

Review Article



Executive Summary of the 2019 International Conference of Korean Dementia Association: Exploring the Novel Concept of Alzheimer's Disease and Other Dementia: a Report from the Academic Committee of the Korean Dementia Association

OPEN ACCESS

Received: Dec 27, 2019
Revised: May 22, 2020
Accepted: May 25, 2020

Correspondence to





Kee Hyung Park


Department of Neurology, Gachon University Gil Medical Center, Gachon University College of Medicine, 21 Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Korea.
E-mail: khpark@gachon.ac.kr

© 2020 Korean Dementia Association

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Kee Hyung Park 
<https://orcid.org/0000-0001-6847-6679>
Jae-Sung Lim 
<https://orcid.org/0000-0001-6157-2908>
Sang Won Seo 
<https://orcid.org/0000-0003-2568-0797>
Yong Jeong 
<https://orcid.org/0000-0002-5907-3787>
Young Noh 
<https://orcid.org/0000-0002-9633-3314>
Seong-Ho Koh 
<https://orcid.org/0000-0001-5419-5761>
Jae-sung Bae 
<https://orcid.org/0000-0002-8270-0072>

Kee Hyung Park ¹, **Jae-Sung Lim** ², **Sang Won Seo** ³, **Yong Jeong** ⁴,
Young Noh ¹, **Seong-Ho Koh** ⁵, **Jae-sung Bae** ⁶, **Sun Ah Park** ⁷,
Soh-Jeong Yang ⁸, **Hee Jin Kim** ³, **Juhee Chin** ³, **Jee-hoon Roh** ⁹,
Seong Soo A. An ¹⁰ on behalf of Academic Committee of the Korean Dementia Association

¹Department of Neurology, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Korea

²Department of Neurology, Hallym University Sacred Heart Hospital, Hallym Neurological Institute, Hallym University College of Medicine, Anyang, Korea

³Department of Neurology, Samsung Medical Center, Sungkyunkwan University College of Medicine, Seoul, Korea

⁴Department of Bio and Brain Engineering, KAIST, Daejeon, Korea

⁵Department of Neurology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea

⁶Department of Physiology, Cell and Matrix Research Institute, School of Medicine, Kyungpook National University, Daegu, Korea

⁷Lab for Neurodegenerative Dementia, Department of Anatomy and Department of Neurology, Ajou University School of Medicine, Suwon, Korea







⁸Department of Neurology, Yonsei University Health System, Seoul, Korea

⁹Department of Neurology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

¹⁰Department of Bionano Technology, Gachon University, Seongnam, Korea

ABSTRACT

Because of repeated failures of clinical trials, the concept of Alzheimer's disease (AD) has been changing rapidly in recent years. As suggested by the National Institute on Aging and the Alzheimer's Association Research Framework, the diagnosis and classification of AD is now based on biomarkers rather than on symptoms, allowing more accurate identification of proper candidates for clinical trials by pathogenesis and disease stage. Recent development in neuroimaging has provided a way to reveal the complex dynamics of amyloid and tau in the brain *in vivo*, and studies of blood biomarkers are taking another leap forward in diagnosis and treatment of AD. In the field of basic and translational research, the development of animal models and a deeper understanding of the role of neuroinflammation are taking a step closer to clarifying the pathogenesis of AD. Development of big data and the Internet of Things is also incorporating dementia care and research into other aspects. Large-

Sun Ah Park 
<https://orcid.org/0000-0002-3027-3259>
Soh-Jeong Yang 
<https://orcid.org/0000-0001-7033-694X>
Hee Jin Kim 
<https://orcid.org/0000-0002-3186-9441>
Juhee Chin 
<https://orcid.org/0000-0002-3784-9716>
Jee-hoon Roh 
<https://orcid.org/0000-0002-3243-0529>
Seong Soo A. An 
<https://orcid.org/0000-0002-8123-6183>

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Park KH, Koh SH; Writing - original draft: Park KH, Lim JS, Seo SW, Jeong Y, Noh Y, Koh SH, Bae JS, Park SA, Yang SJ, Kim HJ, Chin J, Roh JH, An SSA; Writing - review & editing: Park KH, Lim JS, Koh SH.

scale genetic research has identified genetic abnormalities that can provide a foundation for precision medicine along with the aforementioned digital technologies. Through the first international conference of the Korean Dementia Association, experts from all over the world gathered to exchange opinions with association members on these topics. The Academic Committee of the Korean Dementia Association briefly summarizes the contents of the lectures to convey the depth of the conference and discussions. This will be an important milestone in understanding the latest trends in AD's pathogenesis, diagnostic and therapeutic research and in establishing a future direction.

Keywords: Alzheimer Disease; Neuroinflammation; Translational Medical Research; Biomarkers; Genetic Research; Neuropsychology

INTRODUCTION

The recent news of the failures of clinical trials with amyloid-based disease-modifying drugs have been disappointing to researchers as well as to dementia patients and their families. From this point of view, the history of drug development to treat Alzheimer's disease (AD) seems not to have a happy ending. But, in a decade of failures, we learned many valuable lessons. It allowed us to recognize that it is important to enroll the correct study subjects by means of precise diagnosis. As a result, we started to use biomarker-based inclusion criteria for clinical trials. Moreover, they brought out the evidence that patients with mild dementia, especially those with prodromal or preclinical AD, are more suitable candidates than mild to moderate AD dementia for developing disease-modifying drugs for AD. Also, they gave us much information about side effects of disease-modifying drugs, which we had not experienced before. For example, previous clinical trials for amyloid-based monoclonal antibodies let us know that amyloid-related imaging abnormality (ARIA) is more frequent in APOE ϵ 4 carriers, most of whom were asymptomatic. In addition, ARIA could be controlled by reducing the drug dosage. This information could make the clinical trials afterwards using a higher doses of monoclonal antibody possible. Furthermore, the differences of drug efficacy depending on APOE ϵ 4 status made us consider the necessity of precision medicine. But above all, the important lessons learned from previous failures showed us the need for an accurate assessment tool for drug efficacy, especially in prodromal or preclinical AD patients, and the importance of a profound understanding of the pathophysiology of AD, which has also been emphasized in the Food and Drug Administration guidance 2018 on AD drug development.

From this point of view, it was the perfect time for the International Conference of the Korean Dementia Association 2019 (IC-KDA 2019), which was held on May 31 to June 1, 2019, with the objective of bringing together leading domestic and international scholars to consider the direction of future research. They shared the results of state-of-the-art studies and discussed the right way to continue AD research. IC-KDA 2019 included 6 scientific sessions, 5 plenary lectures, and a luncheon symposium and poster session for 2 days. Based on the theme of "Exploring the Novel Concept of Alzheimer's Disease and Other Dementias," the scientific sessions were divided into 6 topics, including neuroimaging, neuro-inflammation, translational science, blood-based biomarkers, neuropsychology, and genetics. Each session had 3 sub-topics. The 5 plenary lectures were presented by invited leading scholars in those fields, and it was a good opportunity to look at the major research achievements from various angles.

The purpose of this article is to provide a comprehensive understanding of the most advanced knowledge in the field of AD by summarizing the key events presented in IC-KDA 2019.

SESSION 1. UPDATE ON NEUROIMAGING IN AD

In this session, we dealt with the role of neuroimaging in diagnosis of AD. Previously, neuroimaging tools were used to exclude other causes of dementia, such as brain tumors, subdural hematomas, and cerebral infarctions. However, with the advances in neuroimaging analysis techniques, structural magnetic resonance imaging (MRI) provides key imaging markers for AD hippocampal volume loss and cortical atrophy. Molecular positron emission tomography (PET) imaging has also had a profound effect on research in aging and dementia. The first publication of an amyloid imaging agent, carbon-11-labelled Pittsburgh Compound B opened the door to *in vivo* detection of a fundamental aspect of AD pathology. This ability to detect and quantify fibrillar brain amyloid- β ($A\beta$) has helped to establish models of disease pathophysiology and biomarker progression to guide the design of clinical trials and to define a multitude of $A\beta$ effects on the brain in asymptomatic older people. Furthermore, the development of tau-selective radiotracers opened a new era of neuroimaging study in neurodegenerative diseases. In this session, 3 speakers gave talks to update 3 topics of MRI, amyloid PET, and tau PET.

Advances of MRI in dementia (Won-Jin Moon, Konkuk University, Seoul, Korea)

Professor Moon talked about recent MRI advances in the field of AD with an emphasis on new imaging markers, such as blood-brain barrier (BBB) permeability imaging and iron mapping. With technical development, advanced MRI can provide a variety of physiological parameters from an AD brain, such as blood flow, BBB integrity, and functional activity/connectivity. BBB permeability disturbance in the early stage of AD has been studied using dynamic contrast-enhanced MRI. In addition, advanced MRI can also detect microstructural abnormalities, such as iron, myelin, and axonal changes.

Update on amyloid PET imaging in dementia (Sang Won Seo, Sungkyunkwan University, Seoul, Korea)

Professor Seo talked about amyloid PET imaging. Recently, ^{18}F -labeled amyloid imaging agents were developed and commercialized, widely increasing the availability of this technology. Translation of research findings to clinical populations, however, poses substantial challenges. Unlike research subjects, clinical patients can exhibit a wide range of mixed-cause dementias and are frequently seen in clinical practice. He covered the cost-effective use of limited health-care resources, because novel molecular markers are expensive. He presented several relevant scenarios and discussed the appropriate uses of amyloid PET. He also discussed several debatable issues of current molecular imaging markers.

***In vivo* tau PET imaging in dementia (Chul Hyung Lyoo, Yonsei University, Seoul, Korea)**

Professor Lyoo talked about tau PET imaging. Among these first-generation radiotracers, ^{18}F -flortaucipir has been most extensively studied in many types of tauopathies. In AD, cortical ^{18}F -flortaucipir binding directly reflects the cortical tau pathology and status of disease progression. Moreover, it is closely associated with the clinical severity and progression of global cognitive dysfunction. Unlike this strong ^{18}F -flortaucipir binding to the paired helical filament form of tau protein that is found in AD, ^{18}F -flortaucipir only weakly binds to the tau proteins

found in clinically diagnosed non-AD, such as behavioral variant frontotemporal dementia (FTD), non-fluent/agrammatic primary progressive aphasia, or semantic variant primary progressive aphasia, or even in some types of Parkinson-plus syndromes associated with non-AD. Next-generation radiotracers specific for these non-AD tauopathies or other proteinopathies will be necessary to take a step forward in neuroimaging study in neurodegenerative diseases.

PLENARY SESSION 1-1. TOWARD A BIOLOGICAL DEFINITION OF AD: NATIONAL INSTITUTE ON AGING-ALZHEIMER'S ASSOCIATION (NIA-AA) RESEARCH FRAMEWORK (CLIFFORD R. JACK, JR., MAYO CLINIC, ROCHESTER, MN, USA)

Why is the biologic definition of AD important?

In 1984, Mckhann et al.¹ proposed probable and definite AD criteria based on clinical and pathological findings, but amnesic dementia was identified as AD in clinical settings. Furthermore, inconsistencies in clinical and pathologic findings have also been commonly reported. To complement this, the international working group in 2007, 2010, and 2014, and the NIA-AA in 2011, presented diagnostic criteria based on clinical findings and biomarkers. Most recently, in 2018, Jack et al.² proposed the NIA-AA research framework. Since this framework basically distinguishes syndromes (symptoms) from biological findings (pathophysiology), amnesic dementia and AD are no longer synonymous. According to this framework, AD is defined by the presence of plaques and tangles biologically found via biomarkers or autopsies, and the disease stages can be identified by biomarkers and clinical symptoms. This NIA-AA research framework applies biomarkers classified by AT(N) in order.³ "A" refers to beta amyloid plaque or related pathology and is defined using A β 42 or A β 42/40 ratio of cerebrospinal fluid (CSF) and/or amyloid PET. "T" refers to the aggregation of 3R and 4R tau or related pathology, which is defined using CSF phosphorylated tau or tau PET. (N) is defined using structural MRI, fluorodeoxyglucose-PET, and the neurofilament light-chain of CSF and plasma to indicate neuronal injury and neurodegeneration. (N) has parentheses because a variety of causes can lead to hippocampal atrophy and therefore have no AD specificity. AT(N) is represented as + or - for each item, resulting in a total of 8 profiles and 3 biomarker categories: normal, AD constant, and suspected non-AD pathophysiology.²

The roles of biomarkers are defining and staging of the diseases. The 2 roles are different, and the measurements defining AD must be specific but not necessarily at staging. The AD continuum is defined as A and T, and the stage can be represented by (N) and cognitive symptoms (C). The cognitive stage is divided into syndromic categorical, cognitively unimpaired, mild cognitive impairment, and dementia.²

The AT(N) framework allows the hypothesis testing of disease models to see whether A and T are epiphenomena or causes of disease. However, because A and T are conditions that define AD, for models where A and T are not the cause of AD, a systematic explanation is required of why they are accompanied. For the current proposed definition of AD, there may be controversy over whether biological definitions are appropriate and when the term AD should be used. However, if cognitive impairment or dementia syndrome is used as the definition of AD, other diseases with similar symptoms, such as FTD and Creutzfeldt-Jakob disease, can be defined as AD. It may be clinically defined as amnesic dementia, but there are limitations

that cannot include AD variants with more distinct symptoms than memory decline and preclinical AD, as previously known.

Why is the multiple biomarker phenotype of AT(N) important?

Pathological findings of AD include amyloid plaque, 3R and 4R tau aggregation, inflammation, and neurodegeneration. Applying it to the dynamic biomarker model has the advantage of confirming the transition to A-T-(N)-, A+T-(N)-, A+T+(N)-, and A+T+(N)+ in order.⁴⁻⁶ The AT(N) multiple biomarker systems are also useful in drug trials. It is possible to select patients according to biomarker phenotypes rather than non-specific symptoms. This may help to select the appropriate target group, because the therapeutic agents will not work the same for A+T-(N)-, A+T+(N)+, or A+T-(N)+. The diagnostic framework is also flexible and extensible. When new biomarkers for A, T, and (N) are developed, they can be integrated into the framework and biomarkers in new categories, such as vascular (V), alpha-synuclein (S), and inflammation (I). If a new biomarker comes out, it can be expressed as X and reflected in the form of ATX(N). This provides a more elaborate approach to treatment development by better understanding the sequential processes of the AD continuum leading to cognitive impairment and the various causes of dementia.

PLENARY SESSION 1-2. TRACKING OF MOLECULAR PATHOLOGY OF AD WITH IMAGING (W. JAGUST, UNIVERSITY OF CALIFORNIA, BERKELEY, BERKELEY, CA, USA)

About 30% of cognitively normal people in their 70s and above have substantial A β accumulation in amyloid PET. As Dr. Jagust⁷ mentioned in his review article, A β accumulation in the medial parietal cortex appears to be the first stage in the development of AD, although tau aggregates in the medial temporal lobe precede A β deposits in cognitively healthy older people. Despite a strong link between A β and tau, the relationship between A β and neurodegeneration is weak^{8,9}; rather, it is tau that is associated with brain atrophy and hypometabolism, which, in turn, are related to cognition.¹⁰ One of his studies showed that tau tangles but not A β plaques correlated with cognition and clinical symptoms.¹¹ Non-local associations linking increased A β accumulation rates with increased tau deposits are of great interest and support the idea that the A β pathology might have remote effects in disease pathology spread potentially via the brain's intrinsic connectivity networks.¹¹ A longitudinal study showed that tau accumulates even in amyloid-negative healthy older adults, and this process can be measured with *in vivo* tau PET. In older adults, tau accumulation and atrophy share a similar topography. In AD, tau increases more rapidly, and accumulation occurs in frontal regions that are not yet undergoing significant atrophy.¹² When we looked at the relationship between tau and neurodegeneration, tau pathology is related in a region-specific manner to cognitive impairment in AD. These regional relationships are weakly related to amyloid burden but are in part mediated by grey matter volumes. This suggests that tau pathology may lead to cognitive deficits through a variety of mechanisms, including, but not restricted to, grey matter loss.¹³ Another study showed that tau in the entorhinal cortex is associated with cortical thinning and memory decline in normal aging.¹⁴

Dr. Jagust raised a question: why have A β -lowering therapeutic trials repeatedly failed? He said that in early trials, participants were not screened for A β and many did not have

brain amyloid. All current trials now required evidence of brain A β . In addition, in recent trials, participants have had cognitive symptoms, which probably reflect extensive tau accumulation. A β -targeting therapies may not be effective once tau has deposited. There is a very long prodromal phase in the development of AD, during which we can measure pathology and intervene. Last, he asked, ‘When will it be too late to lower the amyloid?’

SESSION 2: OVER THE HORIZON OF NEUROINFLAMMATION OF AD

Research on AD pathogenesis has focused on hypotheses about damage to neuronal cells caused by amyloid and tau. However, failure of many clinical trials based on those hypotheses has led us consider other pathogenesis for AD. Increasing evidence suggests that neuroinflammation plays critical roles in AD pathogenesis. Aggregated A β proteins bind to receptors on glial cells, such as microglia and astroglia, and trigger an innate immune response characterized by release of inflammatory mediators. These inflammatory mediators induce active inflammation, damage neuronal cells, and contribute to disease progression.

There was a special session for the discussion of the importance of neuroinflammation in AD in IC-KDA 2019.

The importance of complement immune signaling in AD pathogenesis (Cynthia A. Lemere, Brigham & Women’s Hospital, Harvard Medical School, Boston, MA, USA)

First, Dr. Cynthia A. Lemere talked about the importance of complement immune signaling in AD pathogenesis. The complement cascade is well-known to be an innate immune response that enables removal of pathogens and to play an important role in microglia-mediated synaptic refinement during brain development. Complement C3 is reported to be elevated in AD, colocalizing with neuritic plaques, and appears to contribute to clearance of A β by microglia in the brain. For complement C3, Dr. Lemere showed her fascinating findings that C3-deficient C57BL/6 mice were protected against age-related and region-specific loss of hippocampal synapses and cognitive decline during normal aging. In addition, she emphasized that complement C3 or downstream complement activation fragments may play an important role in A β plaque pathology, glial responses to plaques, and neuronal dysfunction in the brains of APP/PS1 mice.¹⁵

Immune-inflammatory modulation as a therapeutic strategy for AD and neurodegenerative diseases (Seung Hyun Kim, Hanyang University, Seoul, Korea)

Dr. Seung Hyun Kim said that the complexity of AD in its biological, genetic, and clinical aspects has hindered the development of effective therapeutic agents. He insisted that a therapeutic strategy that is based on immune-inflammation modulation for a subgroup of AD and related dementias is a promising way to achieve targeted medicine. He insisted that sphingosine kinase 1 (SphK1) and its metabolites, triggering a receptor expressed on myeloid cells-2 (TREM2) related signals, and actin motility-related proteins, including Nck-associated protein 1, were selected as promising targets to modulate neuroinflammation.¹⁶

Implications of soluble TREM2 (sTREM2) in Alzheimer’s disease (Jae-Hong Lee, University of Ulsan College of Medicine, Seoul, Korea)

Dr. Jae-Hong Lee explained genome-wide analysis, suggesting that several genes that increase the risk for sporadic AD encode factors that regulate glial clearance of misfolded

proteins and the inflammatory reaction. Among them, variants in the microglia-expressed receptor TREM2 are associated with a 2- to 4-fold increased risk of developing AD.¹⁷⁴⁹ Therefore, TREM2 has been emphasized as a new target or marker in the pathogenesis of AD. Since the discovery of a link between TREM2 and AD, many studies to measure sTREM2 in serum and CSF as a biomarker for AD have been reported. He also showed his preliminary data about the relationship between serum and CSF sTREM2 and the status of AD in Korean patients. Although the relationship has not been confirmative, CSF sTREM2 seemed to be well-correlated with the condition of the patients at least.

Taken all together, neuroinflammation is thought to be in the center of the pathogenesis of AD, and it should be controlled for the treatment of AD. Considering all these things, new drugs targeting neuroinflammation need to be developed.

SESSION 3. BASIC TO TRANSLATIONAL SCIENCE FOR AD

This session was focused on basic to translational science for AD. All speakers have explored recent progress and challenges in biomedical research, therapeutics and diagnostics development, and regulatory science related to AD. We had presentations and discussion together with 3 speakers, 1) Dr. Takaomi Saido based on RIKEN, Wako, Japan, 2) Dr. Hee Kyung Jin, Kyungpook National University, Daegu, Korea, and 3) Dr. Tetsuya Suhara, from the National Institute of Radiological Sciences, Chiba, Japan.

Modelling AD: from mice to non-human primates (Takaomi Saido, RIKEN, Wako, Japan)

To elucidate AD mechanisms, several mouse models have been developed. However, most of these are transgenic mouse models that employ overexpression paradigms. This unphysiological production of proteins most likely induces artifacts that hinder the interpretation of the data obtained from these mice. Therefore, his laboratory generated knock-in mice that harbor Swedish and Beyreuther/Iberian mutations with and without the Arctic mutation in the APP gene. The mice showed typical A β pathology, neuroinflammation, and memory impairment in an age-dependent manner. Importantly, he also briefly introduced a generation of non-human primate models of familial AD.

A spotlight on novel pathogenesis & drug targets in AD: lessons from sphingolipid metabolism (Hee Kyung Jin, Kyungpook National University, Daegu, Korea)

The presentation by Dr. Jin focused on novel pathogenesis and drug targets in AD, especially targeting for sphingolipid metabolism. Her laboratory has previously demonstrated a new role of SphK1-acetyltransferase activity on COX2 and showed that it was reduced in AD neurons. They confirmed that increased SphK1 promoted specialized pro-resolving mediators (SPMs) secretion in neurons by acetylating serine residue 565 (S565) of COX2, which improved AD-like pathology. Recently, her lab also showed that acetyl-CoA binds to the ATP binding site in SphK1, and that reaction of acetyl-CoA and sphingosine within SphK1 generates intermediate X (IX). IX produced by SphK1 binds COX2, and acetylated the S565. IX-acetylated COX2 increased SPM secretion, similar to aspirin-acetylated COX2. Finally, the treatment of APP/PS1 mice with IX increased IX-induced SPMs in microglia via S565 acetylation of COX2, resulting in the direct regulation of microglial function. Finally, the IX-triggered SPMs led to resolution of neuroinflammation and upregulation of several

reactive microglial genes linked to phagocytosis compared with untreated APP/PS1 microglia, leading to amelioration of AD pathology. Together, her results uncovered a novel mechanism and function of IX, which played a major role in the dysfunction of microglia in AD, and suggested the therapeutic potential of IX for AD.

Translational molecular imaging of the pathological processes in AD (Tetsuya Suhara, National Institute of Radiological Sciences, Chiba, Japan)

Dr. Suhara presented translational molecular imaging of the pathological processes in AD. The onset and progression of neuropsychiatric disorders such as depression, schizophrenia, and AD are not well understood. The elucidation of the mechanism has become an urgent task in the development of diagnosis and therapeutics. *In vivo* imaging is one of the best technologies as well as gene analysis for brain research. Especially PET, which enables direct visualization of brain molecules, is expected to play a crucial role for drug development. His laboratory is trying to reveal brain functions by using a variety of imaging technologies with a focus on PET. His talk aimed to elucidate the cause of symptoms such as reduced motivation, delusions or memory impairment of neuropsychiatric disorders, and to contribute to the development of diagnosis and therapeutics by translational research between human and animal disease models of mice or monkeys by combination of imaging, biochemical, and pathological analyses.

SESSION 4: PRACTICAL ADVANCES IN AD BLOOD BIOMARKER DEVELOPMENT IN KOREA

This session was for a focused review of the current state of blood biomarker development in Korea. The hope is to be able to diagnose AD can be diagnosed by means of one drop of blood in the near future. Many academic publications have been released in relation to this topic. In Korea, many researchers and companies are devoted to the research field of AD blood biomarkers. To develop a useful blood-based screening tool for AD would fundamentally make the early management of AD and trial of prevention strategies much easier. All 3 invited speakers in this session were experts in blood biomarker development. Their talks all covered the new technologies to measure blood A β . However, the applied technique and approach were different from study to study, which widened the viewpoint on blood biomarker development in our country to the audience.

Measurement of A β oligomer (A β O) using a multiuser detection system (Seung Soo Alexander An, Department of Bionano Technology, Gachon University, Seongnam, Korea)

The novel technology of multimer detection system to detect A β O in blood was introduced.²⁰ Clinical values of A β O levels in the diagnosis of AD were computed through various cohort studies. The A β O levels were much higher in AD, which quite differentiated AD patients from normal control individuals.

Measurement of disaggregated A β after treatment of 4-(2-Hydroxyethyl)-1-piperazinepropanesulfonic acid (EPPS) (YoungSoo Kim, Yonsei University, Seoul, Korea)

The highly sensitive measurement technique based on a microfluidic device was mentioned during the talk.²¹ Furthermore, the efficiency of pretreatment of the blood using EPPS, aggregation inhibitors, was shown to markedly improve the measurement of A β , which was more accurate and enriched by this new technique.

Blood biomarkers for brain A β deposition and tau (Inhee Mook-Jung, Seoul National University, Seoul, Korea)

The clinical validity of plasma t-tau/A β 1-42 levels that were measured using Simoa analyzer was illustrated.²² The values were highly predictable of the brain tau deposits on tau-PET imaging. The future decline in brain glucose metabolism, amyloid deposits, and hippocampal atrophy were associated with high plasma t-tau/A β 1-42 ratio.

PLENARY SESSION 2-1. ADVANCES IN PRECISION BRAIN HEALTH: THE EMERGENCE OF DIGITAL BIOMARKERS (RHODA AU, BOSTON UNIVERSITY, BOSTON, MA, USA)

Overcoming AD is a worldwide growing problem for which early interventions are crucial. Biomarkers enabling an early diagnosis can be obtained by using neuroimaging techniques, such as PET scans or CSF A β positivity. However, these methods are costly and invasive to the patient, which yields a biased sample of the population that can benefit from them. An additional confounding factor is, as been mentioned in the literature for years, the heterogeneity of the disease. What we now must do is to shift our focus to novel biomarkers and to step forward to a precision brain-health approach.

The Framingham Heart Study, a multigenerational cohort study that has been running since 1948, encompasses an extensive scope of health-related data, not only cardiovascular factors but also those that could contribute to developing dementia. Participants who were cognitively intact at their initial assessment were later re-tested after their cognitive function had declined. Along with conventional data collection including neuroimaging and neuropathology, digital voice recordings were made while administering traditional neuropsychological assessment. Rhoda Au compared the recordings of the 2 different timepoints and pointed out that analyzing the qualitative components of the voice features, i.e., how the person struggles to get the answer, could be significant indices for prognosis of cognitive disorders. Her research was then expanded to written digital phenotypes. The participants were given a ball-point pen with a small camera attached on it so their performances in a trail-making or clock-drawing test could be captured. Digital quantification of the data revealed meaningful results in an autopsy-based study, proving that these kinds of innovative digital biomarkers could be a promising concept of prevention.

But how can we transform this concept into reality and optimize a person's brain health across the entire lifespan? Today we are surrounded by smartphones, tablets, GPS locators, and numerous other electronic devices that can transmit health-related information via mobile networks. Since AD is a life-course disease, we need to use the leverage of digital technologies that go with our everyday life: monitor a person on a continual basis, and when the first negative trajectory of change in a persistent pattern appears, early intervention can be made even before the clinical diagnoses are met. What Rhoda Au suggests is collaboration with data scientists and artificial intelligence experts in an open data-sharing community, building a plug-and-play system to make it easy to use, and with investments from private companies, considering the value proposed to stakeholders. To achieve this, a strong and secure data infrastructure is needed to allow scalability as the longitudinal study proceeds, and one must be flexible and agnostic in choosing the device, with balanced criteria. Furthermore, leveraging the resources from other well-defined National Institutes of Health

cohorts across different diseases and layering a brain-aging component could widen our view to find out the complexity of the disease in many dimensions.

PLENARY SESSION 2-2. COMPREHENSIVE GENETIC ASSOCIATION STUDY OF AD (LINDSAY FARRER, BOSTON UNIVERSITY, BOSTON, MA, USA)

In the plenary session 2, Professor Lindsay Farrer focused on identifying biological mechanisms and therapeutic targets for AD using genetic approaches. Genomic studies have revealed that late onset AD is highly polygenic, with 20 to 25 susceptibility loci identified through large-scale meta-analysis of genome-wide association studies (GWAS).²³ Although AD is highly heritable (h^2 , 0.58–0.79), only a third of AD heritability is explained by common variants discovered through GWAS. Much of unexplained AD heritability may be result from rare variants. Moreover, the genetic architecture of AD differs by ethnicity and sex.

Professor Farrer introduced the Alzheimer Disease Sequencing Project (ADSP) and highlighted his recent research on identifying several novel, rare, and common AD-related genes. The ADSP undertook approximately 11,000 whole-exome and 5,000 whole-genome sequencings from AD cases and controls, and identified AD-risk variants in 3 novel genes (*IGHG3*, *AC099552.4*, and *STAG3*).²⁴ He also conducted an association study for AD using whole-sequence data from genetically enriched AD cases (cases having close relatives affected by AD) and identified a rare *CASP7* missense variant.²⁵ Recently, he applied a strategy focused on rare variants occurring only in AD cases to identify and characterize additional high-penetrance risk variants in AD.²⁶ He found genes affecting multiple dementias, such as the *NOTCH3* (rs149307620) gene, in which coding mutations are associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and *TREM2* (rs104894002), a high-impact mutation that, in homozygous form, causes Nasu-Hakola disease.²⁶ The rare variant loci, in agreement with those identified by common-variant GWAS, have collective roles in several pathways leading to disease.

He summarized by emphasizing that newly identified genes, or their close biological pathway neighbors, may themselves be potential targets for development of novel biomarkers and therapy.

SESSION 5. NEUROPSYCHOLOGY: DEMENTIA CARE UPDATE

In the neuropsychology section, 3 presenters gave informative lectures about new trends in neuropsychology dealing with preclinical AD, poststroke dementia, and issues for caregivers of dementia patients.

Early detection of cognitive and behavioral symptoms in the patients with preclinical AD (Juhee Chin, Sungkyunkwan University, Seoul, Korea)

The first presenter, Dr. Juhee Chin, reviewed the subtle cognitive deficits that are correlated with early biomarkers of AD. Cognitive decline related to amyloid burden in cognitively normal older adults is mainly focused on memory. In addition, recent studies have looked

into detailed neuropsychological characteristics, such as the paired-association memory paradigm, serial position effect, and semantic-cued memory recall. Cognitive composite scores (e.g., the Alzheimer's Disease Cooperative Study–Preclinical Alzheimer Cognitive Composite) were developed to detect cognitive decline related to biomarkers in the longitudinal studies of preclinical AD. Finally, Dr. Chin briefly reviewed the mild behavioral impairment related to amyloid burden in preclinical AD.

What does the brain tell you after a stroke? (Adrian Wong, The Chinese University of Hong Kong, Shenzhen, China)

Dr. Adrian Wong introduced important research on poststroke dementia based on the Chinese University of Hong Kong Stroke Registry Investigating Cognitive Decline study. He also introduced cognitive function assessment tools for stroke patients in Hong Kong, including the Montreal Cognitive Assessment, computerized cognitive screening, and the detailed cognitive assessment tests. Furthermore, he addressed research which showed that increasing cognitive resilience/reserve through active engagement (e.g., participation in leisure, physical, and intellectual activities before a stroke) could reduce the risk of dementia and improve cognitive functions after a stroke/transient ischemic attack. However, poststroke depression could be a risk factor for cognitive decline in the patients with stroke. Therefore, treatments such as cognitive behavioral therapy and repetitive transcranial magnetic stimulation would be necessary.

Care and rehabilitation for people living with dementia (Eun-Jeong Lee, Illinois Institute of Technology, Chicago, IL, USA)

Dr. Eun-Jeong Lee presented information about the challenges caregivers face while living with a dementia patient. According to her presentation, compared with caregivers of individuals with other conditions, caregivers of patients with dementia must provide more assistance, must give up their vacations or hobbies, and often have more physical and mental health problems. The risk factors identified for caregiver burden were female sex, low level of education, and many hours spent caregiving. Moreover, caregiver burden could cause more depressive symptoms, anxiety, and a lower quality of life. For this reason, caregivers have been identified as “hidden patients.” Dr. Lee's presentation introduced the Savvy Caregiver program, which is an evidence-based curriculum to teach strategies, practical real-world skills, and ways to reduce stress in both the caregiver and the person with dementia.

PLENARY SESSION 3. GENETICS IN NEURODEGENERATIVE DISEASE (JOHN HARDY, UNIVERSITY COLLEGE LONDON, LONDON, UK)

In his plenary talk, Dr. John Hardy presented updates on genetics in AD, tauopathies, and Parkinson's disease (PD) in discussing genomic analysis of neurodegenerative disease, especially late onset diseases as a failure of damage clear-up where the deposited protein is the major substrate of the clear-up process. After a brief introduction of causative genes inducing overproduction of proteins to be aggregated in autosomal dominant neurodegenerative disorders, Dr. Hardy focused on the clear-up process in late onset neurodegeneration.²⁷⁻²⁹ Regarding AD genetics, he presented recent GWAS findings and TREM2 with the role of the immune system and cholesterol metabolism.^{17,18,30,31} He summed up diverse mechanisms involved in the pathogenesis of late onset AD, including lipid metabolism (APOE, CLU,

ABCA7), innate immunity (CLU, CR1, MS4AE), or endosomal vesicle recycling (PICALM, BIN1). He highlighted that late onset AD may also develop as a damage response to diverse insults.^{4,32} For the PD pathogenesis associated with genetics, he highlighted 2 mechanisms: 1) too much synuclein deteriorating the lysosomal function and 2) failure in mitophagy hampering the removal of damaged mitochondria through the lysosome.³³⁻³⁵ In primary tauopathies, abnormal aggregation of tau was explained with a ubiquitin proteasome system.^{36,37} He summarized the role of genetics in neurodegenerative diseases with protein aggregation as follows.

First, in all diseases, genetic overproduction of protein leads to autosomal dominant disease. Second, in all diseases, other genes are involved in protein/damage clearance (e.g., A β /microglia, synuclein/lysosomes, and tau/ubiquitin proteasome). Finally, he suggested that the more important issue may be the age-dependent failure of the clearance pathway rather than the intrinsic distinctiveness of aggregating proteins. Prospectively, he said that expected early diagnosis based on genetics and/or biomarkers may provide chances for therapies aimed at potentiating clearance mechanisms in late-onset neurodegenerative diseases.

SESSION 6. ADVANCES IN THE GENETICS OF DEMENTIA

At the 1st IC-KDA, the research on genes in neurodegenerative diseases was presented under the theme of “Advances in the genetics of dementia.” At this conference, the world's leading genetic experts attended and presented their cutting-edge results and their insights into investigating the genetic structures and causal relationships of the pathogenicity of the neurodegenerative diseases.

AD genetics in Korea (Chang-Seok Ki, Green Cross Genome, Yongin, Korea)

Dr. Chang-Suk Ki gave a presentation on the updated status of dementia genetic research in Korea. Several novel AD-related mutations were reported among Korean AD patients in APP, PSEN1 and PSEN2 genes. Even though they were novel variants with interesting MRI, PET, and biomarker studies, their pathogenicity should be investigated with cellular functional or animal studies for verification.

Imaging genetics: Alzheimer's Disease Neuroimaging Initiative (ADNI) experiences (Kwang-Sik Nho, Indiana University, Bloomington, IN, USA)

Dr. Kwang-Sik Nho presented his research experiences in the United States. He with Dr. Andrew Saykin are responsible for the genetic core of ADNI, as a leading center of imaging genetics in the world. At the IC-KDA, the state-of-the-art results, promises, and challenges on the importance of combining genetic, MRI, and PET imaging data with multi-omics results were presented. Neuroimaging genomics is an emerging and rapidly evolving data science field for studying genetic mechanisms of brain structure and function in AD by integrating multimodal neuroimaging, such as MRI and PET. Neuroimaging genomics would provide deeper mechanistic insights into the molecular mechanisms of AD and may help in identifying new therapeutic targets and diagnostic/biomarker strategies. In addition, Dr. Nho emphasized that only about 50% of AD heritability could be accounted for by the known AD susceptibility genes, leaving a substantial proportion of the heritability as unidentified or missing. Hence, the integration of different types of high-throughput data (neuroimaging, multi-omics of genomics, transcriptomics, metabolomics, and clinical information) would be important through multivariate analyses and a systematic approach for identifying AD biomarkers and the missing heritability in understanding the mechanistic insights and their pathomechanisms.

Contribution of rare and common variants in AD: genome analysis of Japanese populations (Takeshi Ikeuchi, Niigata University, Niigata, Japan)

Dr. Ikeuchi argued that the effects of familial genes were likely to be influenced by representative common variants, APP, PSEN1, PSEN2, and APOE genes, and additional unreported rare variants from genome analysis of Japanese populations. Other risk factors were identified by GWAS and whole-genome/exome sequencing. Hospitals in Japan gather samples from patients with dementia and do targeted gene analysis for different dementias, followed by genetic counseling. Several known and novel mutations were identified in different disease-associated genes, APP, PSEN1, GRN, MAPT, CSF1R, AARS2, and LMNB1.^{38,39} Japanese Familial Alzheimer's Disease (JFAD) is a Japanese database for familial AD and frontotemporal dementia with parkinsonism diseases, launched in 2014. Whole-exome analysis provided more opportunities for genetic screening and diagnosis. For example, they analyzed 2 siblings who were diagnosed with FTD and Huntington's disease and found an NPC1, suggesting that the patients had Niemann-Pick type C disease. Several CSF1R mutations were also found, associated with white-matter degeneration. GWAS studied from Japan found strong associations with genes in chromosome 19.³⁹ J-ADNI did whole-exome analysis, and several rare variants were found in the ABCA7 and SORL1 coding regions, which may also affect the disease onset.³⁸

In conclusion, the presentations in the genetic session indicated that studying the above common and rare variants in AD may improve clinical diagnosis and provide better treatments for patients. However, the follow-up functional study would be important for the verification of the pathogenic variants with the supportive biomarker profiling, preferably with the least invasive samples. The findings would be important, since “each new rare genetic variant may provide something of a ‘natural experiment’—each providing a window into the possible underlying mechanisms and pathways that led to AD” (Dr. Lindsay Farrer). Last, better understanding of these mechanisms and pathways may lead to new drug targets for prevention or treatment of AD or other neurodegenerative diseases.

REFERENCES

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
[PUBMED](#) | [CROSSREF](#)
2. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018;14:535-562.
[PUBMED](#) | [CROSSREF](#)
3. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology* 2016;87:539-547.
[PUBMED](#) | [CROSSREF](#)
4. Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron* 2013;80:1347-1358.
[PUBMED](#) | [CROSSREF](#)
5. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013;12:207-216.
[PUBMED](#) | [CROSSREF](#)
6. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;9:119-128.
[PUBMED](#) | [CROSSREF](#)

7. Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. *Nat Rev Neurosci* 2018;19:687-700.
[PUBMED](#) | [CROSSREF](#)
8. Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner MW, Aisen PS, et al. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA* 2017;317:2305-2316.
[PUBMED](#) | [CROSSREF](#)
9. Dubois B, Epelbaum S, Nyasse F, Bakardjian H, Gagliardi G, Uspenskaya O, et al. Cognitive and neuroimaging features and brain β -amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study. *Lancet Neurol* 2018;17:335-346.
[PUBMED](#) | [CROSSREF](#)
10. Adams JN, Lockhart SN, Li L, Jagust WJ. Relationships between tau and glucose metabolism reflect Alzheimer's disease pathology in cognitively normal older adults. *Cereb Cortex* 2019;29:1997-2009.
[PUBMED](#) | [CROSSREF](#)
11. Tosun D, Landau S, Aisen PS, Petersen RC, Mintun M, Jagust W, et al. Association between tau deposition and antecedent amyloid- β accumulation rates in normal and early symptomatic individuals. *Brain* 2017;140:1499-1512.
[PUBMED](#) | [CROSSREF](#)
12. Harrison TM, La Joie R, Maass A, Baker SL, Swinnerton K, Fenton L, et al. Longitudinal tau accumulation and atrophy in aging and Alzheimer disease. *Ann Neurol* 2019;85:229-240.
[PUBMED](#) | [CROSSREF](#)
13. Bejanin A, Schonhaut DR, La Joie R, Kramer JH, Baker SL, Sosa N, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain* 2017;140:3286-3300.
[PUBMED](#) | [CROSSREF](#)
14. Maass A, Lockhart SN, Harrison TM, Bell RK, Mellinger T, Swinnerton K, et al. Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging. *J Neurosci* 2018;38:530-543.
[PUBMED](#) | [CROSSREF](#)
15. Shi Q, Chowdhury S, Ma R, Le KX, Hong S, Caldarone BJ, et al. Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Sci Transl Med* 2017;9:eaaf6295.
[PUBMED](#) | [CROSSREF](#)
16. Kim SH, Noh MY, Kim HJ, Oh KW, Park J, Lee S, et al. A therapeutic strategy for Alzheimer's disease focused on immune-inflammatory modulation. *Dement Neurocogn Disord* 2019;18:33-46.
[PUBMED](#) | [CROSSREF](#)
17. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, et al. TREM2 variants in Alzheimer's disease. *N Engl J Med* 2013;368:117-127.
[PUBMED](#) | [CROSSREF](#)
18. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med* 2013;368:107-116.
[PUBMED](#) | [CROSSREF](#)
19. Neumann H, Daly MJ. Variant TREM2 as risk factor for Alzheimer's disease. *N Engl J Med* 2013;368:182-184.
[PUBMED](#) | [CROSSREF](#)
20. Wang MJ, Yi S, Han JY, Park SY, Jang JW, Chun IK, et al. Oligomeric forms of amyloid- β protein in plasma as a potential blood-based biomarker for Alzheimer's disease. *Alzheimers Res Ther* 2017;9:98.
[PUBMED](#) | [CROSSREF](#)
21. Yoo YK, Kim J, Kim G, Kim YS, Kim HY, Lee S, et al. A highly sensitive plasma-based amyloid- β detection system through medium-changing and noise cancellation system for early diagnosis of the Alzheimer's disease. *Sci Rep* 2017;7:8882.
[PUBMED](#) | [CROSSREF](#)
22. Park JC, Han SH, Yi D, Byun MS, Lee JH, Jang S, et al. Plasma tau/amyloid- β 1-42 ratio predicts brain tau deposition and neurodegeneration in Alzheimer's disease. *Brain* 2019;142:771-786.
[PUBMED](#) | [CROSSREF](#)
23. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A β , tau, immunity and lipid processing. *Nat Genet* 2019;51:414-430.
[PUBMED](#) | [CROSSREF](#)
24. Bis JC, Jian X, Kunkle BW, Chen Y, Hamilton-Nelson KL, Bush WS, et al. Whole exome sequencing study identifies novel rare and common Alzheimer's-Associated variants involved in immune response and transcriptional regulation. *Mol Psychiatry*. Forthcoming 2018.
[PUBMED](#) | [CROSSREF](#)

25. Zhang X, Zhu C, Beecham G, Vardarajan BN, Ma Y, Lancour D, et al. A rare missense variant of CASP7 is associated with familial late-onset Alzheimer's disease. *Alzheimers Dement* 2019;15:441-452.
[PUBMED](#) | [CROSSREF](#)
26. Patel D, Mez J, Vardarajan BN, Staley L, Chung J, Zhang X, et al. Association of rare coding mutations with Alzheimer disease and other dementias among adults of European ancestry. *JAMA Netw Open* 2019;2:e191350.
[PUBMED](#) | [CROSSREF](#)
27. Rovelet-Lecrux A, Hannequin D, Guillin O, Legallic S, Jurici S, Wallon D, et al. Frontotemporal dementia phenotype associated with MAPT gene duplication. *J Alzheimers Dis* 2010;21:897-902.
[PUBMED](#) | [CROSSREF](#)
28. Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, et al. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet* 2006;38:24-26.
[PUBMED](#) | [CROSSREF](#)
29. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, et al. α -Synuclein locus triplication causes Parkinson's disease. *Science* 2003;302:841.
[PUBMED](#) | [CROSSREF](#)
30. Jones L, Holmans PA, Hamshere ML, Harold D, Moskva V, Ivanov D, et al. Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. *PLoS One* 2010;5:e13950.
[PUBMED](#) | [CROSSREF](#)
31. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* 2013;45:1452-1458.
[PUBMED](#) | [CROSSREF](#)
32. Matarin M, Salih DA, Yasvoina M, Cummings DM, Guelfi S, Liu W, et al. A genome-wide gene-expression analysis and database in transgenic mice during development of amyloid or tau pathology. *Cell Reports* 2015;10:633-644.
[PUBMED](#) | [CROSSREF](#)
33. Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, et al. Gaucher disease glucocerebrosidase and α -synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell* 2011;146:37-52.
[PUBMED](#) | [CROSSREF](#)
34. Robak LA, Jansen IE, van Rooij J, Uitterlinden AG, Kraaij R, Jankovic J, et al. Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. *Brain* 2017;140:3191-3203.
[PUBMED](#) | [CROSSREF](#)
35. Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med* 2009;361:1651-1661.
[PUBMED](#) | [CROSSREF](#)
36. Jabbari E, Woodside J, Tan MM, Shoai M, Pittman A, Ferrari R, et al. Variation at the TRIM11 locus modifies progressive supranuclear palsy phenotype. *Ann Neurol* 2018;84:485-496.
[PUBMED](#) | [CROSSREF](#)
37. Myeku N, Clelland CL, Emrani S, Kukushkin NV, Yu WH, Goldberg AL, et al. Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. *Nat Med* 2016;22:46-53.
[PUBMED](#) | [CROSSREF](#)
38. Iwatsubo T, Iwata A, Suzuki K, Ihara R, Arai H, Ishii K, et al. Japanese and North American Alzheimer's Disease Neuroimaging Initiative studies: harmonization for international trials. *Alzheimers Dement* 2018;14:1077-1087.
[PUBMED](#) | [CROSSREF](#)
39. Konno T, Kasanuki K, Ikeuchi T, Dickson DW, Wszolek ZK. *CSF1R*-related leukoencephalopathy: a major player in primary microgliopathies. *Neurology* 2018;91:1092-1104.
[PUBMED](#) | [CROSSREF](#)