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STEREOTYPIC BCR CLONOTYPES IN ALZHEIMER'S DISEASE PATIENTS AND USE THEREOF

Abstract

The present specification discloses a composition, a system, and a method for predicting or diagnosing Alzheimer's disease, comprising a detecting agent of a B cell receptor clonotype specific to an Alzheimer's disease patient, and the composition according to one aspect of the present invention has an excellent effect in predicting or diagnosing Alzheimer's disease by simply using peripheral blood mononuclear cells isolated from a subject, in addition to methods such as MRI and PET scans using radioactive substances, by comprising a detecting agent of a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient.

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATION [0001] This application is a continuation-in-part of application Ser. No. 18/827,742 filed Sep. 7, 2024, which claims priority to Korean Patent Application No. 10-2023-0118789 filed on Sep. 7, 2023, the entire contents of each of which is incorporated herein by reference.

INCORPORATION BY REFERENCE STATEMENT OF THE MATERIAL IN THE SEQUENCE LISTING XML FILE
[0002] The XML file submitted herewith is incorporated by reference in the Specification. The XML file is identified as follows: (i) Name of the File: OF24P125US_sequence list; (ii) Date of Creation: Jan. 22, 2025; (iii) Size of File: 33,390,077 bytes.
TECHNICAL FIELD
[0003] The present specification discloses a composition, a system, and a method for predicting or diagnosing Alzheimer's disease, comprising a detecting agent of a B cell receptor clonotype specific to an Alzheimer's disease patient.
[0004] [National Research and Development Project Supporting This Invention]
[0005] [Project Identification Number] 1465039792
[0006] [Project Number] HU20C0339000023
[0007] [Name of Department] Ministry of Health and Welfare
[0008] [Name of Project Management (Professional) Institution] Korea Health Industry Development Institute (KHIDI)
[0009] [Research Business Name] Dementia Research and Development Program (2023-KHIDI-4635)
[0010] [Research Project Title] Investigation of Antibody-Mediated Pathogenesis through B Cell Receptor Repertoire Analysis in Alzheimer's Disease Patients
[0011] [Contribution Rate] 1/1
[0012] [Name of Project Performing Organization] Seoul National University Research & Development Business Foundation
[0013] [Research Period] Apr. 1, 2023 to May 31, 2023
BACKGROUND
[0014] Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes dementia, cognitive decline, memory loss and impaired daily functioning. The major pathological hallmark of AD is the presence of plaques of the amyloid beta peptide (Aβ) and neurofibrillary tangles (NFTs) of the phosphorylated tau protein1, which are accompanied by neuroinflammation in the central nerve system (CNS). Recent studies have revealed that the pathogenesis of AD is not solely restricted to these changes in the brain. There is mounting evidence that the peripheral immune system is intimately linked to AD pathology, particularly emphasizing the crucial involvement of immune cells in the development of AD. However, there has been minimal discourse concerning the contribution of T and B lymphocytes in AD. Several studies have demonstrated that peripheral homeostasis of T lymphocyte is changed in AD patients, whereas little is known about the role of

peripheral B lymphocytes.
[0015] Meanwhile, to date, there are few diagnostic tools in the clinical field of AD [5,6]. Although several alternative methods have been developed, people suspected of AD have to rely on several factors such as medical history, neuroimaging data from magnetic resonance imaging (MRI) or position emission tomography (PET), and neuropsychological examination. There are still shortcomings and concerns regarding the molecular accuracy of MRI and PET scans using radioactive substances. In particular. PET imaging, which is considered a first-line diagnostic method based on AD-specific pathological features such as decreased synaptic activity and accumulation of amyloid plaques in the brain, has several considerations that should be carefully considered. It takes time for brain Aβ to accumulate to a certain level of SUV [7,8]. In addition, additional time is needed until pathological symptoms develop and translate into cognitive changes in daily life [9]. In particular, phosphorylated tau protein has been considered a subsequent consequence after the appearance of Δβ, but it appears with a relatively long time interval of about 5 years[10]. Most blood biomarker tests have detected AD-specific pathologic proteins in human blood, serum, and CSF [11,12].
[0016] In other words, the current diagnosis of Alzheimer's disease relies on the patient's medical history, brain imaging data, and neuropsychological scale evaluation, and with the development of molecular imaging technology, the presence or absence of medial temporal lobe atrophy and ventricular enlargement due to neurodegeneration can be diagnosed with structural brain imaging tests such as magnetic resonance imaging (MRI) and computed tomography (CT). In addition, the presence or absence of brain function decline and the area of decline can be visualized and confirmed through functional brain imaging tests such as PET (position emission tomography) and SPECT (single-photon emission computed tomography) using fluoro-deoxy-D-glucose (FDG), amyloid tracer, and tau ligand (Cold Spring Harb Perspect Med. 2012 April; 2 (4): a006213, Hum Brain Mapp. 2019 Dec. 15; 40 (18): 5424-5442).
[0017] However, structural brain imaging has the disadvantage of low molecular accuracy and cannot detect histopathological features such as amyloid neuritic plaques and neurofibrillary tangles specific to Alzheimer's disease. Functional brain imaging based on synaptic activity and the pathogenesis of Alzheimer's disease (amyloid hypothesis) has relatively high diagnostic accuracy, but there are high screening costs and risks of exposure to radioactive drugs in the human body through intravenous injection. Additionally, FDG residual amount in the brain acts as a nonspecific indicator of metabolic processes, so there is a possibility that it may decrease due to various causes such as ischemia and inflammation unrelated to Alzheimer's disease (Alzheimers Dement. 2018 November; 14 (11): 1522-1552).
[0018] In addition, it takes an average of more than 15 years for the standardized uptake values (SUV) of Aβ measured through FDG-PET to reach the Alzheimer's disease-specific threshold value (Neurology. 2013 Mar. 5; 80 (10): 890-6, JAMA. 2017 Jun. 13; 317 (22): 2305-2316), and hyperphosphorylated tau gradually accumulates and spreads together with amyloid neuritic plaques as the clinical stage of the disease progresses (J Neurosci. 2018 May 9; 38 (19): 4482-4489), making it unsuitable for early diagnosis of the disease (Neurology. 2021 Mar. 2; 96 (9): e1347-e1357).
[0019] Therefore, in addition to traditional biomarkers, there is a need to explore various targets that can be used for early diagnosis (Front Immunol. 2022; 13:1010946), and there is a growing need for biomarkers that can be detected in a cost-effective and non-invasive manner.
[0020] It is believed that blood-based biomarkers are likely to meet these needs, and attempts are actively being made to use them as alternative diagnostic methods by measuring the ratio of Aβ42 and Aβ40 present in the patient's blood, the concentration of tau phosphorylated with specific amino acids, and neurofilament light chain (NfL)-related biomarkers of neurodegeneration (Lancet Neurol. 2022 January; 21 (1): 66-77, J Clin Neurol. 2022 July; 18 (4): 401-409).
[0021] Currently, there are three blood-based diagnostic tests for Alzheimer's disease approved by

the FDA, but there are differing opinions in the academic community that question the efficacy and necessity of blood-based biomarkers due to the lack of standardized measurement techniques, lack of cutoff values for individual biomarkers, and lack of evaluation of confounding factors such as aging, underlying diseases, and racial differences (Biomark Insights. 2020 Aug. 21; 15:1177271920950319). In addition, blood-based tests cannot be used as a standalone test for diagnosing Alzheimer's disease, and the clinical validity of blood biomarkers can be proven only when the presence and ratio of the corresponding biomarker in the patient's cerebrospinal fluid (CSF) corresponds to the results in blood and also matches the results of existing molecular brain imaging tests.

[0022] Accordingly, the present inventors completed the present invention by discovering a BCR clonotype group that is not present in a normal human cohort but is found only in a group of Alzheimer's disease patients through research under the assumption that Alzheimer's disease patients have various B cell receptors associated with the progression or suppression of the disease.

DETAILED DESCRIPTION

[0023] The present inventors confirmed that AD patients share stereotypic BCR clonotypes that are not found in the CG (control group) and that the degree of overlap between patient pairs is higher than that between CG pairs.

[0024] Specifically, the present inventors confirmed that the BCR repertoire of AD patients has unique characteristics, and then discovered disease-specific sequences that can be utilized to discover antibodies that bind to pathological markers, and identified 3986 unique BCR clonotypes that are specific only to the AD patient cohort. In addition, the present inventors selected the most prominent clonotypes in terms of degree of sharing and persistence within time points, and confirmed that they have affinity for the Aβ42 peptide, one of the major Δβ peptide isoforms found in amyloid plaques in the brain with AD and reported as an autoantigen. Accordingly, the present inventors confirmed that AD can be predicted or diagnosed by detecting the Alzheimer's-specific B cell receptor (BCR) clonotype.

[0025] Therefore, in one aspect, an object of the present invention is to provide a composition, a system, and a method for providing information for predicting or diagnosing Alzheimer's disease.

Solution to Problem

[0026] In one aspect, the present invention provides a composition for predicting or diagnosing Alzheimer's disease, comprising a detecting agent of a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient in a sample of a subject, wherein the BCR clonotype comprises the V gene; and the J gene; and an amino acid sequence of complementary determining region 3 (CDR3) of the heavy chain of the BCR.

[0027] In other aspect, the present invention provides a system for predicting or diagnosing Alzheimer's disease comprising the composition for predicting or diagnosing Alzheimer's disease.

[0028] In another aspect, the present invention provides a method for providing information for predicting or diagnosing Alzheimer's disease comprising: detecting a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient in a sample of a subject, wherein the BCR clonotype comprises the V gene; and the J gene; and an amino acid sequence of complementary determining region 3 (CDR3) of the heavy chain of the BCR.

Advantageous Effects of Invention

[0029] A composition according to one aspect of the present invention has an excellent effect in predicting or diagnosing Alzheimer's disease by simply using peripheral blood mononuclear cells isolated from a subject, in addition to methods such as MRI and PET scans using radioactive substances, by comprising a detecting agent of a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIGS. **1**A to IC are schematic diagrams illustrating a sample acquisition schedule and BCR repertoire analysis pipeline according to one example of the present invention. FIG. **1**A shows the peripheral blood samples of 44 patients from 2 different time points were collected for the Alzheimer's disease cohort (AD). The second blood samples from this cohort are chronologically separated by 13.3 months maximum and 3.4 months minimum. The black arrowheads represent the exact sampling points of the samples in the given time frame. FIG. **1**B shows the vaccinated control group (CG) comprises of 55 vaccine recipients who were subjected to peripheral blood sampling before the first shot (TP1), 1 week after the 1st shot (TP2), 1 week after the 2nd shot (TP3), 1 month after the 2nd shot (TP4), 6 months after the 2nd shot (TP5), and 1 month after the 3rd shot (TP6). FIG. **1**C show the process of performing sequence filtering based on the shown flow chart to obtain BCR clonotypes that are representative of each cohort for further analyses. Clonotypes which were comprised fully of naive sequences were removed and cohort unique clonotypes were obtained. Next, clonotypes that were present in two or more subjects in a cohort were selected. Due to the potential risk of sequence contamination during NGS library prep and during sequencing, clonotypes where patients did not possess unique nucleotide sequences and were completely eclipsed by other patients were ruled out.

[0031] FIGS. **2**A to **2**E are diagrams showing the results of analysis according to one embodiment of the present invention, wherein Alzheimer patients show distinctly high similarity within the AD cohort in context of stereotypic and group specific BCR clonotypes. FIG. **2**A is a heat map of the BCR similarity values between each subject pair within each group and time point, and the similarity is calculated as the cosine similarity between two one-hot encoded linear vectors representing the presence (1) or absence (0) of group specific and shared clonotypes within each subject's BCR repertoire. The collection period is denoted inside parentheses. FIGS. **2**B and **2**C are the boxplots representing the distribution of BCR similarity for all subject pairs of the group and the heat map representing the P-values between them. The dashed line represents the median value for the CG TP1 repertoires. The color of the heat maps show whether the median value of the group written on the y axis is larger (red) or smaller (blue) while the intensity of said colors is encoded by the P-value. FIG. **2**D is a Chord plot displaying the similarity matrix of the top 20 AD patient pairs. The similarities were calculated from the combined repertoires of both time points if they existed. The chord width represents the similarity value with the thickest chord connecting patient 26 and 28 represent the value 0.961 while the thinnest chord connecting patients 11 and 25 represents a value of 0.063. FIG. **2**E is a diagram showing the number of shared clonotypes between each AD patient pairs for the time point combined repertoires, and the pair with the most number of shared clonotypes is denoted with a red star pattern.

[0032] FIGS. **3**A to **3**E are diagrams showing the results of an in vitro reactivity experiment for Aβ42 peptide according to one embodiment of the present invention, wherein the in vitro experimental results show highly shared BCR sequences within the Alzheimer patient cohort weakly bind to Aβ42 peptide. FIG. **3**A is a table displaying the AD group specific BCR clonotypes that are shared by at least 4 different patients. The grey columns represent samples omitted from the TP2 stage due to dropouts. Patients who possess similar clonotypes, 1 amino acid mismatch in the CDR3 sequence, are also shown in the table and are coded with lighter colors. FIG. **3**B is a graph showing the number of CG repertoires that possess similar clonotypes for the AD specific clonotypes shown in FIG. **3**A. FIG. **3**C shows amino acid sequence alignment and representation of highly shared and highly persistent BCR sequence. FIG. **3**D shows the light chain sequence information for the Aβ42 binders found via biopanning, A-4-3 and A-4-52. FIG. **3**E is ELISA results of recombinant scFv of A-4-3 and A-4-52 clones against Aβ42, and the graph is normalized by the absorbance difference between Aβ42 and BSA (blocking only) signal.

[0033] FIGS. **4**A to **4**C are graphs showing the results of analyzing the similarity of Alzheimer's-

specific-stereotypic BCR clonotypes according to one embodiment of the present invention, wherein Alzheimer patients show distinctly high similarity within the AD cohort in context of stereotypic BCR clonotypes even without filtering by the control group. FIG. **4**A is a heat map of the BCR similarity values between each subject pair within each group and time point. The similarity is calculated as the cosine similarity between two one-hot encoded linear vectors representing the presence (1) or absence (0) of shared and not group specific clonotypes within each subject's BCR repertoire. The collection period is denoted inside parentheses. FIGS. **4**B and **4**C are the boxplots representing the distribution of BCR similarity for all subject pairs of the group and the heat map representing the P-values between each group. The dashed line represents the median value for the CG TP1 repertoires. The color of the heat maps shows whether the median value of the cohort written on the y axis is larger (red) or smaller (blue) while the intensity of said colors is encoded by the P-value.

[0034] FIG. **5** is a diagram showing the experimental results confirming the expression of scFv-hFc fusion proteins according to one embodiment of the present invention. Total six out of eight Aβ42-binding scFv clones were successfully expressed in mammalian expression system. All recombinant scFv proteins tagged with human IgG1 FC (hFc), a. Representation of scFv-hFc fusion protein. The expected protein size is 56 kDa in non-reducing state (NR) and double in reducing condition (R) because of the dimerization via disulfide bond with cysteine residue in hFc tag.

[0035] Hereinafter, the present invention will be described in detail.

[0036] In one aspect of the present invention, the “Alzheimer prediction” may refer to predicting or diagnosing whether a patient has a risk for Alzheimer, whether the risk for Alzheimer is relatively high, what the cause of Alzheimer is, or whether Alzheimer has already occurred. Additionally, in one aspect of the present invention, the “Alzheimer diagnosis” may refer to confirming presence or features of pathological conditions. On the purpose of one aspect of the present invention, diagnosis may refer to confirming whether Alzheimer has occurred. The composition, kit or method according to one aspect of the present invention may be used to delay the onset or prevent the occurrence of Alzheimer through special and appropriate care for a specific patient, who is a patient having a high risk of developing Alzheimer. In addition, the composition, kit or method according to one aspect of the present invention may be clinically used to determine treatment by selecting the most appropriate treatment method through early diagnosis of Alzheimer.

[0037] In one aspect of the present invention, the “BCR clonotype” may comprise an amino acid sequence of a V gene; a J gene; and a complementary determining region 3 (CDR3) of a heavy chain of a B cell receptor (BCR), or may consist of an amino acid sequence of a V gene; and a J gene; and a CDR3 of a heavy chain of a BCR, or may be a combination of an amino acid sequence of a V gene; and a J gene; and a CDR3 of a heavy chain of a BCR.

[0038] In one aspect of the present invention, “detecting a BCR clonotype” may be detecting at least one selected from the group consisting of the following a), b), and c): [0039] a) detecting at least one of the V gene type of the BCR heavy chain, a base sequence of the V gene, and an amino acid sequence encoded from the base sequence of the V gene; at least one of the J gene type of the BCR heavy chain, a base sequence of the J gene, and an amino acid sequence encoded from the base sequence of the J gene; and at least one of the base sequence and amino acid sequence of CDR3 of the BCR heavy chain; [0040] b) detecting the entire base sequence of the BCR clonotype comprising the specific base sequence of the V gene of the BCR heavy chain; the specific base sequence of the J gene of the BCR heavy chain; and the base sequence of the CDR3 of the BCR heavy chain; and [0041] c) detecting the entire amino acid sequence of the BCR clonotype comprising the specific amino acid sequence encoded from the V gene of the BCR heavy chain; the specific amino acid sequence encoded from the J gene of the BCR heavy chain; and the amino acid sequence of the CDR3 of the BCR heavy chain.

[0042] For example, detecting a BCR clonotype from a sample of a subject may be detecting a

BCR clonotype in which the V gene of the heavy chain of the BCR is IGHV1-18, the J gene is IGHJ1, and the amino acid sequence of the CDR3 is SEQ ID NO: 72 from the sample of the subject, or may be detecting the entire base sequence of the BCR clonotype including a specific base sequence encoding a specific base sequence of the IGHV1-18, a specific base sequence of the IGHJ1, and a base sequence encoding an amino acid sequence of the CDR3 represented by SEQ ID NO: 72, or may be detecting the entire amino acid sequence of the BCR clonotype including a specific amino acid sequence encoded by the IGHV1-18, a specific amino acid sequence encoded by the IGHJ1, and an amino acid sequence of the CDR3 represented by SEQ ID NO: 72.

[0043] In one aspect of the present invention, “homology of 80 to 100%” may mean that the homology is 80% or more, 81% or more, 82% or more, 83% or more, 84% or more, 85% of more, 86% or more, 87% or more, 88% or more, 89% or more, 90% or more, 91% or more, 92% or more, 93% or more, 94% or more, 95% or more, 96% or more, 97% or more, 98% or more, or 99% or more, and the homology is 100% or less, 99% or less, 98% or less, 97% or less, 96% or less. 95% or less. 94% or less, 93% or less, 92% or less, 91% or less, 90% or less, 89% or less, 88% or less, 87% or less, 86% or less, 85% or less, It could mean 84% or less, 83% or less, 82% or less, or 81% or less.

[0044] In one aspect, the present invention provides a composition for predicting or diagnosing Alzheimer's disease, comprising a detecting agent of a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient in a sample of a subject, wherein the BCR clonotype comprises the V gene; and the J gene; and an amino acid sequence of complementary determining region 3 (CDR3) of the heavy chain of the BCR.

[0045] The composition according to one aspect of the present invention may comprise a detecting agent of a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient. A composition according to one aspect of the present invention may predict or diagnose a subject as having a BCR clonotype specific to an Alzheimer's patient, and specifically may predict or diagnose the subject as having Alzheimer's disease, if a BCR clonotype specific to an Alzheimer's patient is detected in a sample of the subject.

[0046] The composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is i) the V gene is at least one selected from the group consisting of IGHV (Immunoglobulin Heavy Variable) 1-18, IGHV1-2, IGHV1-24, IGHV1-3, IGHV1-46, IGHV1-58, IGHV1-69, IGHV1-8, IGHV2-26, IGHV2-5, IGHV2-70, IGHV3-11, IGHV3-13, IGHV3-15, IGHV3-20, IGHV3-21, IGHV3-23, IGHV3-30, IGHV3-30-3, IGHV3-33, IGHV3-43, IGHV3-43D, IGHV3-48, IGHV3-49, IGHV3-53, IGHV3-64, IGHV3-64D, IGHV3-66, IGHV3-7, IGHV3-72, IGHV3-73, IGHV3-74, IGHV3-9, IGHV4-30-2, IGHV4-30-4, IGHV4-31, IGHV4-34, IGHV4-38-2, IGHV4-39, IGHV4-4, IGHV4-59, IGHV4-61, IGHV5-10-1, IGHV5-51, IGHV6-1, and IGHV7-4-1, ii) the J gene in the BCR clonotype detected from a sample of the subject is at least one selected from the group consisting of IGHJ (Immunoglobulin Heavy Joining) 1, IGHJ2, IGHJ3, IGHJ4, IGHJ5, and IGHJ6, and iii) the amino acid sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of SEQ ID NOs: 72 to 4047, and 32396 to 32481.

[0047] The composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the amino acid sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of SEQ ID NOs: 72 to 4047, and 32396 to 32481. Specifically, the composition may predict or diagnose the subject as having Alzheimer's disease when the amino acid sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of ARDLPATGAFDI (SEQ ID NO: 214), VRLAEYFQN (SEQ ID NO: 875), TRDRRGWD (SEQ ID NO: 1211), ALGRGMDV (SEQ ID NO: 1048), VLRGSAFDI (SEQ ID NO: 798), ARSGGLDP (SEQ ID NO: 668), AGGRSFDY

(SEQ ID NO: 613), AGNLMDV (SEQ ID NO: 2257), ARRGEY (SEQ ID NO: 2070), ARDMFRGIPDYLDY (SEQ ID NO: 1988), AKSLGSGTYSFDY (SEQ ID NO: 1326), ARNAGLDY (SEQ ID NO: 1128), ARDDGYRSIDY (SEQ ID NO: 990), VRGGGSGWPFES (SEQ ID NO: 3709), SRGRDGIG (SEQ ID NO: 2815), ARSGGLDV (SEQ ID NO: 2415), ARSRSGSYYYGMDV (SEQ ID NO: 1198), AGDWNDDDIFDY (SEQ ID NO: 32396), ARKGEQLWHY (SEQ ID NO: 965), and ARDPIAVPGLFDY (SEQ ID NO: 347).

[0048] The composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is at least one of BCR clonotypes of the V gene; the J gene; and the amino acid sequence of CDR3.

[0049] For example, the composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the V gene and J gene in the BCR clonotype detected from the sample of the subject are IGHV3-7 and IGHJ1, and the amino acid sequence of CDR3 is the amino acid sequence of SEQ ID NO: 875.

[0050] The composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the detecting agent of a BCR clonotype according to one aspect of the present invention is a detecting agent of the entire amino acid sequence of the BCR clonotype, comprising an amino acid sequence encoded from the V gene of the heavy chain of the BCR; an amino acid sequence encoded from the J gene of the heavy chain of the BCR; and an amino acid sequence of CDR3 of the heavy chain of the BCR and the entire amino acid sequence of the BCR clonotype detected from the sample of the subject is at least one of SEQ ID NOs: 18222 to 32395. For example, the composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the entire amino acid sequence of the BCR clonotype detected from the sample of the subject is SEQ ID NO: 21427.

[0051] The composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the detecting agent of a BCR clonotype according to one aspect of the present invention is a detecting agent of the entire base sequence of the BCR clonotype, comprising a base sequence of the V gene of the heavy chain of the BCR; a base sequence of the J gene of the heavy chain of the BCR; and a base sequence encoding an amino acid sequence of CDR3 of the heavy chain of the BCR and the entire base sequence of the BCR clonotype detected from the sample of the subject is at least one of SEQ ID NOs: 4048 to 18221. For example, the composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the entire base sequence of the BCR clonotype detected from the sample of the subject is SEQ ID NO: 7253.

[0052] The composition according to one aspect of the present invention may predict or diagnose the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is at least one of BCR clonotypes of the V gene; the J gene; and the amino acid sequence of CDR3.

[0053] The detecting agent according to one aspect of the present invention may comprise a detecting agent of a protein specific to the BCR clonotype or a detecting agent of a nucleic acid encoding the protein.

[0054] For example, the detecting agent may comprise the below A) or B): [0055] A) a protein detecting agent capable of detecting at least one selected from the group consisting of an amino acid sequence encoded by a base sequence of a V gene included in the BCR clonotype; an amino acid sequence encoded by a base sequence of a J gene included in the BCR clonotype; an amino acid sequence of CDR3; and an entire amino acid sequence of a BCR clonotype including a specific amino acid sequence encoded by the V gene, a specific amino acid sequence encoded by the J gene, and an amino acid sequence of CDR3; or [0056] B) a detection agent capable of detecting at least one selected from the group consisting of a base sequence of a V gene included in the BCR clonotype; a base sequence of a J gene included in the BCR clonotype; a base sequence of

a CDR3; and an entire base sequence of a BCR clonotype including a specific base sequence of the V gene, a specific base sequence of the J gene, and a base sequence of CDR3.
[0057] The detecting agent of a protein according to one aspect of the present invention may comprise an antibody or aptamer specific to the BCR clonotype.
[0058] Specifically, the antibody may be one or more selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a recombinant antibody, and a combination thereof. More specifically, the antibody may include all of not only the polyclonal antibody, the monoclonal antibody, the recombinant antibody, and a complete form having two light chains with the full length and two heavy chains with the full length, but also functional fragments of the antibody molecules, for example, Fab, F(ab′), F(ab′)2, and Fv. The antibodies may be easily prepared by using a well-known technique in the art and antibodies which are prepared and commercially sold may be used.
[0059] In addition, specifically, the aptamer refers to a single-stranded oligonucleotide, and refers to a nucleic acid molecule having binding activity to a predetermined target molecule. The aptamer may have various three-dimensional structures depending on its base sequence, and may have high affinity for a specific substance, such as an antigen-antibody reaction. The aptamer may inhibit the activity of a predetermined target molecule by binding to the predetermined target molecule. The aptamer of the present invention according to one aspect of the present invention may be RNA, DNA, a modified nucleic acid, or a mixture thereof, and may have a linear or cyclic shape, but is not limited thereto. The aptamer according to one aspect of the present invention may be used for the BCR clonotype. The aptamer having binding activity to the protein may be easily produced by a person skilled in the art by referring to each base sequence according to a known method.
[0060] The detecting agent of a nucleic acid encoding the protein specific for a BCR clonotype according to one aspect of the present invention may comprise at least one selected from the group consisting of antisense oligonucleotide, primer pair, probe, and polynucleotide that specifically binds to mRNA or DNA encoding the BCR clonotype. That is, detection of a nucleic acid may be performed by an amplification reaction using one or more oligonucleotide primer that hybridizes to a nucleic acid molecule encoding a gene or a complement of the nucleic acid molecule. For example, the detection of a nucleic acid using a primer may be performed by amplifying a gene sequence using an amplification method such as PCR, and then confirming whether the gene is amplified by a method known in the art.
[0061] In one aspect of the present invention, the “primer” refers to a polynucleotide having a base sequence that can complementarily bind to the end of a specific region of a gene, or a mutant thereof, which is used for amplifying the specific region corresponding to a target region of the gene by PCR. The primer is not required to be completely complementary to the end of the specific region, and may be used as long as it is complementary to the end to such an extent that it can form a double-stranded structure by hybridizing with the end.
[0062] In one aspect of the present invention, the “probe” refers to a polynucleotide having a base sequence that can complementarily bind to a target of a gene, a mutant thereof, or a polynucleotide and a labeling substance bound thereto.
[0063] In one aspect of the present invention, “hybridization” means that 2 single-stranded nucleic acids form a duplex structure by pairing complementary base sequences. Hybridization may occur not only when there is complete complementary pairing between single-stranded nucleic acid sequences (perfect match), but also when there are partially mismatched (mismatch) bases.
[0064] The composition according to one aspect of the present invention may further comprise labels which may quantitatively or qualitatively measure formation of an antigen-antibody complex, general tools used in the immunological analysis, reagents, and the like as well as the detecting agent of a protein specific to the BCR clonotype or the detecting agent of a nucleic acid encoding the protein.
[0065] In one aspect of the present invention, the labels which may quantitatively or qualitatively

measure the formation of the antigen-antibody complex include enzymes, fluorescent substances, ligands, luminescent substances, microparticles, redox molecules, radioactive isotopes, and the like, and are not necessarily limited thereto. The enzymes usable as the detection label include β-glucuronidase, β-glucosidase, β-galactosidase, urease, peroxidase, alkaline phosphatase, acetylcholinesterase, glucose oxidase, hexokinase and GDPase, RNase, glucose oxidase and luciferase, phosphofructokinase, phosphoenolpyruvate carboxylase, aspartate aminotransferase, phosphenolpyruvate decarboxylase, β-lactamase, and the like, and are not limited thereto. The fluorescent substances include fluorescein, isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde, fluorescamine, and the like, and are not limited thereto. The ligands include biotin derivatives and the like, and are not limited thereto. The luminescent substances include acridinium ester, luciferin, luciferase, and the like, and are not limited thereto. The microparticles include colloidal gold, colored latex, and the like, and are not limited thereto. The redox molecules include ferrocene, ruthenium complex compounds, viologen, quinone, Ti ions, Cs ions, diimide, 1,4-benzoquinone, hydroquinone, K.sub.4W(CN).sup.8, [Os(bpy).sub.3].sup.2+, [RU(bpy).sub.3].sup.2+, [MO(CN).sub.8].sup.4−, and the like, and are not limited thereto. The radioactive isotopes include .sup.3H, .sup.14C, .sup.32P, .sup.35S, .sup.36Cl, .sup.51Cr, .sup.57Co, .sup.58Co, .sup.59Fe, .sup.90Y, .sup.125I, .sup.131I, .sup.186Re, and the like, and are not limited thereto.

[0066] In one aspect of the present invention, an example of the tool or the reagent includes suitable carriers, solubilizing agents, detergents, buffering agents, stabilizers, and the like, but is not limited thereto. When the marker is the enzyme, a substance and a quencher which may measure the enzyme activity may be included. The carriers include a soluble carrier, and an insoluble carrier. An example of the soluble carrier includes a buffer solution that is physiologically acceptable and known in the art, for example, PBS, and an example of the insoluble carrier may include polystyrene, polyethylene, polypropylene, polyester, polyacrylonitrile, fluororesin, cross-linked dextran, polysaccharide, other papers, glass, metal, agarose, and a combination thereof.

[0067] The composition according to one aspect of the present invention may be applied to a sample of a subject, and the sample refers to all samples obtained from an individual from which a protein detection agent specific for a B cell receptor (BCR) clonotype specific for an Alzheimer's patient or a nucleic acid encoding the protein according to one aspect of the present invention may be detected. Specifically, the sample may be one or more selected from the group consisting of saliva, biopsy, blood, skin tissue, liquid culture, feces and urine, but is not limited thereto, and may be treated and prepared by a method which is generally used in the art.

[0068] In other aspect, the present invention provides a system for predicting or diagnosing Alzheimer's disease comprising the composition for predicting or diagnosing Alzheimer's disease. The description of the Alzheimer's disease, the B cell receptor (BCR) clonotype specific to the Alzheimer's patient, the detecting agent, and the prediction or diagnosis of Alzheimer's is as described above.

[0069] The system according to one aspect of the present invention may further comprise an instruction.

[0070] The instruction according to one aspect of the present invention may describe that when the BCR clonotype specific to the Alzheimer's patient is detected in the sample of the subject, the subject is predicted or diagnosed as having the BCR clonotype specific to the Alzheimer's patient, and specifically, the subject is predicted or diagnosed as having Alzheimer's.

[0071] The system according to one aspect of the present invention may be applied to a sample of a subject, and the sample refers to all samples obtained from an individual from which a protein detection agent specific for a B cell receptor (BCR) clonotype specific for an Alzheimer's patient or a nucleic acid encoding the protein according to one aspect of the present invention may be detected. Specifically, the sample may be one or more selected from the group consisting of saliva, biopsy, blood, skin tissue, liquid culture, feces and urine, but is not limited thereto, and may be

treated and prepared by a method which is generally used in the art.
[0072] In another aspect, the present invention provides a method for providing information for predicting or diagnosing Alzheimer's disease comprising: detecting a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient in a sample of a subject, wherein the BCR clonotype comprises the V gene; and the J gene; and an amino acid sequence of complementary determining region 3 (CDR3) of the heavy chain of the BCR. The description of the Alzheimer's disease, the B cell receptor (BCR) clonotype specific to the Alzheimer's patient, the detecting agent, and the prediction or diagnosis of Alzheimer's is as described above.
[0073] The method for providing information according to one aspect of the present invention may further comprise predicting or diagnosing the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is i) the V gene is at least one selected from the group consisting of IGHV (Immunoglobulin Heavy Variable) 1-18, IGHV1-2, IGHV1-24, IGHV1-3, IGHV1-46, IGHV1-58, IGHV1-69, IGHV1-8, IGHV2-26, IGHV2-5, IGHV2-70, IGHV3-11, IGHV3-13, IGHV3-15, IGHV3-20, IGHV3-21, IGHV3-23, IGHV3-30, IGHV3-30-3, IGHV3-33, IGHV3-43, IGHV3-43D, IGHV3-48, IGHV3-49, IGHV3-53, IGHV3-64, IGHV3-64D, IGHV3-66, IGHV3-7, IGHV3-72, IGHV3-73, IGHV3-74, IGHV3-9, IGHV4-30-2, IGHV4-30-4, IGHV4-31, IGHV4-34, IGHV4-38-2, IGHV4-39, IGHV4-4, IGHV4-59, IGHV4-61, IGHV5-10-1, IGHV5-51, IGHV6-1, and IGHV7-4-1, ii) the J gene in the BCR clonotype detected from a sample of the subject is at least one selected from the group consisting of IGHJ (Immunoglobulin Heavy Joining) 1, IGHJ2, IGHJ3, IGHJ4, IGHJ5, and IGHJ6, and iii) the amino acid sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of SEQ ID NOs: 72 to 4047, and 32396 to 32481.
[0074] The method for providing information according to one aspect of the present invention may further comprise predicting or diagnosing the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is at least one of BCR clonotypes of the V gene; the J gene; and the amino acid sequence of CDR3. For example, the method for providing information according to one aspect of the present invention may further comprise predicting or diagnosing the subject as having Alzheimer's disease when the V gene and J gene in the BCR clonotype detected from the sample of the subject are IGHV3-7 and IGHJ1, and the amino acid sequence of CDR3 is the amino acid sequence of SEQ ID NO: 875.
[0075] The method for providing information according to one aspect of the present invention may further predicting or diagnosing the subject as having Alzheimer's disease when the entire amino acid sequence of the BCR clonotype detected from the sample of the subject comprising an amino acid sequence encoded from the V gene of the heavy chain of the BCR; an amino acid sequence encoded from the J gene of the heavy chain of the BCR; and an amino acid sequence of CDR3 of the heavy chain of the BCR is at least one of SEQ ID NOs: 18222 to 32395. For example, the method for providing information according to one aspect of the present invention may further comprise predicting or diagnosing the subject as having Alzheimer's disease when the entire amino acid sequence of the BCR clonotype detected from the sample of the subject is SEQ ID NO: 21427.
[0076] The method for providing information according to one aspect of the present invention may further predicting or diagnosing the subject as having Alzheimer's disease when the entire base sequence of the BCR clonotype detected from the sample of the subject comprising a base sequence of the V gene of the heavy chain of the BCR; a base sequence of the J gene of the heavy chain of the BCR; and a base sequence encoding an amino acid sequence of CDR3 of the heavy chain of the BCR is at least one of SEQ ID NOs: 4048 to 18221. For example, the method for providing information according to one aspect of the present invention may further comprise predicting or diagnosing the subject as having Alzheimer's disease when the entire base sequence of the BCR clonotype detected from the sample of the subject is SEQ ID NO: 7253.
[0077] The method for providing information according to one aspect of the present invention may further predicting or diagnosing the subject as having Alzheimer's disease when the amino acid

sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of SEQ ID NOs: 72 to 4047, and 32396 to 32481. Specifically, the method for providing information may comprise predicting or diagnosing the subject as having Alzheimer's disease when the amino acid sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of ARDLPATGAFDI (SEQ ID NO: 214), VRLAEYFQN (SEQ ID NO: 875), TRDRRGWD (SEQ ID NO: 1211), ALGRGMDV (SEQ ID NO: 1048), VLRGSAFDI (SEQ ID NO: 798), ARSGGLDP (SEQ ID NO: 668), AGGRSFDY (SEQ ID NO: 613), AGNLMDV (SEQ ID NO: 2257), ARRGEY (SEQ ID NO: 2070), ARDMFRGIPDYLDY (SEQ ID NO: 1988), AKSLGSGTYSFDY (SEQ ID NO: 1326), ARNAGLDY (SEQ ID NO: 1128), ARDDGYRSIDY (SEQ ID NO: 990), VRGGGSGWPFES (SEQ ID NO: 3709), SRGRDGIG (SEQ ID NO: 2815), ARSGGLDV (SEQ ID NO: 2415), ARSRSGSYYYGMDV (SEQ ID NO: 1198), AGDWNDDDIFDY (SEQ ID NO: 32396), ARKGEQLWHY (SEQ ID NO: 965), and ARDPIAVPGLFDY (SEQ ID NO: 347).

[0078] The method for providing information according to one aspect of the present invention may further comprise predicting or diagnosing the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is at least one of BCR clonotypes of the V gene; the J gene; and the amino acid sequence of CDR3.

[0079] The sample of the subject according to one aspect of the present invention may comprise nucleic acid of the subject, wherein the nucleic acid may comprise DNA, mRNA, or cDNA synthesized from mRNA.

[0080] Hereinafter, the configuration and effects of the present invention will be described in more detail by way of examples. However, the following examples are for illustrative purposes only and it will be apparent to those of ordinary skill in the art that the scope of the present invention is not limited by the examples.

[0081] The present inventors identified BCR clonotypes persistently present and shared among AD patients but not present in normal healthy populations and analyzed their characteristics. For this, we collected peripheral blood (PB) from 44 AD patients at two sampling points with the interval of 14-53 weeks and used them to re-constitute in silico BCR repertoires of these patients. As a control group, the inventors used the BCR repertoire from 55 healthy volunteers vaccinated with SARS-CoV2 mRNA vaccine whose PB samples were collected for six times over 42 weeks 15. In comparison, the AD patients showed much higher sharing of stereotypic patient-specific BCR clonotypes compared to the control group. One of these BCR clonotypes was found to encode antibodies reactive to Aβ42 peptide, which are the well-known antigen of autoantibodies found in AD patients.

Statistical Analysis

[0082] In the below Examples and Experimental examples, the P values were calculated using the student t-test unless specified during comparison of BCR repertoire characteristics. Unless otherwise indicated. P-value <0.05 was regarded as significant.

Example 1—Blood Sampling and Peripheral Blood Mononuclear Cell Isolation from Study Subjects

[0083] The present inventors acquired data of all subjects, including demographic information, subtypes of dementia, Clinical Dementia Rating (CDR), comprehensive neuropsychological tests with Mini-Mental State Examination (MMSE), neuroimaging results by using magnetic resonance imaging (MRI) and amyloid-PET, from the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) [16]. Each data was valid for 6 months except amyloid-PET. This study was approved under the recommendations of the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital (SNUBH, IRB approval number, B-2102-664-305), South Korea. Protocols and manuals were also approved by the IRB of the SNUBH.

[0084] Total 55 of vaccinees who received BNT162b2 mRNA vaccine were participated, and their

peripheral blood sampling was approved by the IRB of Seoul National University Hospital (SNUH, IRB approval number, 2102-032-1193). The details of the vaccination cohort data are described in previous article[1].

[0085] Additionally, for the above subjects, all peripheral blood samples were collected by EDTA tubes (BD Vacutainer K2EDTA tubes, 367525) at least 15 ml in total per a patient[17]. Peripheral blood mononuclear cells (PBMCs) and plasma were separated by density-gradient centrifugation using Ficoll (Cytiva Ficoll-Paque Plus, 17-1440-02) solution. After the PBMC suspension was resuspended in CELLBANKER (Amsbio CELLBANKER 2, 11914), the collected PBMCs were immediately cryopreserved and stored in a Freezing container (Nalgene Mr. Frosty, C1562) for a week. Total RNA was isolated by TRIzol Reagent (Invitrogen TRIzol Reagents, 15596026) following the manufacturer's instructions.

Example 2—Preparation of Next-Generation Sequencing (NGS) Library and NGS Data Processing

[0086] An NGS library was prepared using the peripheral blood mononuclear cells of Example 1 above by the following method, and the NGS data obtained therefrom were processed as follows.

[0087] Specifically, for the NGS library preparation of BCR heavy chain sequence, genes encoding the variable region of the heavy chain (V.sub.H) at the 5 prime forward part and the first constant region of the heavy chain (CH1) domain at the 3 prime reverse part were amplified by specific PCR primers as reported previously[4]. All primer sequences are listed in Tables 1 and 2. In short, one microgram of total RNA was used as the input template for library preparation. Next, reverse transcription was conducted as following the manufacturer's instructions using SuperScript IV First-Strand Synthesis System (Invitrogen, 18091050) with CH1 gene-specific primers for five immunoglobulin heavy chain isotypes containing UMI (unique molecular identifiers) barcodes that consist of 12 random nucleotides. 14 base pair in total; NNNNTNNNNTNNNN, and partial Illumina adapters (No. 1-8). After first-strand cDNA synthesis, it was purified with SPRI beads (Beckman Coulter AMPure XP Reagents, A63882) at a 1:1.8 ratio and second-strand cDNA was synthesized using a KAPA Biosystems kit (Roche KAPA HiFi Hotstart PCR kit, KK2502) with VH genespecific primers (No. 9-14; 95° C. for 3 min, 98° C. for 30 s, 60° C. for 45 s, and 72° C. for 6 min). Double-stranded cDNA was purified through SPRI beads at a 1:1 ratio.

[0088] Following that, it was amplified using KAPA Biosystems kit and double primers containing Illumina adapters and index sequences (No. 15, 16; 95° C. for 3 min, 25 cycles of 98° C. for 30 s, 60° C. for 30 s, 72° C. for 1 min, and 72° C. for 5 min). The PCR products were subjected to electrophoresis on a 1.5% agarose gel to separate through the length of DNA and purified using QIAquick gel extraction kit (QIAGEN, 28704) following the manufacturer's protocols. The final NGS libraries were obtained using SPRI beads at a 1:1 ratio and quantified with a 4200 TapeStation System (Agilent Technologies, G2991BA) for QC. Libraries with a single peak of appropriate length were subjected to NGS analysis using the Illumina Nocaseq6000 platform.

TABLE-US-00001 TABLE 1 Primers used in the study Primer used for the preparation of BCR repertoire Primer Sequence No. Name (5′-Primer Seq-3′) Step 1 RT_ TGACTGGAGTTCAGACGTGTGC cDNA IgG_ TCTTCCGATCTNNNNTNNNNTN synthesis 1_ NNNAGCCCAGGGCCGCTGTGC 250PE (SEQ ID NO: 1) 2 RT_ TGACTGGAGTTCAGACGTGTGC cDNA IgG_ TCTTCCGATCTNNNNTNNNNTN synthesis 2_ NNNAGCCCAGGGCTGCTGTGC 250PE (SEQ ID NO: 2) 3 RT_ TGACTGGAGTTCAGACGTGTGC cDNA IgG_ TCTTCCGATCTNNNNTNNNNTN synthesis 3_ NNNAGCCCAGGGCGGCTGTGC 250PE (SEQ ID NO: 3) 4 RT_ TGACTGGAGTTCAGACGTGTGC cDNA IgA1_ TCTTCCGATCTNNNNTNNNNTN synthesis 2_ NNNGCAGGCGATGACCACGTTC 50PE C (SEQ ID NO: 4) 5 RT_ TGACTGGAGTTCAGACGTGTGC cDNA IgA2_ TCTTCCGATCTNNNNINNNNTN synthesis 2_ NNNGCATGCGACGACCACGTTC 50PE C (SEQ ID NO: 5) 6 RT_ TGACTGGAGTTCAGACGTGTGC cDNA IgE_ TCTTCCGATCTNNNNTNNNNTN synthesis 250 NNNGAGTCACGGAGGTGGCATT PE GG (SEQ ID NO: 6) 7 RT_

TGACTGGAGTTCAGACGTGTGC cDNA IgM_ TCTTCCGATCTNNNNTNNNNTN synthesis 25 NNNCAACGGCCACGCTGCTCG 0PE (SEQ ID NO: 7) 8 RT_ TGACTGGAGTTCAGACGTGTGC cDNA IgD_ TCTTCCGATCTNNNNTNNNNTN synthesis 25 NNNATGCCAGGACCACAGGGCT 0PE G (SEQ ID NO: 8) 9 PCR_ ACACTCTTTCCCTACACGACGC Second- f_VH1 TCTTCCGATCTGGCCTCAGTGA strand AGGTCTCCTGCAAG synthesis (SEQ ID NO: 9) 10 PCR_ ACACTCTTTCCCTACACGACGC Second- f_VH2 TCTTCCGATCTGTCTGGTCCTA strand CGCTGGTGAAACCC synthesis (SEQ ID NO: 10) 11 PCR_ ACACTCTTTCCCTACACGACGC Second- f_VH3 TCTTCCGATCTCTGGGGGGTCC strand CTGAGACTCTCCTG synthesis (SEQ ID NO: 11) 12 PCR_ ACACTCTTTCCCTACACGACGC Second- f_VH4 TCTTCCGATCTCTTCGGAGACC strand CTGTCCCTCACCTG synthesis (SEQ ID NO: 12) 13 PCR_ ACACTCTTTCCCTACACGACGC Second- f_VH5 TCTTCCGATCTCGGGGAGTCTC strand TGAAGATCTCCTGT synthesis (SEQ ID NO: 13) 14 PCR_ ACACTCTTTCCCTACACGACGC Second- f_VH6 TCTTCCGATCTTCGCAGACCCT strand CTCACTCACCTGTG synthesis (SEQ ID NO: 14) 15 Illumida AATGATACGGCGACCACCGAGA Indexing adaptor TCTACAC [i5 index] PCR amp-fwd ACACTCTTTCCCTACACGACGC TCTTCCGATC (SEQ ID NO: 15) 16 Illumida CAAGCAGAAGACGGCATACGAG Indexing adaptor AT [i7 index] PCR amp-rev GTGACTGGAGTTCAGACGTGTG CTCTTCCG (SEQ ID NO: 16)

TABLE-US-00002 TABLE 2 Primers used in the study Primer used for the construction of human scFv libraries Primer No. Name Sequence (5′-Primer Seq-3′) Step 17 KC GGCACACAACAGAGGCAGTTCC (SEQ ID NO: 17) cDNA synthesis 18 LC_RT1 GCTTGAAGCTCCTCAGAGGAGG (SEQ ID NO: 18) cDNA synthesis 19 LC_RT2 GCTTGGAGCTCCTCAGAGGAGG (SEQ ID NO: 19) cDNA synthesis 20 LC_RT3 TGGAGCTCCCTGCCTCTGG (SEQ ID NO: 20) cDNA synthesis 21 KV1 GGGCCCAGGCGGCCGAGCTCCAGATGACCCAGTCTCCATCCTC Second- (SEQ ID NO: 21) strand synthesis 22 KV2 GGGCCCAGGCGGCCGAGCTCGTGATGACTCAGTCTCCACTCTCC Second- (SEQ ID NO: 22) strand synthesis 23 KV3 GGGCCCAGGCGGCCGAGCTCGTGTTGACACAGTCTCCAGCC Second- (SEQ ID NO: 23) strand synthesis 24 KV4 GGGCCCAGGCGGCCGAGCTCGTGATGACCCAGACTCCACTCTC Second- (SEQ ID NO: 24) strand synthesis 25 KV5 GGGCCCAGGCGGCCGAGCTCGTGCTGACTCAGTCTCCAGAC Second- (SEQ ID NO: 25) strand synthesis 26 KV6 GGGCCCAGGCGGCCGAGCTCCAGATGACCCAGTCTCCATCTTC Second- (SEQ ID NO: 26) strand synthesis 27 KV7 GGGCCCAGGCGGCCGAGCTCCAGATGACCCAGTCTCCTTCCAC Second- (SEQ ID NO: 27) strand synthesis 28 KV8 GGGCCCAGGCGGCCGAGCTCTGGATGACCCAGTCTCCATCC Second- (SEQ ID NO: 28) strand synthesis 29 KV9 GGGCCCAGGCGGCCGAGCTCCAGATGACCCAGTCTCCATCTGC Second- (SEQ ID NO: 29) strand synthesis 30 KV10 GGGCCCAGGCGGCCGAGCTCGTGTTGACGCAGTCTCCAGG Second- (SEQ ID NO: 30) strand synthesis 31 KV11 GGGCCCAGGCGGCCGAGCTCGTAATGACACAGTCTCCACCCAC Second- (SEQ ID NO: 31) strand synthesis 32 KV12 GGGCCCAGGCGGCCGAGCTCACACTCACGCAGTCTCCAGC Second- (SEQ ID NO: 32) strand synthesis 33 LV1

GGGCCCAGGCGGCCGAGCTCGCCCTGACTCAGCCTGCC Second- (SEQ ID NO: 33) strand synthesis 34 LV2 GGGCCCAGGCGGCCGAGCTCGCCCTGACTCAGCCTCCC Second- (SEQ ID NO: 34) strand synthesis 35 LV3 GGGCCCAGGCGGCCGAGCTCGTGCTGACTCAGCCACCC Second- (SEQ ID NO: 35) strand synthesis 36 LV4 GGGCCCAGGCGGCCGAGCTCGAGCTGACACAGCCACCC Second- (SEQ ID NO: 36) strand synthesis 37 LV5 GGGCCCAGGCGGCCGAGCTCGTGCTGACTCAATCATCCTCTGC Second- (SEQ ID NO: 37) strand synthesis 38 LV6 GGGCCCAGGCGGCCGAGCTCGTGCTGACTCAGCCGTCTTC Second- (SEQ ID NO: 38) strand synthesis 39 LV7 GGGCCCAGGCGGCCGAGCTCGTGGTGACTCAGGAGCCCTC Second- (SEQ ID NO: 39) strand synthesis 40 LV8 GGGCCCAGGCGGCCGAGCTCGTGCTGACTCAGCCACCTTC Second- (SEQ ID NO: 40) strand synthesis 41 LV9 GGGCCCAGGCGGCCGAGCTCGTCGTGACGCAGCCGCC Second- (SEQ ID NO: 41) strand synthesis 42 LV10 GGGCCCAGGCGGCCGAGCTCGCCCTGACTCAGCCTCGC Second- (SEQ ID NO: 42) strand synthesis 43 LV11 GGGCCCAGGCGGCCGAGCTCGAGCTGACTCAGCCACACTC Second- (SEQ ID NO: 43) strand synthesis 44 LV12 GGGCCCAGGCGGCCGAGCTCGTGCTGACTCAGCCAACCTC Second- (SEQ ID NO: 44) strand synthesis 45 LV13 GGGCCCAGGCGGCCGAGCTCGTGGTGACCCAGGAGCCATC Second- (SEQ ID NO: 45) strand synthesis 46 LV14 GGGCCCAGGCGGCCGAGCTCGAGCTGACTCAGGACCCTGC Second- (SEQ ID NO: 46) strand synthesis 47 LV15 GGGCCCAGGCGGCCGAGCTCGAGCTGATGCAGCCACCC Second- (SEQ ID NO: 47) strand synthesis 48 LV16 GGGCCCAGGCGGCCGAGCTCGAGCTGACACAGCCATCCTC Second- (SEQ ID NO: 48) strand synthesis 49 LV17 GGGCCCAGGCGGCCGAGCTCGTGCTGACTCAGCCCCCG Second- (SEQ ID NO: 49) strand synthesis 50 KJ1 GGAAGATCTAGAGGAACCACCTTTGATCTCCAGCTTGGTCCC Second- (SEQ ID NO: 50) strand synthesis 51 KJ2 GGAAGATCTAGAGGAACCACCTTTGATTTCCACCTTGGTCCCTTG Second- (SEQ ID NO: 51) strand synthesis 52 KJ3 GGAAGATCTAGAGGAACCACCTTTGATATCCACTTTGGTCCCAGG Second- (SEQ ID NO: 52) strand synthesis 53 KJ4 GGAAGATCTAGAGGAACCACCTTTAATCTCCAGTCGTGTCCCTTG Second- (SEQ ID NO: 53) strand synthesis 54 LJ1 GGAAGATCTAGAGGAACCACCGCCTAGGACGGTCAGCTTGGTCC Second- (SEQ ID NO: 54) strand synthesis 55 LJ2 GGAAGATCTAGAGGAACCACCGCCTAGGACGGTGACCTTGGTCC Second- (SEQ ID NO: 55) strand synthesis 56 LJ3 GGAAGATCTAGAGGAACCACCGCCGAGGACGGTCACCTTGGTG Second- (SEQ ID NO: 56) strand synthesis 57 LJ4 GGAAGATCTAGAGGAACCACCGCCGAGGGCGGTCAGCTGGG Second- (SEQ ID NO: 57) strand synthesis 58 AMP_H_ GGTGGTTCCTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG First forward (SEQ ID NO: 58) round PCR 59 AMP_H_ CCTGGCCGGCCTGGCCAC (SEQ ID NO: 59) First reverse round PCR 60 AMP_K/L_ GGGCCCAGGCGGCCGAG (SEQ

ID NO: 60) First forward round PCR 61 AMP_K/L_ GGAAGATCTAGAGGAACCACC (SEQ ID NO: 61) First reverse round PCR 62 EXT-fwd GGCGGGGCCCAGGCGGCCGAGCTC (SEQ ID NO: 62) Overlap extension PCR 63 EXT-rev GAGCCTGGCCGGCCTGGCCACTAGT (SEQ ID NO: 63) Overlap extension PCR

[0089] Then, the raw NGS forward (R1) and reverse (R2) reads were merged, filtered based on Phred scores, and subclustered using UMI using paired-end read merger (PEAR), v0.9.10, and Clustal Omega, v1.2.4, with the default setting[18, 19]. The sequence annotation process used the IMGT (International Immunogenetics Information System) constant gene database[20] to obtain the isotype, and IgBLAST, v1.17.1 to obtain VJ genes, CDR1/2/3 sequences, and the number of mutations from the corresponding V genes as previously described[4]. To eliminate the possibility of contamination due to index swapping within Illumina flow cells between samples, reads with identical sequences including the UMI from different samples were excluded on the basis that such an event is highly unlikely without contamination[22]. The combined NGS throughput of each sample is listed in Tables 1 and 2. Sequencing reads that have survived through the entire process is considered to be a productive BCR sequence.

Example 3—BCR Repertoire Sharing and Exclusion Analysis

[0090] First, shared BCR clonotypes are defined in this study as a unique combination of V gene, J gene, and CDR3 amino acid sequence which are present in 2 or more subjects within a cohort. The shared BCR sequences in this context refer to the collective BCR sequences that can be grouped into each shared BCR clonotype.

[0091] Clonotypes which consist only of naïve sequences in the NGS data obtained the above Example 2, those with the IgM or IgD isotype with 1 or less somatic mutations were excluded from further analysis to account only for shared clonotypes arising from shared antigenic stimuli[3]. Due to potential risk of molecular contamination during the NGS library preparation stage, an additional strict in silico filtering step was employed. Shared clonotypes that have patient specific sets of unique BCR nucleotide sequences that are completely eclipsed by another patient's set was considered as contamination due to the low likelihood of 2 different people sharing only the same exact somatic mutations in the nucleotide level.

[0092] The similarity score based on shared cohort specific BCR clonotypes was calculated as the cosine similarity of the two vectors each representing a subject's repertoire. The vectorization process involved utilizing one-hot encoding to create a vector with the length equal to the total number of cohort specific and shared BCR clonotypes.

[0093] The presence or absence of each clonotypes for the patient was encoded as either the value 1 or 0. The cosine similarity being calculated as the inner product divided by the product of the size of each vector can be interpreted as the number of shared cohort specific shared clonotypes both present in a patient pair divided by the square root of the product of the total number of cohort specific shared clonotypes for each patient.

Example 4—Construction of scFv Phage Display Library and Bio-Panning

[0094] In BCR repertoire of the above Example 3, for the V.sub.H gene, V3-7/J1 VRLAEYFQN clonotype which is the most shared among all patients was chosen to test the affinity to Aβ42 peptide. In total, 16 sequences are included in that of clonotype and 9 out of 16 were presented in TP2. And 4 out of 9 sequences were synthesized in gBlocks Gene Fragments (Integrated DNA Technologies) depending on their sequence diversity of the CDR1, 2 regions at the amino acid level and somatic hypermutation status. For the construction of V.sub.κ/V.sub.λ shuffled libraries, total RNA from patients who possess the V3-7/J1 VRLAEYFQN clonotype in TP2 (AD9, AD14 and AD34) was used to synthesize cDNA using SuperScript IV First-Strand Synthesis System (Invitrogen) with gene-specific primers amplifying the J.sub.H and C.sub.κ/λ genes (No. 17, 18-20), respectively. Patient 35 also had that of heavy chain, however, experiments were preceded before he joined the second blood drawing. It was purified with SPRI beads (Beckman Coulter

AMPure XP Reagents) at a 1:1.8 ratio and the purified cDNA was used for the first round of PCR synthesis using V.sub.κ/V.sub.λ and J.sub.κ/J.sub.λ gene-specific primers (No. 21-57; 95° C. for 3 min. 4 cycles of 98° C. for 1 min, 60° C. for 1 min, 72° C. for 1 min, and 72° C. for 10 min). Likewise, it was purified with SPRI beads at a 1:1 ratio. After that, both 4 synthesized V.sub.H gene and V.sub.κ/V.sub.λ genes from 3 patients' total RNA were amplified using a KAPA Biosystems kit (Roche) with following primers (No. 58-61; 95° C. for 3 min. 27 cycles of 98° C. for 30 s, 65° C. for 30 s, 72° C. for 1 min, and 72° C. for 10 min). Then, each gene fragment of V.sub.H and V.sub.κ/V.sub.λ was subjected to electrophoresis on a 1.5% agarose gel and purified through the size of each DNA using QIAquick gel extraction kit (QIAGEN) following the manufacturer's instructions. The amplified 4 V.sub.H and V.sub.κ/V.sub.λ gene fragments from 3 patients were mixed at equal ratio to make a single pool of V.sub.H and V.sub.κ/V.sub.λ gene, respectively. From the equally mixing pool of V.sub.H and V.sub.κ/V.sub.λ, same amount (100 ng) of each gene fragments were subjected to overlap extension PCR to generate final scFv genes by using a KAPA Biosystems kit (Roche) with overlap extension primers (No. 62, 63:95° C. for 3 min. 25 cycles of 98° C. for 30 s, 65° C. for 30 s, 72° C. for 1 min 30 s, and 72° C. for 10 min). After that, the amplified scFv genes were purified and cloned into a phagemid vector as described previously[23].

[0095] Phage display of the human scFv library with 1.1×10.sup.9 colony-forming units was generated using 4 types of synthesized V.sub.H gene fragment and shuffled V.sub.κ/V.sub.λ gene which derived from the cDNA of patient No. 6, 14 and 34. Following library was subjected to four rounds of bio-panning against the human Aβ42 peptide (Tocris Bioscience Amyloid β-Peptide 1-42 human, 1428) as described previously[24, 25]. Phage-display experiments including reamplification, rescue and PEG precipitation of library were mainly carried out with the protocols described in *Phage Display: A Laboratory Manual [*26]. Briefly, 2 μg of the Aβ42 peptide was coated to the surface of the immunotube with high binding surface (SPL Life Sciences, 43015) at 4° C. for 16 hours and blocked with 5 ml of 3% bovine serum albumin (BSA) in PBS (w/v). Then, the scFv phage library (about 1013 phages) was incubated for 2 hours at room temperature. During the first round of panning, the tube was washed once with 5 ml of 0.05% (v/v) Tween 20 (Sigma-Aldrich, P1379) in phosphate-buffered saline (PBST). After each round of panning, remaining phages bound to the coated antigen were eluted and rescued for the next round of bio-panning as described above. For the other rounds of panning, the number of washes was increased to three. To select antigen reactive scFv phage clones, each phage clones from the titration plate of the last round of panning was subjected to phage ELISA, using the antigen-coated microtiter plates, as described previously[26]. Reactive scFv clones were analyzed through Sanger nucleotide sequencing using their phagemid DNA extracted from the individual phage clones as discussed before[4]. A recombinant scFv protein tagged with human IgG1 FC (hFc) was expressed in mammalian expression system and purified as describe previously[4].

Example 5—Enzyme-Linked Immunosorbent Assay

[0096] The specificity and antigen affinity of individual phage scFv clones and recombinant scFv-hFc fusion proteins of the above Example 4 were assessed by ELISA. 100 nM of human Aβ42 peptides, dissolved in 50 μl of 0.1 M sodium bicarbonate coating buffer (pH 8.6), were added to each well of 96-well microtiter plates (Corning, 3690) as described earlier. Shortly, the plates were coated with the antigen by incubation at 4° C. for 16 hours and blocked with 3% BSA in PBS (w/v) at 37° C. for 1 hours. After shaking off the blocking solution, serially diluted phage supernatant (twofold) or scfv-hFc (fivefold, S dilutions, starting from 1 μM to 12.8 pM) in blocking buffer were added to the wells of microtiter plates and incubated at 37° C. for 2 hours. Then, plates were washed three times with 0.05% PBST (v/v). For ELISAs with phage clones, HRP-conjugated rabbit antihuman IgG Fc antibody (Invitrogen, 31423, 1:5,000) and HRP-conjugated anti-M13 antibody (Sino Biological, 11973-MM05T-H, 1:4,000) were diluted in blocking buffer as manufacturer's protocols, followed by adding to wells and incubated at 37° C. for 1 hours. It performed

respectively in the duplicated batch to determine the amount of antigen-reactive antibody or M13 bacteriophage. In ELISA for the recombinant scFvhFc fusion proteins, HRP-conjugated rabbit anti-human IgG Fc antibody (Invitrogen, 31423, 1:5,000) was added to wells and incubated at 37° C. for 1 hours. After washing three times with 0.05% PBST, 2,2′-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid solution (Invitrogen, 002024) was added to the wells as an HRP substrate. Absorbance was measured at 415 nm, respectively, using a microplate spectrophotometer (Thermo Fisher Scientific Inc., Multiskan GO). All assays were carried out in duplicate.

Example 6—Selection of Stereotypic AD Patient-Specific Non-Naïve BCR Clonotypes

[0097] For a period of 75 weeks, peripheral blood (PB) samples were collected from 44 Alzheimer patients with a median age of 75 years (standard deviation; 7.04) and sex ratio of 34% and 66% (male vs female). Except for seven patients (Patient ID 3, 5, 8, 19, 28, 30, and 37), PB samples were collected twice with interval between 14 and 53 weeks (FIG. **1**A). The duration for the first and second PB sampling was 61 and 34 weeks, respectively. From these 81 PB samples, cDNA was prepared and subjected to the amplification of a gene fragment encoding variable domain (VH) and Nterminal part of constant domain 1 (CH1) of B cell receptor (BCR) heavy chain using a specific primer set (Tables 1 and 2), which were analyzed in next generation sequencing with a median read of 245,033 (standard deviation of 184,462, Tables 4 and 5). For the analysis of BCR repertoire, we first removed naïve BCR sequences, which we define as those with IgM or ID isotype containing less than 1 somatic hypermutation (SHM). Then we grouped the remaining sequences into clonotypes, which was defined as a collection of sequences sharing the same CDR3 sequence at the amino acid level as well as encoded by identical IGHV and IGHJ genes[3]. Among these BCR clonotypes, AD patient-specific clonotypes were selected by excluding clonotypes found in a control group (CG) established in our prior studies, which was constituted with 55 vaccinees (285 PB samples obtained chronologically) injected three times with COVID-19 vaccine15 (FIG. **1**B, Table 3). Control group specific non-naïve BCR clonotypes were also obtained following the same procedures. Before further analysis, we tried to remove any possibility of aerosol molecular contamination during NGS library preparation and index switching during sequencing[1]. For this, we excluded all the stereotypic clonotypes in which each patient or control did not show unique BCR sequences at the nucleotide level.

[0098] After all these selection processes we could select 3.983 and 83,821 BCR clonotypes specific to AD patient group or control group, respectively (FIG. **1**C).

TABLE-US-00003 TABLE 3 Demographics of AD and CG group Characteristics AD cohort CG cohort Number 44 55 Age (years) 74.9 ± 6.9* 33.2 ± 9.1 Sex (M:F) 15:29 26:29 AD, Alzheimers disease; approved under the recommendations of the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital (SNUBH, IRB approval number, B-2102-664-305), South Korea. CG, Vaccination control group; approved by the IRB of Seoul National University Hospital (SNUH, IRB approval number, 2102-032-1193), South Korea. *Age based on time of first sampling (TP1)

TABLE-US-00004 TABLE 4 Vaccine cohort subject TP1 TP2 TP3 TP4 TP5 TP6 1 116846 74116 N/A 308607 503110 363352 2 N/A 412242 359933 637596 N/A N/A 3 N/A 233382 386838 207509 200078 392932 4 297560 295471 288481 298874 225565 159801 5 277423 338856 276439 292434 100454 328502 6 117645 304697 281448 261449 N/A 90170 7 167730 447446 396370 425845 N/A 308297 8 201381 272153 238318 250530 98330 N/A 9 71061 312156 268349 146753 177497 166913 10 110138 328043 321325 225229 311158 426625 11 115745 304497 349801 219420 296670 N/A 12 83882 367630 386806 480477 N/A N/A 13 94375 285776 365978 210716 540447 132993 14 136815 277598 73364 394457 452999 398426 15 257019 287627 352889 436163 292988 131853 16 69313 264901 N/A N/A 380708 N/A 17 186003 254969 411110 155924 185741 433726 18 143543 89465 447991 352477 384304 N/A 19 188195 N/A 434379 411592 535408 N/A 20 79075 763067 332463 634987 N/A N/A 21 130318 44297 251913 327060 236588 526006 22 108257 127565 611092 186488 N/A 239071 23 106012 N/A 622746 193718

343870 182295 24 86189 125168 381850 N/A 135668 N/A 25 217788 290448 307991 244198 386140 N/A 26 268423 269479 287259 527800 115860 N/A 27 276442 294510 397970 327793 470213 494132 28 73922 170608 229818 153453 298818 272185 29 106076 160933 284978 198595 210089 N/A 30 350181 137372 376001 93516 98233 172479 31 57928 156320 712424 209826 217594 N/A 32 520050 186185 506773 289453 353165 543473 33 139592 161044 272372 196285 327832 297902 34 111086 250341 283938 194308 59673 N/A 35 164995 234015 416674 N/A 371122 354917 36 108078 306270 266945 137483 274328 289645 37 N/A 915107 335969 391259 409694 N/A 38 205087 357783 379389 221707 668335 379577 39 180835 355525 121246 N/A 255377 208146 40 151495 223316 133059 178507 322811 112402 41 171548 N/A 389549 186037 243664 132788 42 135524 271827 295086 239576 N/A N/A 43 166742 239590 128758 64537 123037 301277 44 137807 367324 494786 91489 661630 363467 45 92714 215559 523444 94863 253647 131049 46 N/A 301442 597236 219932 N/A N/A 47 69303 279692 447821 116292 184017 N/A 48 N/A 274990 264335 277660 339829 103204 49 170408 253677 312839 146165 175187 435089 50 235553 310495 234564 153694 383540 395902 51 19505 N/A 290752 125531 280175 N/A 52 86072 389170 441317 201485 373482 276724 53 232760 345513 541998 109294 259369 302281 54 66017 300447 565089 125593 176918 92764 55 N/A 314304 276673 79930 277668 375069

TABLE-US-00005 TABLE 5 Alzheimer's disease subject TP1 TP2 1 278490 298543 2 482372 386775 3 375502 N/A 4 238549 255707 5 430371 N/A 6 216502 172377 7 163212 228539 8 357746 N/A 9 462337 264165 10 736856 190256 11 646467 376727 12 134150 177258 13 644200 126737 14 403475 334311 15 592160 139445 16 333471 367383 17 230042 235500 18 291166 301188 19 639201 N/A 20 168072 132959 21 193563 223286 22 263507 280624 23 252792 56821 24 383144 171485 25 457475 161323 26 82630 135646 27 138279 138835 28 116251 N/A 29 454885 245033 30 851831 N/A 31 317011 122818 32 506812 286435 33 724754 108953 34 919858 193478 35 225313 164490 36 235339 112636 37 658256 N/A 38 392077 205251 39 194282 178175 40 267038 177530 41 38294 63111 42 141594 172079 43 262308 192285 44 273453 331364

Example 7 Stereotypic AD Patient-Specific Non-Naïve Clonotypes Showed Significantly Higher Degree of Overlap in Patient Pairs Compared to CG Pairs

[0099] Then, the present inventors analyzed the distribution of stereotypic AD patient-specific BCR clonotypes in 1,892 ((44 X 44)-44) or 1,332 ((37 X 37)-37) patient pairs in the first and the second PB samples, respectively. The present inventors calculated the degree of overlap for stereotypic BCR clonotypes in each pair as the cosine similarity of one-hot encoded vectors representing the presence or absence of each stereotypic clonotype in a patient's BCR repertoire. The present inventors also obtained the degree of overlap for the CG pairs in six PB sampling points. As expected, there was dramatic increase in the average cosine similarity at time point (TP) 3, the TP4 and TP6 PB samples obtained right after the second-, 1 month after the second-, and right after the third-injection of COVID-19 vaccine, respectively, due to the concerted BCR response toward the immunogen compared to the pre-vaccinated state (TP1) (FIG. **2**A-C, p=4.92×10.sup.6, p=2.52×10.sup.−30, p=2.26×10.sup.−112). AD patient pairs showed much higher average cosine similarity at both sampling points compared to CG TP1 with statistical significance (p=2.06×10.sup.−21, p=1.22×10.sup.−169). The value was higher at the second PB samples and might be originated from shorter PB sampling duration (61 weeks vs 34 weeks), which would provide less diverse seasonal antigens to AD patients. It was quite astonishing that the average cosine similarity of the second PB samples was higher than that of TP6 PB samples of CG showing the highest value among CG PB samples with statistical significance (p=1.86×10.sup.−6). This observation was extra-ordinary when we consider that PB sampling duration was much longer in AD patients (34 weeks vs 6 weeks). As the present inventors do not aware of COVID-19 infection history or vaccination of AD patients, the present inventors performed the same analysis without excluding stereotypic BCR clonotype of AD patients from stereotypic clonotypes of CG. The

cosine similarity value of AD patients' PB samples at both TP1 and TP2 were higher than those of CG's PB samples with statistical significance at all TPs except for TP6, which were similar (FIGS. **4**A-C). These analysis clearly showed that AD patients shares stereotypic BCR clonotypes at an equivalent or higher degree compatible to vaccinees who received their third injection for the previous six weeks before PB sampling irrespective of AD patients much longer PB sampling period of 34 weeks.

[0100] Analysis of the present inventors showed that the degree of overlap on the stereotypic AD patient-specific BCR clonotypes significantly differs in patients pairs suggesting the existence of patient subgroups categorized by their BCR clonotypes. To find these patient subgroups, the stereotypic AD patient-specific BCR clonotypes at all TPs in each patient were combined and the cosine similarity of patient pairs were calculated. Twenty patient pairs with the highest cosine value were selected and displayed in Chord plot (FIG. **2**D), in which the patients were divided to six subgroups. Among these pairs, one patient pair (patient ID 26 and 28) had an outlying degree of cosine similarity value of 0.961. And the number of BCR clonotypes was also extraordinarily high (FIG. **2**E). Indeed, among 1,225 and 1,228 stereotypic BCR clonotypes in patient ID 26 and patient ID 28, respectively. 1,179 clonotypes were shared by these two patients. The presence of AD patient subgroups showing high degree of overlap in their BCR clonotypes strongly suggested the existence of common and possibly auto-antigens shared by the subgroup.

[0101] Results of the present inventors suggest that the antibodies encoded by stereotypic AD patient-specific BCR clonotypes are developed by chronic exposure to autoantigens through the progression of disease.

[0102] It can be confirmed that the presence of common immunogen among AD patients shaping their BCR repertoire to coordinated directions through this. It was also found that many of these stereotypic AD patient-specific BCR clonotypes or their very homologous clonotypes persisted over a period of 14 and 53 weeks (FIG. **3**A). And when examining one group of long-lasting homologous BCR clonotypes at the individual sequence level, the present inventors could find not only the occurrence of CSR but also the accumulation of SHM at degree achievable only after the third injection of COVID-19 vaccine[1] (FIG. **3**B). This finding revealed that the exposure to this common immunogen was not a single event in AD patients sharing these homologous clonotypes.

[0103] Collectively, the above results of the present inventors strongly suggested the existence of common autoantigens persisting inside AD patients provoking concerted humoral immunity.

Example 8—a Highly Shared and Persistent AD Patient-Specific BCR Clonotype Encoded Antibody Reactive to Aβ42 Peptide

[0104] To identify the antigens to which these stereotypic AD patient-specific BCR clonotypes are reactive, we selected twenty most highly shared clonotypes present in four or higher number of patients (FIG. **3**A). We also focused on the persistence of these clonotypes through the two TPs. One clonotype encoded by IGHV3-7/IGHJ1 genes with the CDR3 sequence of VRLAEYFQN were present at both TPs in three patients. And when we allow one amino acid mismatch in CDR3, one more patient (patient ID 34) with the similar clonotype (CDR3 sequence: VRLAEYFQH) at TP1 was found (FIG. **3**A). In 285 PB samples of CG, we could not find any BCR clonotypes encoded by IGHV3-7/IGHJ1 genes and with CDR3 sequences homologous to VRLAEYFQN with amino acid mismatch allowance (FIG. **3**B). The present inventors collected BCR sequences of all clonotypes encoded by IGHV3-7/IGHJ1 and with CDR3 sequences homologous to VRLAEYFQN with one amino acid mismatch allowance (FIG. **3**C). The class switch recombination (CSR) to IgG1 and IgG3 was found in three patients. And the BCR sequences harbored somatic hypermutation (SHM) ranging from 4 to 19 in CDR1, CDR2 and the framework regions. As the occurrence of CSR and accumulation of SHM on these BCR sequences is the hallmark of chronic repeated exposure to antigen[4], there was a possibility for these clonotypes to develop by autoantigen.

[0105] Among these BCRs, the present inventors synthesized four BCR heavy chain genes (Table

6) and used them to construct a single-chain variable fragment (scFv) phage display library using the amplified light chain genes of AD patients (patient ID 6, 14, and 34) possessing IGHV3-7/IGHJ1 VRLAEYFQN clonotype. Then the present inventors performed biopanning of this library on Aβ42 peptide, a well-known autoantigen in AD [2], and could get antigen-reactive scFv clones. When the present inventors expressed these clones as recombinant scFv-human Fc fusion proteins and performed an ELISA, two scFv clones with different k light chains (FIGS. **3**C, and **5**) showed reactivity against the Aβ42 peptide, with half-maximal effective concentrations (EC50) of 48.37 nM and 58.27 nM, respectively (FIG. **3**D).

TABLE-US-00006 TABLE 6 Synthesized BCR heavy chain sequences Se- Con- Somatic quence verged V J C hyper- ID patients Germline_alignment gene gene gene Sequence mutation SNUBH- SNUBH- TGCAGCCTCTGGATTCACCTTTAGTAG IGHV3- IGHJ1 IGHM GAGGTGCAGCTGGTGGAGTCTGGGG 5 34-2- 14- ATATTGGATGAGCTGGGTCCGCCAGG 7*01 *01 *04 GAGGCTTGGTCCAGCCTGGGGGGTC 91969 2|SNUBH- CTCCAGGGAAGGGGCTGGAGTGGGT CCTGAGACTCTCCTGTGCAGCCTCTG 34- GGCCAACATAAAGCAAGATGGAAGT GATTCACCTTTAGTAGATATTGGATGA 2|SNUBH- GACAAATACTATGTGGACTCTGTGAA GCTGGGTCCGCCAGGCTCCAGGGAA 6-2 GGGCCGAGTCACCATCTCCAGAGACA GGGGCTGGAGTGGGTGGCCAACATA ACGCCAAGAACTCACTGTATCTGCAA AAGCAAGATGGAAGTGACAAATACTA ATGAACAGCCTGAGAGCCGAGGACA TGTGGACTCTGTGAAGGGCCGAGTCA CGGCTGTATATTACTGTGTGAG---- CCATCTCCAGAGACAACGCCAAGAAC GCTGAATACTTCCAGCACTGGGGCCA TCACTGTATCTGCAAATGAACAGCCTG GGGCACCCTGGTCACCGTCTCCTCA AGAGCCGAGGACACGGCTGTATATTA (SEQ ID NO: 64) CTGTGTGAGACTCGCTGAATACTTCCA GAACTGGGGCCAGGGCACCCTGGTC ACCGTCTCCTCA (SEQ ID NO: 65) SNUBH- SNUBH- TGCAGCCACTGGATTCGTCTTTAGTCG IGHV3- IGHJ1 IGHG3 GAGGTGCAGCTGGTGGAGTCTGGGG 17 14-2- 14- TTATTGGATGAGTTGGGTCCGCCAGG 7*03 *01 *29 GAGGCTTGGTCCAGCCTGGGGGGTC 24582 2|SNUBH- CTCCAGGGAAGGGGCTGGAGTGGGT CCTGAGACTCTCCTGTGCAGCCACTG 34- GGCCAATTTAAAATATGATGGAAGTG GATTCGTCTTTAGTCGTTATTGGATGA 2|SNUBH- AGAAACACTATGTGGACTCTGTGAAG GTTGGGTCCGCCAGGCTCCAGGGAA 6-2 GGCCGATTCACCATCTCCAGAGACAA GGGGCTGGAGTGGGTGGCCAATTTA CGCCAAGAACTCAGTCTATCTGCAAAT AAATATGATGGAAGTGAGAAACACTA GAACAGCCTGAGAGCCGAGGACACG TGTGGACTCTGTGAAGGGCCGATTCA GCCGTGTATTTCTGTGTAAG---- CCATCTCCAGAGACAACGCCAAGAAC GCTGAATACTTCCAGCACTGGGGCCA TCAGTCTATCTGCAAATGAACAGCCTG GGGCACCCTGGTCACCGTCTCCTCA AGAGCCGAGGACACGGCCGTGTATTT (SEQ ID NO: 66) CTGTGTAAGACTCGCTGAATACTTTCA GAACTGGGGCCAGGGCACCCTAGTC ACCGTCTCCTCA (SEQ ID NO: 67) SNUBH- SNUBH- TGCAGCCTCTGGATTCACCTTTAGTAG IGHV3- IGHJ1 IGHM GAGGTGCAGCTGGTGGAGTCTGGGG 7 14-2- 14- GTTTTGGATGAGTTGGGTCCGCCAGG 7*03 *01 *04 GAGGCTTGGTCCAGCCTGGGGGGTC 24702 2|SNUBH- CTCCAGGGAAGGGGCTGGAGTGGGT CCTGAGACTCTCCTGTGCAGCCTCTG 34- GGCCAACATAAACCAAGATGGAAGTG GATTCACCTTTAGTAGGTTTTGGATGA 2|SNUBH- AGAAATACTATGTGGACTCTGTGAAG GTTGGGTCCGCCAGGCTCCAGGGAA 6-2 GGCCGATTCACCCTCTCCAGAGACAA GGGGCTGGAGTGGGTGGCCAACATA CGCCAAGAACTCACTGTATTTGCAAAT AACCAAGATGGAAGTGAGAAATACTA GAACAGTCTGAGAGCCGAGGACACG TGTGGACTCTGTGAAGGGCCGATTCA

GCCGTGTATTACTGT--------- CCCTCTCCAGAGACAACGCCAAGAAC GCTGAATACTTCCAGCACTGGGGCCA TCACTGTATTTGCAAATGAACAGTCTG GGGCACCCTGGTCACCGTCTCCTCA AGAGCCGAGGACACGGCCGTGTATTA (SEQ ID NO: 68) CTGTGTAAGGCTCGCTGAATACTTCCA GAACTGGGGCCAGGGCACCCTGGTC ACCGTCTCCTCA (SEQ ID NO: 69) SNUBH- SNUBH- TGTAGCCTCTGGATTCACCTTTAGTAG IGHV3- IGHJ1 IGHM GAGGTGCAGCTGGTGGAGTCTGGGG 11 6-2- 14- GTATTGGATGAGCTGGGTCCGCCAGG 7*01 *01 *04 GAGGCTTGGTCCAGCCTGGGGGGTC 27474 2|SNUBH- CTCCAGGGAAGGGGCTGGAGTGGGT CCTGAGACTCTCCTGTGTAGCCTCTGG 34- GGCCAACATAAAGCACGATGGCAGTG ATTCACCTTTAGTAGGTATTGGATGAG 2|SNUBH- AGGAAGACTATGTGGACTCTGTGAAG CTGGGTCCGCCAGGCTCCAGGGAAG 6-2 GGCCGATTCACCCTCTCCAGAGACAG GGGCTGGAGTGGGTGGCCAACATAA CGCCAAGAACTCACTGTATCTGCAAAT AGCACGATGGCAGTGAGGAAGACTAT GAACAGCCTGAGAGTCGAGGACACG GTGGACTCTGTGAAGGGCCGATTCAC GCTATATATTACTGTG-- CCTCTCCAGAGACAGCGCCAAGAACT CGTTTGGCTGAATACTTCCAGCACTG CACTGTATCTGCAAATGAACAGCCTGA GGGCCAGGGCACCCTGGTCACCGTCT GAGTCGAGGACACGGCTATATATTACT CCTCA (SEQ ID NO: 70) GTGTTCGTTTGGCTGAATACTTCCAGA ACTGGGGCCAGGGCACCCTGGTCAC CGTCTCCTCA (SEQ ID NO: 71)

[0106] With this, the present inventors identified BCR clonotypes that are AD specific and convergent among multiple patients using a total of 81 repertoires from 44 patients. Despite the stringent filtering process, both distribution and clonotype cosine similarity of stereotypic group specific clonotypes among Alzheimer patients were significantly increased compared to the repertoires of VC. When it comes to individual clonotypes, among the top 20 highly shared in AD patients, the V3-7/J1 VRLAEYFQN clonotype showed distinct characteristics such as full persistence in all possessing patients, exclusion from VC repertoires even for the extended clonotype, class switching in multiple patients, and a highly diverse mutation profile. Therefore, it was chosen for phage library construction and subsequent bio-panning. As a result, two scFv clones showed binding affinity against the human Aβ42 peptide.

[0107] Through this, it was confirmed that the composition according to one aspect of the present invention has an excellent effect in predicting or diagnosing Alzheimer's disease by simply using peripheral blood mononuclear cells isolated from a subject, in addition to methods such as MRI and PET scans using radioactive substances, by comprising a detecting agent of a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient.

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Claims

1. A composition for predicting or diagnosing Alzheimer's disease, comprising a detecting agent of a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient in a sample of a subject, wherein the BCR clonotype comprises the V gene; and the J gene; and an amino acid sequence of complementary determining region 3 (CDR3) of the heavy chain of the BCR.

2. The composition according to claim 1, wherein when the BCR clonotype detected from the sample of the subject is below i) to iii), the subject is predicted or diagnosed as having Alzheimer's disease: i) the V gene is at least one selected from the group consisting of IGHV (Immunoglobulin Heavy Variable) 1-18, IGHV1-2, IGHV1-24, IGHV1-3, IGHV1-46, IGHV1-58, IGHV1-69, IGHV1-8, IGHV2-26, IGHV2-5, IGHV2-70, IGHV3-11, IGHV3-13, IGHV3-15, IGHV3-20, IGHV3-21, IGHV3-23, IGHV3-30, IGHV3-30-3, IGHV3-33, IGHV3-43, IGHV3-43D, IGHV3-48, IGHV3-49, IGHV3-53, IGHV3-64, IGHV3-64D, IGHV3-66, IGHV3-7, IGHV3-72, IGHV3-73, IGHV3-74, IGHV3-9, IGHV4-30-2, IGHV4-30-4, IGHV4-31, IGHV4-34, IGHV4-38-2, IGHV4-39, IGHV4-4, IGHV4-59, IGHV4-61, IGHV5-10-1, IGHV5-51, IGHV6-1, and IGHV7-4-1, ii) the J gene in the BCR clonotype detected from a sample of the subject is at least one selected from the group consisting of IGHJ (Immunoglobulin Heavy Joining) 1, IGHJ2, IGHJ3, IGHJ4, IGHJ5, and IGHJ6, and iii) the amino acid sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group

consisting of SEQ ID NOS: 72 to 4047, and 32396.

3. The composition according to claim 1, wherein when the BCR clonotype detected from the sample of the subject is at least one of BCR clonotypes of the V gene; the J gene; and the amino acid sequence of CDR3, the subject is predicted or diagnosed as having Alzheimer's disease:

4. The composition according to claim 1, wherein the detecting agent of a BCR clonotype is a detecting agent of the entire amino acid sequence of the BCR clonotype, comprising an amino acid sequence encoded from the V gene of the heavy chain of the BCR; an amino acid sequence encoded from the J gene of the heavy chain of the BCR; and an amino acid sequence of CDR3 of the heavy chain of the BCR, and wherein the composition is a composition that when the entire amino acid sequence of the BCR clonotype detected from the sample of the subject is at least one of SEQ ID NOS: 18222 to 32395, the subject is predicted or diagnosed as having Alzheimer's disease.

5. The composition according to claim 1, wherein the detecting agent of a BCR clonotype is a detecting agent of the entire nucleic acid sequence of the BCR clonotype, comprising a nucleic acid sequence of the V gene of the heavy chain of the BCR; a nucleic acid sequence of the J gene of the heavy chain of the BCR; and a nucleic acid sequence encoding CDR3 of the heavy chain of the BCR, and wherein the composition is a composition that when the entire nucleic acid sequence of the BCR clonotype detected from the sample of the subject is at least one of SEQ ID NOS: 4048 to 18221, the subject is predicted or diagnosed as having Alzheimer's disease.

6. The composition according to claim 2, wherein when the amino acid sequence of CDR3 in the BCR clonotype detected from the sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of ARDLPATGAFDI (SEQ ID NO: 214), VRLAEYFQN (SEQ ID NO: 875), TRDRRGWD (SEQ ID NO: 1211), ALGRGMDV (SEQ ID NO: 1048), VLRGSAFDI (SEQ ID NO: 798), ARSGGLDP (SEQ ID NO: 668), AGGRSFDY (SEQ ID NO: 613), AGNLMDV (SEQ ID NO: 2257), ARRGEY (SEQ ID NO: 2070), ARDMFRGIPDYLDY (SEQ ID NO: 1988), AKSLGSGTYSFDY (SEQ ID NO: 1326), ARNAGLDY (SEQ ID NO: 1128), ARDDGYRSIDY (SEQ ID NO: 990), VRGGGSGWPFES (SEQ ID NO: 3709), SRGRDGIG (SEQ ID NO: 2815), ARSGGLDV (SEQ ID NO: 2415), ARSRSGSYYYGMDV (SEQ ID NO: 1198), AGDWNDDDIFDY (SEQ ID NO: 32396), ARKGEQLWHY (SEQ ID NO: 965), and ARDPIAVPGLFDY (SEQ ID NO: 347) the subject is predicted or diagnosed as having Alzheimer's disease.

7. The composition according to claim 1, wherein the detecting agent comprises a detecting agent of a protein specific to the BCR clonotype or a detecting agent of a nucleic acid encoding the protein.

8. The composition according to claim 7, wherein the detecting agent of a protein comprises an antibody or aptamer specific to the BCR clonotype.

9. The composition according to claim 7, wherein the detecting agent of a nucleic acid comprises at least one selected from the group consisting of antisense oligonucleotide, primer pair, probe, and polynucleotide that specifically binds to a mRNA or DNA encoding the BCR clonotype.

10. A system for predicting or diagnosing Alzheimer's disease comprising the composition according to claim 1.

11. A method for providing information for predicting or diagnosing Alzheimer's disease comprising: detecting a B cell receptor (BCR) clonotype specific to an Alzheimer's disease patient in a sample of a subject, wherein the BCR clonotype comprises the V gene; and the J gene; and an amino acid sequence of complementary determining region 3 (CDR3) of the heavy chain of the BCR.

12. The method for providing information according to claim 11, further comprising predicting or diagnosing the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is below i) to iii): i) the V gene is at least one selected from the group consisting of IGHV (Immunoglobulin Heavy Variable) 1-18, IGHV1-2, IGHV1-24, IGHV1-3,

IGHV1-46, IGHV1-58, IGHV1-69, IGHV1-8, IGHV2-26, IGHV2-5, IGHV2-70, IGHV3-11, IGHV3-13, IGHV3-15, IGHV3-20, IGHV3-21, IGHV3-23, IGHV3-30, IGHV3-30-3, IGHV3-33, IGHV3-43, IGHV3-43D, IGHV3-48, IGHV3-49, IGHV3-53, IGHV3-64, IGHV3-64D, IGHV3-66, IGHV3-7, IGHV3-72, IGHV3-73, IGHV3-74, IGHV3-9, IGHV4-30-2, IGHV4-30-4, IGHV4-31, IGHV4-34, IGHV4-38-2, IGHV4-39, IGHV4-4, IGHV4-59, IGHV4-61, IGHV5-10-1, IGHV5-51, IGHV6-1, and IGHV7-4-1, ii) the J gene in the BCR clonotype detected from a sample of the subject is at least one selected from the group consisting of IGHJ (Immunoglobulin Heavy Joining) 1, IGHJ2, IGHJ3, IGHJ4, IGHJ5, and IGHJ6, and iii) the amino acid sequence of CDR3 in the BCR clonotype detected from a sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of SEQ ID NOs: 72 to 4047, and 32396.

13. The method for providing information according to claim 11, further comprising predicting or diagnosing the subject as having Alzheimer's disease when the BCR clonotype detected from the sample of the subject is at least one of BCR clonotypes of the V gene; the J gene; and the amino acid sequence of CDR3.

14. The method for providing information according to claim 11, further comprising predicting or diagnosing the subject as having Alzheimer's disease when the entire amino acid sequence of the BCR clonotype detected from the sample of the subject which comprises an amino acid sequence of the V gene of the heavy chain of the BCR; an amino acid sequence of the J gene of the heavy chain of the BCR; and an amino acid sequence of CDR3 of the heavy chain of the BCR is at least one of SEQ ID NOS: 18222 to 32395.

15. The method for providing information according to claim 11, further comprising predicting or diagnosing the subject as having Alzheimer's disease when the entire nucleic acid sequence of the BCR clonotype detected from the sample of the subject is at least one of SEQ ID NOS: 4048 to 18221 detected from the sample of the subject which comprises a nucleic acid sequence of the V gene of the heavy chain of the BCR; a nucleic acid sequence of the J gene of the heavy chain of the BCR; and a nucleic acid sequence encoding CDR3 of the heavy chain of the BCR.

16. The method for providing information according to claim 12, further comprising predicting or diagnosing the subject as having Alzheimer's disease when the amino acid sequence of CDR3 in the BCR clonotype detected from the sample of the subject is 80 to 100% homologous to at least one selected from the group consisting of ARDLPATGAFDI (SEQ ID NO: 214), VRLAEYFQN (SEQ ID NO: 875), TRDRRGWD (SEQ ID NO: 1211), ALGRGMDV (SEQ ID NO: 1048), VLRGSAFDI (SEQ ID NO: 798), ARSGGLDP (SEQ ID NO: 668), AGGRSFDY (SEQ ID NO: 613), AGNLMDV (SEQ ID NO: 2257), ARRGEY (SEQ ID NO: 2070), ARDMFRGIPDYLDY (SEQ ID NO: 1988), AKSLGSGTYSFDY (SEQ ID NO: 1326), ARNAGLDY (SEQ ID NO: 1128), ARDDGYRSIDY (SEQ ID NO: 990), VRGGGSGWPFES (SEQ ID NO: 3709), SRGRDGIG (SEQ ID NO: 2815), ARSGGLDV (SEQ ID NO: 2415), ARSRSGSYYYGMDV (SEQ ID NO: 1198), AGDWNDDDIFDY (SEQ ID NO: 32396), ARKGEQLWHY (SEQ ID NO: 965), and ARDPIAVPGLFDY (SEQ ID NO: 347).