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 relate 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, preclinical 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 bioinformatic 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 ε4 and ε3 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 ε4 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-ε4/4 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-1α gene; C511T of IL-1β; C857T of TNF-α; T1031C and C29T of TGF-β1) [21]. NOTCH3 mutations are thought to be related to the pathogenesis mechanism of VD. Muño 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 AFGIL, 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
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 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 increase 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-
microbiota 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 Akkermania 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 quinolonic 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, Strep-
**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 αvβ5 (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-κB, 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 (DNAAJ1) were upregulated in vascular dementia patients. Again, in this study, upregulation of nuclear factor kappa beta (NF-kB) 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 hypoperfusion 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. Yıldırım 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, CRTC, 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, SEL, 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 (Aβ) [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

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References

[1] Ricci G. Social Aspects of Dementia Prevention from a Worldwide to National Perspective: a Review on the International Situation and the Example of Italy. Behavioural Neurology. 2019; 2019: 8720904.

[2] Duong S, Patel T, Chang F. Dementia: what pharmacists need to know. Canadian Pharmacists Journal. 2017; 150: 118–129.

[3] Factora RM, Tousi B. Don’t forget non-Alzheimer dementias. Cleveland Clinic Journal of Medicine. 2014; 81: 243–254.

[4] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet. 2020; 396: 413–446.

[5] Hampel H, O’Bryant SE, Castrillo JH, Ritchie C, Rojkova K, Broich K, et al. PRECISION MEDICINE - The Golden Gate for Detection, Treatment and Prevention of Alzheimer’s Disease. The Journal of Prevention of Alzheimer’s Disease. 2016; 3: 243–259.

[6] Nyholm L, Koziol A, Marcos S, Botnen AB, Aizpurua O, Gopalakrishnan S, et al. Holo-Omics: Integrated Host-Microbiota Multi-omics for Basic and Applied Biological Research. iScience. 2020; 23: 101414.

[7] Grenham S, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. Frontiers in Physiology. 2011; 2: 94.

[8] Avetisyan M, Schill EM, Heuckeroth RO. Building a second brain in the bowel. The Journal of Clinical Investigation. 2015; 125: 899–907.

[9] Saji N, Murotani K, Hisata T, Tsuduki T, Sugimoto T, Kimura A, et al. The relationship between the gut microbiome and mild cognitive impairment in patients without dementia: a cross-sectional study conducted in Japan. Scientific Reports. 2019; 9: 19227.

[10] Saji N, Murotani K, Hisata T, Kunihito T, Tsuduki T, Sugimoto T, et al. Relationship between dementia and gut microbiome-associated metabolites: a cross-sectional study in Japan. Scientific Reports. 2020; 10: 8088.

[11] Alkasir R, Li J, Li X, Jin M, Zhu B. Human gut microbiota: the links with dementia development. Protein & Cell. 2017; 8: 90–102.

[12] Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology. 2015; 28: 203–209.

[13] Roth SC. What is genomic medicine? Journal of the Medical Library Association. 2019; 107: 442–448.

[14] Perarakis N, Yazdani A, Karmiadakis GE, Mantzoros C. Omics, big data and machine learning as tools to propel understanding of biological mechanisms and to discover novel diagnostics and therapeutics. Metabolism. 2018; 87: A1–A9.

[15] Thomas T, Gilbert J, Meyer F. Metagenomics - a guide from sampling to data analysis. Microbial Informatics and Experimentation. 2012; 2: 3.

[16] Prayogo FA, Budiharjo A, Kusumaningrum HP, Wijanarka W, Suprihadi A, Nurhayati N. Metagenomic applications in exploration and development of novel enzymes from nature: a review. Journal of Genetic Engineering and Biotechnology. 2020; 18: 39.

[17] Peña-Bautista C, Baquero M, Vento M, Cháfer-Pericás C. Omics-based Biomarkers for the Early Alzheimer Disease Diagnosis and Reliable Therapeutic Targets Development. Current Neuropharmacology. 2019; 17: 630–647.

[18] Rivero-Segura NA, Bello-Chavolla OY, Barrera-Vázquez OS, Gutierrez-Roblado LM, Gomez-Verjan JC. Promising biomarkers of human aging: in search of a multi-omics panel to understand the aging process from a multidimensional perspective. Ageing Research Reviews. 2020; 64: 101164.

[19] Luc M, Misias B, Pawlowski M, Statyczkiewicz B, Zabolocka A, Szczesniak D, et al. Gut microbiota in dementia. Critical review of novel findings and their potential application. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2021; 104: 110039.

[20] Schrijvers EMC, Schürmann B, Koudstaal PJ, van den Bussche
Murray ME, Meschia JF, Dickson DW, Ross OA. Genetics of Vascular Dementia. Minerva Psichiatria. 2010; 51: 9–25.

Chia R, Sabir MS, Bañares-Ciga S, Saez-Atienza R, Reynolds RH, Gustavsson E, et al. Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. Nature Genetics. 2021; 53: 294–303.

Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A, Kwok JBJ, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. The Lancet Neurology. 2014; 13: 686–699.

Yin Y, Li J, Wang J, Li B, Pi Y, Yang Q, et al. Association between apolipoprotein E gene polymorphism and the risk of vascular dementia: a meta-analysis. Neuroscience Letters. 2012; 514: 6–11.

Ikram MA, Bersano A, Manso-Calderón R, Jia J, Schmidt H, Middleton L, et al. Genetics of vascular dementia - review from the ICVD working group. BMC Medicine. 2017; 15: 48.

Cacabelos R, Martínez, Fernández-Novoa L, Carril JC, Lombardi V, Carrera I, et al. Genomics of Dementia: APOE- and CYP2D6-Related Pharmacogenetics. International Journal of Alzheimer’s Disease. 2012; 2012: 518901.

Muiño E, Fernández-Cadenas I, Arboix A. Contribution of “Omic” Studies to the Understanding of Cadasil. A Systematic Review. International Journal of Molecular Sciences. 2021; 22: 7357.

Guerreiro RJ, Lohmann E, Kinsella E, Brás JM, Luu N, Guirriñan N, et al. Exome sequencing reveals an unexpected genetic cause of disease: NOTCH3 mutation in a Turkish family with Alzheimer’s disease. Neurobiology of Aging. 2013; 33: 1008.e17–1008.e23.

Swaminathan S, Shen L, Kim S, Inlow M, West JD, Faber KM, et al. Analysis of copy number variation in Alzheimer’s disease: the NIALOAD/ NCRAD Family Study. Current Alzheimer Research. 2012; 9: 801–814.

Delghani N, Guven G, Kan-Rodrigues C, Gouveia C, Foster K, Hanagasi H, et al. A comprehensive analysis of copy number variation in a Turkish dementia cohort. Human Genomics. 2021; 15: 48.

Llibre-Guerra JJ, Behrens MI, Hosogi ML, Montero L, Tornáva T, Custodio N, et al. Frontotemporal Dementias in Latin America: History, Epidemiology, Genetics, and Clinical Research. Frontiers in Neurology. 2021; 12: 710332.

Reus LM, Jansen JE, Mol MO, van Ruisen F, van Rooij J, van Schoor NM, et al. Genome-wide association study of frontotemporal dementia identifies a C9ORF72 haplotype with a median of 12-G4C2 repeats that predisposes to pathological repeat expansions. Translational Psychiatry. 2021; 11: 451.

Rongve A, Witoelar A, Ruiz A, Athanasiu L, Abdelnour C, Claustin J, et al. GBA and APOE ε4 associate with sporadic dementia with Lewy bodies in European genome wide association study. Scientific Reports. 2019; 9: 7013.

Kun-Rodrigues C, Orme T, Carmona S, Hernandez DG, Ross OA, Eicher JD, et al. A comprehensive screening of copy number variability in dementia with Lewy bodies. Neurobiology of Aging. 2019; 75: 223.e1–223.e10.

Martin R, Miquel S, Langella P, Bermúdez-Humarán LG. The role of metagenomics in understanding the human microbiome in health and disease. Virulence. 2014; 5: 413–423.

Kowalski K, Mulak A. Brain-Gut-Microbiota Axis in Alzheimer’s Disease. Journal of Neurogastroenterology and Motility. 2019; 25: 48–60.

Ogunrinola GA, Oywale JO, Oshamika OO, Olashinde GI. The Human Microbiome and its Impacts on Health. International Journal of Microbiology. 2020; 2020: 8045646.

Whiteside SA, Razvi H, Dave S, Reid G, Burton JP. The microbiome of the urinary tract—a role beyond infection. Nature Reviews. Urology. 2015; 12: 81–90.

Morgan XC, Huttenhower C. Chapter 12: Human microbiome analysis. PLoS Computational Biology. 2012; 8: e1002808.

Grochowska M, Laskus T, Radkowski M. Gut Microbiota in Neurological Disorders. Archivum Immunologicum et Therapie Experimentalis. 2019; 67: 375–383.

Tyler Patterson T, Grandhi R. Gut Microbiota and Neurologic Diseases and Injuries. Advances in Experimental Medicine and Biology. 2020; 38: 73–91.

Suganya K, Koo BS. Gut-Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. International Journal of Molecular Sciences. 2020; 21: 7551.

Heiss CN, Ofolosin LE. The role of the gut microbiota in development, function and disorders of the central nervous system and the enteric nervous system. Journal of Neuroendocrinology. 2019; 31: e12684.

Hyland NP, Cryan JF. Microbe-host interactions: Influence of the gut microbiota on the enteric nervous system. Developmental Biology. 2016; 417: 182–187.

Tremlett H, Bauer KC, Appel-Cresswell S, Finlay BB, Waubant E. The gut microbiome in human neurological disease: a review. Annals of Neurology. 2017; 81: 369–382.

Liu J, Sun J, Wang F, Yu X, Ling Z, Li H, et al. Neurprotective Effects of Clostridium butyricum against Vascular Dementia in Mice via Metabolic Butyrate. BioMed Research International. 2015; 2015: 412946.

Musa NH, Mani V, Lim SM, Vidyadaran S, Abdul Majeed AB, Ramasamy K. Lactobacilli-fermented cow’s milk attenuated lipopolysaccharide-induced neuroinflammation and memory impairment in vitro and in vivo. The Journal of Dairy Research. 2017; 84: 488–495.

Chunchai T, Thunapong W, Yasom S, Wanchai K, Eaimworawuthikul S, Metzler G, et al. Decreased microglial activation through gut-brain axis by prebiotics, probiotics, or symbiotics effectively restored cognitive function in obese-insulin resistant rats. Journal of Neuroinflammation. 2018; 15: 11.

Stadlbauer V, Engertberger L, Komarova I, Feldbacher N, Leber B, Pichler G, et al. Dysbiosis, gut barrier dysfunction and inflammation in dementia: a pilot study. BMC Geriatrics. 2020; 20: 248.

Ticinesi A, Tana C, Nouvenne A, Prati B, Laureniti F, Meschi T. Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review. Clinical Interventions in Aging. 2018; 13: 1497–1511.

Araos R, Andreatos N, Ugalde J, Mitchell S, Mylonakis E, D’Agata EMC. Fecal Microbiome among Nursing Home Residents with Advanced Dementia and Clostridium difficile. Digestive Diseases and Sciences. 2018; 63: 1525–1531.

Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic Supplementation in Patients with Alzheimer’s Dementia - An Explorative Intervention Study. Current Alzheimer Research. 2018; 15: 1106–1113.

Demirci M, Tokman HB, Uysal HK, Demirayas S, Karakullukcu A, Sarisab S, et al. Reduced Akkermansia muciniphila and Faecalibacterium prausnitzii levels in the gut microbiota of children with allergic asthma. Allergologia Et Immunopathologia. 2019; 47: 365–371.

Jiang Y, Zhu Z, Shi J, An Y, Zhang K, Wang Y, et al. Metabolomics in the Development and Progression of Dementia: A Systematic Review. Frontiers in Neuroscience. 2019; 13: 343.
Teruya T, Chen Y, Kondoh H, Fukui Y, Yanagida M. Whole-blood metabolomics of dementia patients reveal classes of disease-linked metabolites. Proceedings of the National Academy of Sciences. 2021; 118: e2022857118.

Westfall S, Lomis N, Kahouli I, Dias SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut-brain axis. Cellular and Molecular Life Sciences. 2017; 74: 3769–3787.

Huo Z, Yu L, Yang J, Zhu Y, Bennett DA, Zhao J. Brain and blood metabolome for Alzheimer’s dementia: findings from a targeted metabolomics analysis. Neurobiology of Aging. 2020; 86: 123–133.

Xu R, Wang Q. Towards understanding brain-gut-microbiome connections in Alzheimer’s disease. BMC Systems Biology. 2010; 16: 63.

Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell. 2016; 165: 1332–1345.

Wang Q, Davis PB, Qi X, Chen SG, Gurney ME, Perry G, et al. Gut–microbiota–microglia–brain interactions in Alzheimer’s disease: knowledge-based, multi-dimensional characterization. Alzheimer’s Research & Therapy. 2021; 13: 177.

Colombo AV, Sadler RK, Llovera G, Singh V, Roth S, Heindl S, et al. Microbiota-derived short chain fatty acids modulate microglia and promote Aβ plaque deposition. Elife. 2011; 10: e59826.

De Vadder F, Grasset E, Mánners Holm L, Karsenty G, Macpherson AJ, Olofsson LE, et al. Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks. Proceedings of the National Academy of Sciences of the United States of America. 2018; 115: 6458–6463.

Reigstad CS, Salmonson CE, Rainey JF, Szurowski JH, Linden DR, Sonnenburg JL, et al. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. FASEB Journal. 2015; 29: 1395–1403.

Soret R, Chevalier J, De Coppet P, Poupeau G, Derkinderen P, Seguin JP, et al. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. Gastroenterology. 2010; 138: 1772–1782.

He Q, Chiu J. Proteomics in biomarker discovery and drug development. Journal of Cellular Biochemistry. 2003; 89: 868–886.

Tanaka T, Lavery R, Varma V, Fantoni G, Colpo M, Thambisetty M, et al. Plasma proteomic signatures predict dementia and cognitive impairment. Alzheimer’s & Dementia. 2020; 6: e12018.

Walker KA, Chen J, Zhang J, Fornage M, Yang Y, Zhou L, et al. Large-scale plasma proteomic analysis identifies proteins and pathways associated with dementia risk. Nature Aging. 2021; 1: 473–489.

Jiang Y, Zhou X, Ip FC, Chan P, Chen Y, Lai NCH, et al. Large-scale plasma proteomic profiling identifies a high-performance biomarker panel for Alzheimer’s disease screening and staging. Alzheimer’s Dement. 2021 May 25. doi: 10.1002/alz.12369.

Yu L, Petyuk VA, Gaiteri C, Mostafavi S, Young-Pearsre T, Shah RC, et al. Targeted brain proteomics uncover multiple pathways to Alzheimer’s dementia. Annals of Neurology. 2018; 84: 78–88.

Swarnap V, Chang TS, Duong DM, Dammer EB, Dai J, Lah JJ, et al. Identification of Conserved Proteomic Networks in Neu rodegenerative Dementia. Cell Reports. 2020; 31: 107807.

Wang C, Zhao J, Xu R, Zhao J, Duan S. Identification of pivotal markers in vascular dementia based on proteomics data. Dementia and Geriatric Cognitive Disorders. 2015; 39: 312–320.

Datta A, Qian J, Chong R, Kalaria RN, Francis P, Lai MKP, et al. Novel pathophysiological markers are revealed by iTRAQ-based quantitative clinical proteomics approach in vascular dementia. Journal of Proteomics. 2014; 99: 54–67.

Schwab K, Melis V, Harrington CR,Wischik CM, Magbagbeolu M, Theuring F, Riedel G. Proteomic Analysis of Dydroxymethylthione in the Line 66 Model of Frontotemporal Dementia Demonstrates Actions on Tau-Dependent and Tau-Independent Networks. Cells. 2021; 10: 2162.

Andrés-Benito P, Gorbi E, Povedano M, Ausín K, Fernández-Irigoyen J, Santamaría E, et al. Combined Transcriptomics and Proteomics in Frontal Cortex Area 8 in Frontotemporal Lobar Degeneration Linked to C9ORF72 Expansion. Journal of Alzheimer’s Disease. 2019; 68: 1287–1307.

Umoh ME, Dammer EB, Dai J, Duong DM, Lah JJ, Levey AI, et al. A proteomic network approach across the ALS-FTD disease spectrum resolves clinical phenotypes and genetic vulnerability in human brain. EMBO Molecular Medicine. 2018; 10: 48–62.

van der Ende EL, Meeter LH, Singl C, van Rooy JG, Stoop MP, Nijholt DAT, et al. Novel CSF biomarkers in genetic frontotemporal dementia identified by proteomics. Annals of Clinical and Translational Neurology. 2019; 6: 698–707.

O’Bryant SE, Ferman TJ, Zhang F, Hall J, Pedraza O, Wszolek ZK, et al. A proteomic signature for dementia with Lewy bodies. Alzheimer’s & Dementia. 2019; 11: 270–276.

Gámez-Valero A, Campdelacreu J, Rehè R, Beyer K, Borrás FE. Comprehensive proteomic profiling of plasma-derived Extracellular Vesicles from dementia with Lewy Bodies patients. Scientific Reports. 2019; 9: 13282.

Santiago JA, Bottero V, Potashkin JA. Transcriptomic and Network Analysis Identifies Shared and Unique Pathways across Dementia Spectrum Disorders. International Journal of Molecular Sciences. 2020; 21: 20509.

Baik S, Selvaraji S, Fann DY, Poh L, Jo D, Herr DR, et al. Hippocampal transcriptome profiling reveals common disease pathways in chronic hypoperfusion and aging. Aging. 2021; 13: 14651–14674.

Yildirim F, Foddis M, Blumenau S, Müller S, Kajetan B, Holt-Westfall S, Lomis N, Kahouli I, van der Ende EL, Meeter LH, Singl C, van Rooy JG, Stoop MP, Nijholt DAT, et al. Novel CSF biomarkers in genetic frontotemporal dementia identified by proteomics. Annals of Clinical and Translational Neurology. 2019; 6: 698–707.

O’Bryant SE, Ferman TJ, Zhang F, Hall J, Pedraza O, Wszolek ZK, et al. A proteomic signature for dementia with Lewy bodies. Alzheimer’s & Dementia. 2019; 11: 270–276.

Gángámez-Valero A, Campdelacreu J, Rehè R, Beyer K, Borrás FE. Comprehensive proteomic profiling of plasma-derived Extracellular Vesicles from dementia with Lewy Bodies patients. Scientific Reports. 2019; 9: 13282.

Santiago JA, Bottero V, Potashkin JA. Transcriptomic and Network Analysis Identifies Shared and Unique Pathways across Dementia Spectrum Disorders. International Journal of Molecular Sciences. 2020; 21: 20509.

Baik S, Selvaraji S, Fann DY, Poh L, Jo D, Herr DR, et al. Hippocampal transcriptome profiling reveals common disease pathways in chronic hypoperfusion and aging. Aging. 2021; 13: 14651–14674.

Yildirim F, Foddis M, Blumenau S, Müller S, Kajetan B, Holt- growe M, et al. Shared and oppositely regulated transcriptomic signatures in Huntington’s disease and brain ischemia confirm known and unveil novel potential neuroprotective genes. Neurobiology of Aging. 2021; 104: 122.e1–122.e17.

Bottero V, Alfarati F, Santiago JA, Potashkin JA. Transcriptomic and Network Meta-Analysis of Frontotemporal Dementias. Frontiers in Molecular Neuroscience. 2021; 14: 747798.

Rajkumar AP, Bidkori G, Shoaei S, Clarke E, Morrin H, Hye A, et al. Postmortem Cortical Transcriptomics of Lewy Body Dementia Reveal Mitochondrial Dysfunction and Lack of Neuroinflammation. The American Journal of Geriatric Psychiatry. 2020; 28: 75–86.

Pietrzak M, Papp A, Curtis A, Handelman SK, Kataliki M, Scharre DW, et al. Gene expression profiling of brain samples from patients with Lewy body dementia. Biochemical and Biophysical Research Communications. 2016; 479: 875–880.

Sanpere G, Garcia-Esparza P, Andres-Benito P, Lorente-Galdos B, Navarro A, Ferrer I. Transcriptonal network analysis in frontal cortex in Lewy body diseases with focus on dementia with Lewy bodies. Brain Pathology. 2021; 28: 315–333.

Quinlan S, Kenny A, Medina M, Engel T, Jimenez-Mateos EM. MicroRNAs in Neurodegenerative Diseases. International Review of Cell and Molecular Biology. 2017; 334: 309–343.

Ragusa M, Bosco P, Tamburrello L, Barbagallo C, Condorelli AG, Torritore M, et al. miRNAs Plasma Profiles in Vascular Dementia: Biomolecular Data and Biomedical Implications. Frontiers in Cellular Neuroscience. 2016; 10: 51.

Grasso M, Piscopo P, Talarico G, Ricci L, Crestini A, Tosto G, et al. Plasma microRNA profiling distinguishes patients with frontotemporal dementia from healthy subjects. Neurobiology
of Aging. 2019; 84: 240.e1–240.e12.

[89] Shi Y, Liu H, Yang C, Xu K, Cai Y, Wang Z, et al. Transcriptomic Analyses for Identification and Prioritization of Genes Associated With Alzheimer’s Disease in Humans. Frontiers in Bioengineering and Biotechnology. 2020; 8: 31.

[90] Feng L, Liao Y, He J, Xie C, Chen S, Fan H, et al. Plasma long non-coding RNA BACE1 as a novel biomarker for diagnosis of Alzheimer disease. BMC Neurology. 2018; 18: 4.

[91] Zhang S, Wang Z, Cai F, Zhang M, Wu Y, Zhang J, et al. BACE1 Cleavage Site Selection Critical for Amyloidogenesis and Alzheimer’s Pathogenesis. Journal of Neuroscience. 2017; 37: 6915–6925.