptomics, and the collective characterization of small molecules is called metabolomics [13]. Metagenomics, on the other hand, has been defined as the genetic analysis of all genomes found in an environmental sample. Microorganisms have a place both in the host and in important processes in different areas. Metagenomic techniques contribute to the functional analysis of microbial genes [15,16]. High throughput data obtained with the development of new omics platforms can be easily compared between patients with dementia and healthy controls by using both new artificial intelligence technologies and/or bioinformatics techniques [9,10]. By using these techniques, high-throughput data can be analyzed in more detail, and thus, biomarker detection, immunopathological and pathophysiological mechanisms of diseases, and new personalized treatment algorithms can be developed for the diagnosis of diseases [17] (Fig. 1). The combined use of these omics technologies will help us to understand both the physiology of aging and the mechanisms of diseases that may develop due to aging [18]. Non-Alzheimer's (non-AD) dementia subtypes were reported as vascular dementia (VD), Lewy body dementia (LBD), and frontotemporal dementia (FTD) [2]. It is noticed that the studies on these dementia subtypes are currently limited and these subtypes are not paid attention in the studies on dementia patients using omics approaches [9,10,19]. The non-AD pathogenesis is still unknown [3,19].

2.1 Genomics and dementia

The term genomics can be defined as the characterization of the genome. It can take different names such as pharmacogenomics and epigenomics according to different biological functions [13].

Studies have been carried out for many years in terms of non-AD dementia subtypes and genomics, and different genome data for different non-AD dementia types were associated with the mechanism of the formation of these diseases [20–23].

The especially sporadic form of vascular dementia has been associated with lipid metabolism in particular, and it has been reported that *apoE* gene $\epsilon 4$ and $\epsilon 3$ carriage in its pathophysiology may cause this type of dementia [24,25]. Similarly, it has been reported in different studies that carriage of the *ApoE* gene $\epsilon 4$ variant is an important factor for the development of vascular dementia. Apart from this gene, it has also been reported that pharmacogenomics changes of the *CYP2D6* gene cause differentiation in drug responses. especially CYP2D6-PMs, CYP2D6-UMs, and APOE- $\epsilon 4/4$ carriers were found to be the worst responders to treatments [26].

In another study, it was reported that the single nucleotide polymorphism (SNP) near the androgen receptor gene rs12007229 on the X gene is associated with vascular dementia [20]. There have been publications reporting that it is associated with SNPs in some inflammation-related cytokine genes (C889T and C4845T of *IL-1 α* gene; C511T of *IL-1 β* ; C857T of *TNF- α* ; T1031C and C29T of *TGF- β 1*) [21]. *NOTCH3* mutations are thought to be related to the pathogenesis mechanism of VD. Muiño *et al.* [27], reported that the change in the cysteine residues on the EGF-like repeat domain of *NOTCH3* mutations can trigger the protein misfolding, autophagy, angiogenesis, and TGF1 signaling pathway, and these can be causing Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). It is observed in many diseases such as dementia and migraine [27]. CADASIL is one of the most common inherited causes of dementia and generated after *NOTCH3* gene mutation cysteine residue on exon 2 and exon 3 clusters of chromosome 19q12 [25]. While mutations observed in *APP*, *PSEN1*, and *PSEN2* genes are known in AD patients, the *NOTCH3* gene mutation (p.R1231C) was detected in patients using exome sequencing methods [28]. The gain or loss (deletion) of genetic material detected in DNA containing a gene or multiple gene regions can be identified by analyzing Copy number variants (CNVs). This gain or loss can affect the function of genes [29]. In a study conducted to detect CNVs in Turkish dementia patients, implicated CNVs were reported in genes such as *ZNF804A*, *SNORA70B*, *USP34*, *XPO1*, which were also reported in previous studies. In addition, in this study, overlapping of *AFG1L*, *SNX3*, *VWDE*, and *BC039545* genes were detected [30].

In frontotemporal dementia, studies have also shown that there is a relationship with many genes. *Microtubule-associated protein tau (MAPT)*, *granulin (GRN)*, *C9orf72*, and the *transactive response DNA-binding protein of 43 kDa (TDP-43)* genes were seen as frequently studied genes. TDP-43 is also known to be a major accumulating pathological protein in amyotrophic lateral sclerosis (ALS) [23,31]. Epigenomic studies have shown that methylation of the HLA-DRA locus and cis changes, especially in the frontal cortex, were effective. It has been reported that immune system changes in the development of frontotemporal dementia originated from the HLA locus [23]. Reus *et al.* [32] reported that 2 SNP variants (*rs147211831* and *rs117204439*) close to the *C9orf72* gene region and pathological *C9orf72 G4C2* repeat detection were also associated with FTD. These SNP variants have also been associated with ALS disease [32].

Chia *et al.* [22], in their study in 2021, showed that 5 loci were associated with LBD. It has been reported those loci with this risk are found in the following genes; *GBA*, *APOE*, *SNCA*, *BIN1*, and *TMEM175*. *BIN1* and *TMEM175* were also found to be associated with AD and Parkinson's disease (PD), respectively [22]. Rongve *et al.* [33] found

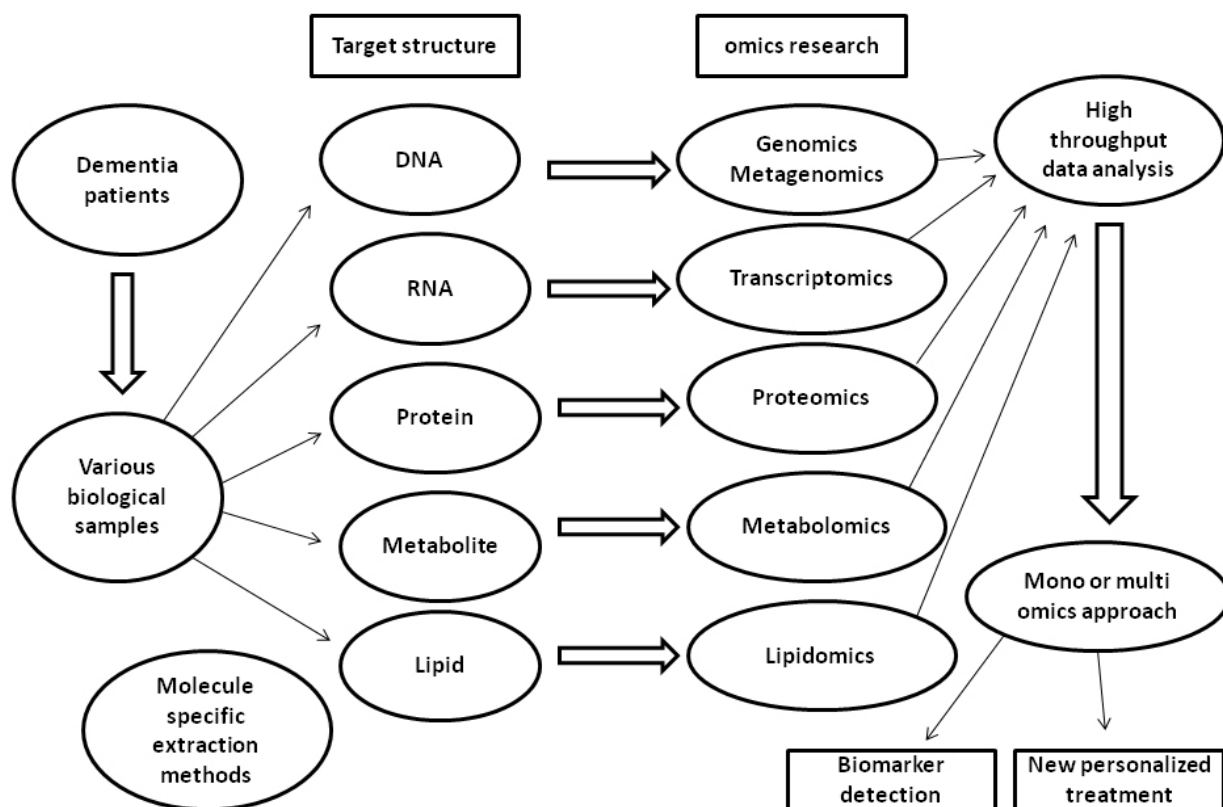


Fig. 1. Omics approaches in dementia.

that *ASH1L/GBA* (Chr1q22) and *APOE ε4* (Chr19) loci variants in the comparative genomics analysis of LBD patients from different parts of Europe. When Kun-Rodrigues *et al.* [34], compared CNVs in 1454 Lewy body dementia patients and 1525 controls, they detected CNVs in the *SNCA*, *APP*, and *MAPT* genes that have also been reported in other neurodegenerative patients. They also found overlapping CNVs in the *LAPTM4B* and *NME1* genes in this study. Another feature observed that as a result, the genes, were shown in association with non-AD dementia subtypes, also have interestingly, detected in other neurodegenerative diseases.

2.2 Metagenomics and dementia

Metagenomics has been defined as the genetic analysis of all genomes found in an environmental sample [15,16]. While microbiota characterizes the microbial taxa found in a certain region of the host, the microbiome is the nomenclature used to characterize the entire microbial genome found in a certain region. After the discovery that we live with 10 times more microbial cells than host cells, it was thought that these microorganisms acted as a supraorganism in the host and provided the balance between health and disease. Therefore, the detection of non-culturable microorganisms using these new techniques has revolutionized research [35]. In recent years, there has been an in-

crease in studies investigating the association between neurodegenerative diseases with microbiota and this has given rise concept of the “brain-gut-microbiota axis” [36]. From birth, there is a constant interaction between the human body and the host microbiota. Along with this interaction, they play an important role in maintaining both general health and well-being in the host [37]. It is known that balanced microbiota plays an important role in the successful maintenance of host health [37,38]. The gut is the region with the largest human microbiome, and therefore the gut resident microbiota has been considered a major player in maintaining human health [39]. The gut microbiota and the Central nervous system (CNS) have a bidirectional interaction and are therefore known to modulate each other’s functioning [40]. The immune system, some hormones, nerve transmission, and other molecular signal mechanisms have been seen as structures that provide this bidirectional communication [41]. It is known that *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria* are the 4 main phyla in the gut microbiota [42]. Evidence has shown that the gut microbiota can influence the development and functions of the CNS and enteric nervous system (ENS), particularly through its interaction and activation with receptors such as Toll-like receptors 2 and 4 (TLR2 and TLR4), which are pattern recognition receptors (PRRs) [42–44]. As a result of the dysbiosis of the mi-

crobiota in the gut, the integrity of the gut barrier is disrupted and the loss of gut permeability causes an increase in the passage of both metabolites and microbe-associated molecular models (MAMPs) produced by the species in the gut microbiota to the mesenteric lymphoid tissues. It has been reported that this transition is especially effective in the progression and development of neurological diseases [41,42,45]. Unlike the data in genomics, it is seen that microbiome or metagenomics studies do not differentiate between dementia subtypes, and studies generally examine changes in dementia status. Among the literature, it has been observed that patient control-based studies are quite limited [9]. Saji *et al.* [9] reported in their study that the rate of *Firmicutes/Bacteroidetes* increased in dementia patients compared to controls. They reported that there was a decrease in *Bacteroides* at the genus level, which may be a biomarker, and even showed a stronger effect than the traditional biomarker data. They have stated that the process that causes inflammation is involved in the immunopathogenesis of diseases such as dementia and that this process may be caused by changes in the gut microbiome [9]. When animal intervention studies were examined, there were data reporting that regressions were observed in the development of the disease, especially after some bacteria were given to experimental animals in dementia models [46–48]. Liu *et al.* [46] reported that when they added *Clostridium butyricum* to the meals of mice with dementia for 6 weeks, BDNF-P13K/Akt pathway-related proteins increased but Bax proteins decreased. They reported that *Clostridium butyricum* increases fecal butyrate, which regulates the gut microbiota and prevents dementia-related spatial learning losses [46]. Musa *et al.* [47] found that antioxidant levels increased due to neuroinflammation, but proinflammatory cytokines and acetylcholinesterase decreased in mice treated with fermented cow's milk containing *Lactobacillus fermentum* LAB9 or *L. casei* LABPC and they also reported increased learning in mice. Chunchai *et al.* [48] reported that hippocampal plasticity and attenuated brain mitochondrial dysfunction were reduced in rats fed with *Lactobacillus paracasei* for 12 weeks, and hippocampal oxidative stress and apoptosis were reduced after probiotic treatment. In particular, the gut microbiota affected the development of the gut-associated lymphoid system (GALT). Because in the gut it's known that there are almost 70% of the lymphocyte cells in the circulation of the host. There are different immune system cells in the lamina propria of the gut and these immune cells play an important role in shaping the immune system of the host. When examining the connection between gut microbiota and systemic inflammation, it was determined that microbiota changes were associated with changes in proinflammatory cytokines, especially IL-8 and IL-6. Low-grade systemic inflammation that develops in this way is seen in both neurodegenerative diseases and vascular diseases, and the increased proinflammatory cytokines due to this inflammation can cross the

blood-brain barrier, whose function is reduced, and affect the neurons, making them more prone to proinflammatory response in the presence of tissue damage [11]. Stadlbauer *et al.* [49] studied gut microbiota in dementia patients and showed that the hypothesis could be correct. They reported that systemic inflammation increased in dementia patients, especially with the increase in gut permeability, and then, serum diamine oxidase (DAO) and the soluble cluster of differentiation 14 (sCD14) increased. They found that microbial taxa such as the *Lachnospiraceae* NK4A136 group, which are especially effective in butyrate production, decreased in dementia patients [49]. Although there are studies on animals and humans examining the immunopathogenesis mechanism of the gut microbiota in neurodegenerative diseases such as dementia, studies on humans are limited, and the data need to be confirmed with comprehensive studies [50]. Araos *et al.* [51] reported that diversity decline in patients with dementia. Similar to other studies, *Firmicutes* increased while *Bacteroidetes* decreased. Leblhuber *et al.* [52] reported that after probiotic supplementation to patients with dementia caused by AD, especially *Faecalibacterium prausnitzii* were increased but *Akkermansia muciniphila* were not changed in the gut microbiota, and also that the metabolism of tryptophan differed significantly. They argued that the data obtained in this study showed an anergic immune system in patients and that amyloid aggregates and damaged cells could not be cleared due to this anergy. In this way, they stated that gut permeability would change and the inflammatory process associated with the development of neurodegenerative diseases could begin [52]. Supporting this data, it is known that *F. prausnitzii* and *A. muciniphila* induce an anti-inflammatory response [53].

2.3 Metabolomics and dementia

Metabolomics has been defined as the collective characterization of small molecules in body fluids, cells, or tissues [13]. Many different metabolic changes in the brain or CSF have been reported in patients with dementia, and these different metabolites can also be detected in the peripheral circulation of patients. These metabolites, especially detected in the peripheral circulation, are considered biomarkers of dementia [54]. Teruya *et al.* [55] detected 33 metabolites in the blood of dementia patients, which they divided into 5 groups, and reported that 26 metabolites in 4 groups decreased and 7 metabolites in one group increased. They argued that increased 7 metabolites including quinolinic acid, kynurenine, and indoxyl-sulfate showed neurotoxin properties for the CNS. Among the metabolites whose levels decreased, there were metabolites with antioxidant properties such as ergothioneine [55]. Saji *et al.* [10] examined the metabolites associated with the gut microbiome of dementia patients and found that fecal ammonia was elevated, but lactic acid was decreased. Alkasir *et al.* [11] reported that some genera such as *Lactobacillus*, *Lactococcus*, *Streptococcus*

Staphylococcus, and *Enterococcus* produce histamine and this reduces *Tumour Necrosis Factor (TNF) alpha (TNF α)* expression in the brain as a modulator of neuroinflammation. It is suggested that bacterial species with probiotic properties such as *Bacillus*, *Lactobacillus*, and *Bifidobacterium* participate in the learning process with the metabolites they synthesize, such as gamma-aminobutyric acid, serotonin, norepinephrine, and acetylcholine [56]. Huo *et al.* [57] detected 4 metabolites (3 different glycerophospholipids and 1 acylcarnitine) in antemortem blood and post-mortem brain samples of AD patients. Jiang *et al.* [54] reported that in the systematic review about the connection between metabolomics and dementia, some lipids, amino acids elevated (phosphatidylcholines, glutamate, *etc.*) or decline (docosahexaenoic acid, taurine *etc.*) respectively. Xu and Wang [58] reported that in AD, microbial metabolites AD-3,4-dihydroxybenzeneacetic acid, AD-mannitol, and AD-succinic acid are associated with the mechanical effect of environmental changes and determined that especially trimethylamine N-oxide (TMAO) metabolites, together with meat and fat foods, affect genetic pathways in patients and that treatment options can be developed by focusing on these metabolites. Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate produced by the main phyla *Firmicutes* and *Bacteroidetes* in the gut microbiota are important metabolites formed by bacteria during the consumption of dietary fibers in the gut [59]. When Wang *et al.* [60] examined the relationship between gut microbiota, microglia, metabolites, pathways, and AD by public data in 2021, they determined that SCFAs were the most important metabolites in the microglia microbial metabolite pathway. Similarly, Colombo *et al.* [61], found that the decrease of microbiota-derived SCFAs would decrease microglia modulation and increase amyloid plaque accumulation in germ-free AD mice. In the gut microbiota, the neurotransmitter Hydroxytryptamine (5-HT) is produced from Tryptophan using the enzyme tryptophan hydroxylase 1 (TPH1). It is known that 5-HT plays a neuronal progenitor role especially in the development of the enteric nervous system (ENS) [62]. It has been reported that both bacteria in the gut microbiota and SCFAs produced by the gut microbiota affect colonic 5-HT production *in vivo* [63]. It is known that SCFAs can potentially affect the neurological functions of the brain through the immune, humoral, vagal, and endocrine pathways [42,64].

2.4 Proteomics and dementia

The characterization of protein sets is called proteomics [13]. The variation of protein levels can change during different disease processes, and it has been reported that proteomics analyzes are used both to determine the basic pathophysiology behind these diseases and to follow the process that develops with the therapeutic intervention [65,66].

Tanaka *et al.* [66] characterized the proteins in the plasma of dementia patients and found that proteins such as peptidase inhibitor 3 (PI3), trefoil factor 3 (TFF3), pregnancy-associated plasma protein-A (PAPPA), and agouti-related peptide (AGRP) were elevated, but myostatin (MSTN), and integrin α Vb5 (ITGAV/ITGB5) were decline. Walker *et al.* [67] determined that 38 proteins were differentiated in the plasma of dementia patients. Among these proteins, SVEP1 was reported to be the protein most strongly associated with the disease. In this study, some patients were followed for up to 20 years and midlife plasma protein levels were compared with older life protein levels and they reported that these proteins are particularly associated with NF- κ B, cytokine signaling, complement activation, and lipid metabolism. In addition, as a result of their analysis, they found that immune signaling proteins such as TREM1, TREM2, IL-18, and LAT were compatible with MRI results of patients with dementia [67]. In the study of Jiang *et al.* [68], protein characterization was performed in the plasma of patients with AD, and as a result of this study, 19 proteins such as PRDX1, VAMP5, and GAMT associated with AD were identified and it was reported that these proteins can be used as biomarkers. Yu *et al.* [69] reported an increase in PLXNB1 protein with amyloid plaque accumulation in AD and found that this was compatible with the pathology of the disease and cognitive decline. On the other hand, they found high levels of IGFBP5, HSPB2, and AK4 proteins and low levels of ITPK1 proteins, but they could not associate this with neurodegenerative disease and cognitive decline [69]. Swarup *et al.* [70] used proteomics, genomics, and transcriptomics approaches in combination with dementia patients and found that most of the protein changes were preserved at the transcriptomics level. As a result of their analysis, they reported that the proteomic and transcriptomic changes that occur in the early period of the disease together with the genetic risk change the biological pathways that cause synaptic loss and glial inflammation pathologies [70].

When proteomics studies specific to the development of vascular dementia were controlled, Wang *et al.* [71] reported that 144 proteins differentiate at different levels and they affected many pathways. By crosstalk analysis, they were determined that protein levels increased in 1 pathway and decreased in 36 pathways [71]. Datta *et al.* [72] reported to change in 144 out of 2281 proteins, they were found to elevate the SOD1 and NCAM and decrease the ATP5A in vascular dementia patients.

When proteomics studies specific to the development of frontotemporal dementia were checked, Schwab *et al.* [73] performed proteomics analysis in transgenic mouse models with frontotemporal dementia to investigate tau protein-dependent and independent pathways. They reported that they observed changes in metabolic, mitochondrial dysfunction, synaptic transmission, and stress responses depending on the increase in tau, and the disorders

in these functions could be treated with hydromethylthionine. Also in this study, hydromethylthionine activated the tau-independent pathway in non-mutagenic mice. Based on these data, the researchers reported that hydromethylthionine can be used to improve frontotemporal dementia cases [73]. When Andrés-Benito *et al.* [74] performed combined proteomic and transcriptomic analysis in patients with frontotemporal dementia, they reported that there were many protein changes at points such as apoptosis, inflammation or affecting microtubule dynamics. When Umoh *et al.* [75] performed proteomics analysis in patients with frontotemporal dementia and ALS, they found that 8 proteins showed significant differences. They also found in this study that proteins with significant changes were associated with TDP43 pathology, cognitive dysfunctions, and inflammation. In their study, van der Ende *et al.* [76] reported that 7 proteins changed significantly in CSF samples of patients with frontotemporal dementia. Neurosecretory protein VGF, neuronal pentraxin receptor (NPTXR), chromogranin-A (CHGA), receptor-type tyrosine-protein phosphatase N2 (PTPRN2), and V-set and transmembrane domain-containing protein 2B (VSTM2B) proteins in carrying GRN mutations, NPTXR, PTPRN2, CHGA, and VSTM2B proteins in carrying C9orf72 mutation, NPTXR and CHGA in carrying MAPT mutation were decreased [76].

When proteomics studies specific to the development of Lewy body dementia were checked, O'Bryant *et al.* [77] reported that sVCAM1, IL5, B2M, IL6, IL1, Adipo, Eotaxin, MIP1, and IL10 were the most differentiated proteins in LBD when compared with controls. Gámez-Valero *et al.* [78] reported that gelsolin and butyrylcholinesterase in plasma of patients with LBD were different in extracellular vesicles compared to controls using LC-MS/MS approaches.

2.5 Transcriptomics and dementia

The characterization of transcripts is called transcriptomics in biologic fluids [13]. Santiago *et al.* [79] reported that genes related to *pre-mRNA processing factor 40 homolog A (PRPF40A)* and *DNAJ heat shock protein family (DNAJ1)* were upregulated in vascular dementia patients. Again, in this study, upregulation of nuclear factor kappa beta (NF- κ B) signal, inflammation, and infection-related pathways were detected, while amino acid biosynthesis and pentose phosphate pathway were inhibited by downregulation of *tumor protein p53 (TP53)* gene [79]. Santiago *et al.* [79] also reported that *the histone deacetylase 1 (HDAC1)* gene was upregulated and *the Y box binding protein 1 (YBX1)* gene was downregulated as a result of transcriptomics analyzes of frontotemporal dementia patients. They found that ECM-receptor interaction, hippo signaling, lysosome, and PI3K-AKT signaling pathway were activated by these genes, while MAPK signaling pathways and glutamatergic synapse were inhibited [79]. Cerebral hypop-

erfusion is known to be characteristic of vascular dementia. therefore, Baik *et al.* [80] induced cerebral hypoperfusion in mouse models and performed transcriptome analysis in hippocampal tissue samples of these mice, reporting that 279 genes were upregulated and 299 genes were downregulated in these samples. Yildirim *et al.* [81] investigated the similarities of Huntington's disease (HD) and subcortical vascular dementia in 2 experimental mouse models and reported that there were 55 shared genes in both diseases and 8 of them were downregulated. In a meta-analysis study of Bottero *et al.* [82] reported that the transcription factors KLF4, CEBPB, GATA3, and MYB were specific for familial FTD patients, and the transcription factors MEF2A, CTCF, IRF1, STAT3, REST, SREBF1, SREBF2, and ZFX specific for sporadic FTD patients. It was reported in this study that 330 and 338 miRNAs were found in these familial and sporadic FTD patients, respectively [82]. Rajkumar *et al.* [83] reported 12 newly expressed genes as a result of transcriptomics analysis of postmortem tissues of patients with Lewy body dementia. these genes were ALPI, ABCA13, CTSG, CSF3, MPO, SELE, GALNT6, SST, RBM3, SLC4A1, OXTR, and RAB44. In addition, they found that some cytokine genes were downregulated significantly [83]. Pietrzak *et al.* [84] reported that 367 genes were downregulated and 123 genes were upregulated in the brain tissues of patients with Lewy body dementia as a result of transcriptomics analysis. They found that differentiated genes are related to myelination, neurogenesis, and nervous system development [84]. Santpere *et al.* [85] reported that dynein and taste receptors genes were upregulated, but genes related to innate inflammation were downregulated in patients with Lewy body dementia. MicroRNAs are defined as small non-coding RNAs and are known to have roles in many biological pathways [86]. It is known that different miRNAs have roles in different types of non-alzheimer's dementia and these have been reported in different studies [78,87,88]. In recent years, besides mRNA and miRNA, RNAs such as Long non-coding RNAs (lncRNAs) have been studied in AD research. lncRNAs is also known to be important in many biological processes in the host. Shi *et al.* [89] reported that 14 lncRNAs downregulated and 39 lncRNAs upregulated. The plasma level of β -site APP cleaving enzyme-1 (BACE1) is a lncRNA and Feng *et al.* [90] reported that the plasma level of BACE1 elevated significantly in AD patients. It is known that BACE1 is required both for the processing of amyloid precursor proteins (APP) and for the production of toxic amyloid- β (A β) [91].

There are some limitations to this review. Methodological, instrumental, and analytical algorithm differences make it difficult to compare the omics data in studies about dementia. It made us think that the methods used in these studies should be standardized. In addition, we believe that raw data should be added to public databases to be able to analyze in the future with the developing bioinformatics and

artificial intelligence techniques. Due to the variation in the prevalence of dementia subtypes also depending on gender (sex) differences, it was not discussed in the review.

3. Conclusions

As a conclusion, it was seen that although there were differences in nonAD subtypes and mechanisms, most of the results obtained with the omics approach drew attention to the neuroinflammation process. It made us think that neuroinflammation may be the focal point for developing cognitive impairment.

Although the large omics data obtained with the developing technologies in recent years have shown that individual significant differences, the use of different sample types, different techniques, different dementia types, and different patient groups (Age, gender or ethnicity, *etc.*) could make it difficult to compare the results. It has been observed that studies are more focused on genetic host DNA and RNA. However, the existence of a microorganism community living with the host should be kept in mind, and it is necessary to design studies with a combined omics approach that can compare the contributions of these microorganisms to the host DNA and RNA.

Author contributions

MD and OAK analyzed the data. MD and OAK wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

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