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(54) **NOVEL BIOMARKERS FOR COGNITIVE IMPAIRMENT AND METHODS FOR DETECTING COGNITIVE IMPAIRMENT USING SUCH BIOMARKERS**

(71) Applicant: **MCBI INC.**, Tsukuba-shi (JP)

(72) Inventors: **Kazuhiko UCHIDA**, Tsukuba-shi (JP); **Kohji MENO**, Tsukuba-shi (JP); **Hideaki SUZUKI**, Tsukuba-shi (JP)

(73) Assignee: **MCBI INC.**, Tsukuba-shi (JP)

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(57) **ABSTRACT**

The present invention aims to provide methods to detect cognitive impairment including mild cognitive impairment and Alzheimer disease by using a protein or its partial peptide that differs in presence or absence, or in quantity between non-cognitive impairment and patients with cognitive impairment and further aims to present biomarkers comprising said protein and said partial peptide to be used to detect cognitive impairment including Alzheimer disease or mild cognitive impairment. Specifically, a biomarker for diagnosis of psychiatry disease or cognitive impairment comprising protein fragment or peptide of not less than 5 amino acid residues arising from at least one protein or peptide selected from the group of proteins consisting of amino acid sequence expressed by SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25 and selected from the group of partial peptide in these proteins consisting of amino acid sequence expressed by SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 27. And further aims to provide diagnostic method using these biomarker.

FIG.1

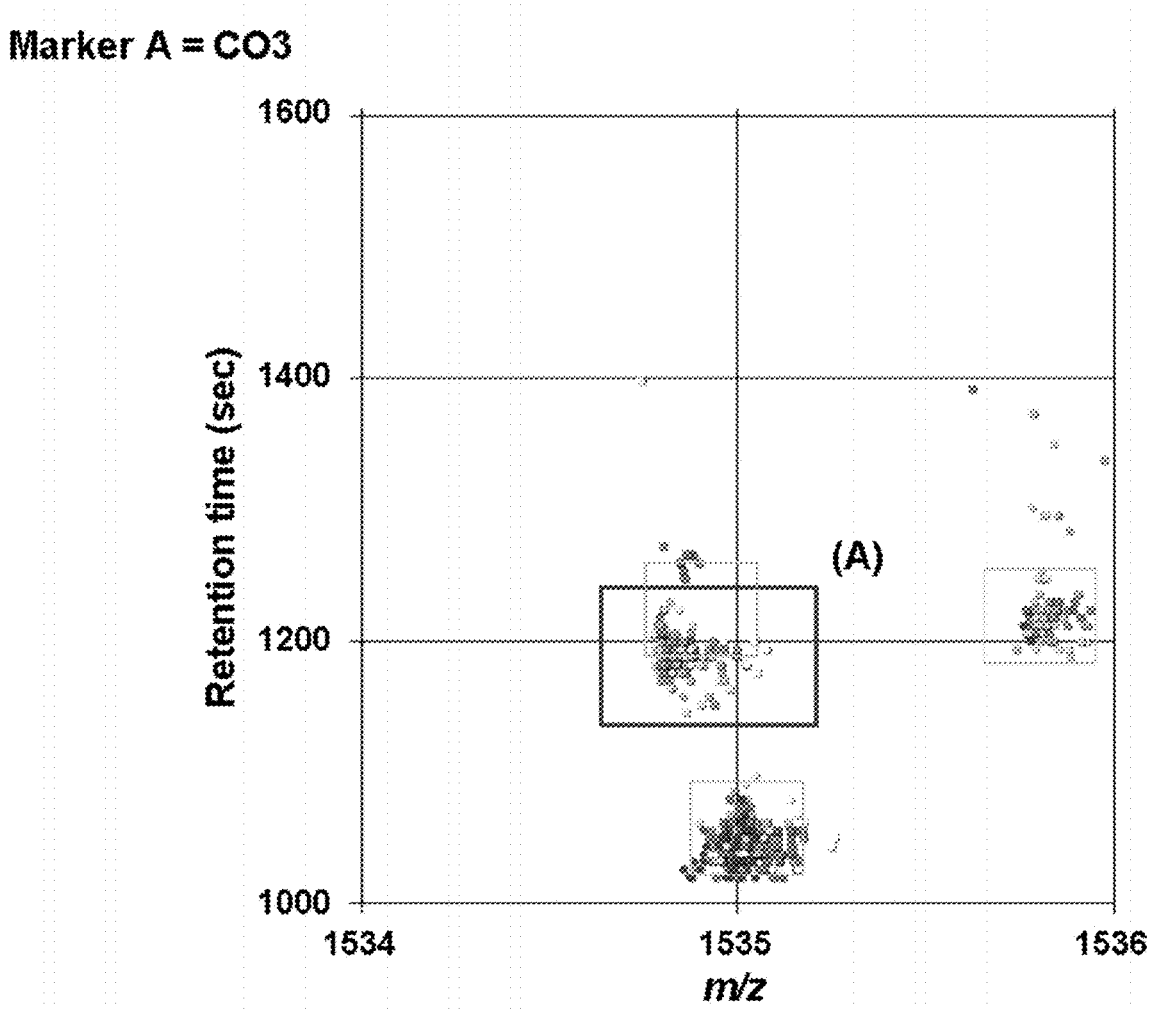

Marker A = CO3
1600
1400
1200
1000
Retention time (sec)
(A)
1534
1535
1536
m/z

FIG.2

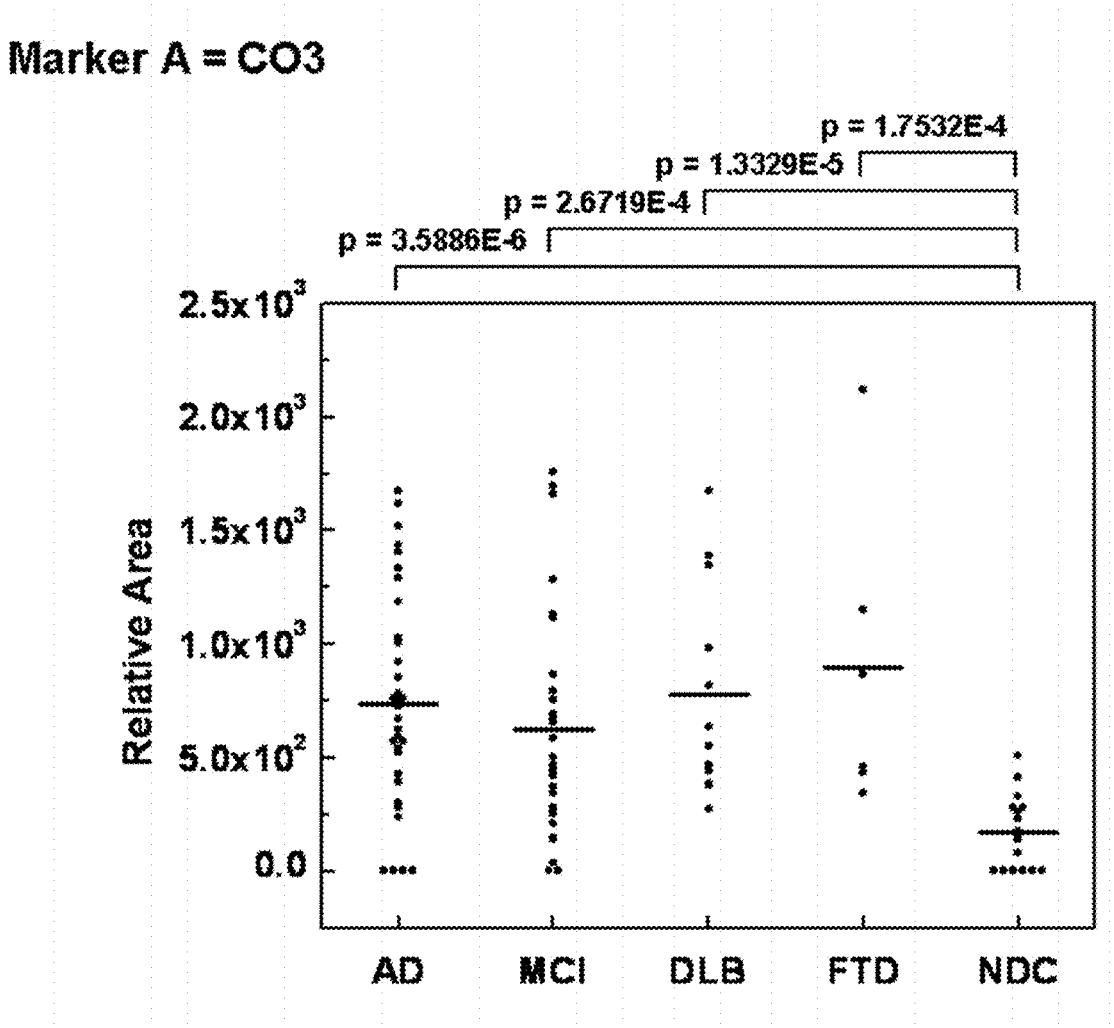

Marker A = CO3
p = 1.7532E-4
p = 1.3329E-5
p = 2.6719E-4
p = 3.5886E-6
2.5x10^3
2.0x10^3
1.5x10^3
1.0x10^3
5.0x10^2
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.3

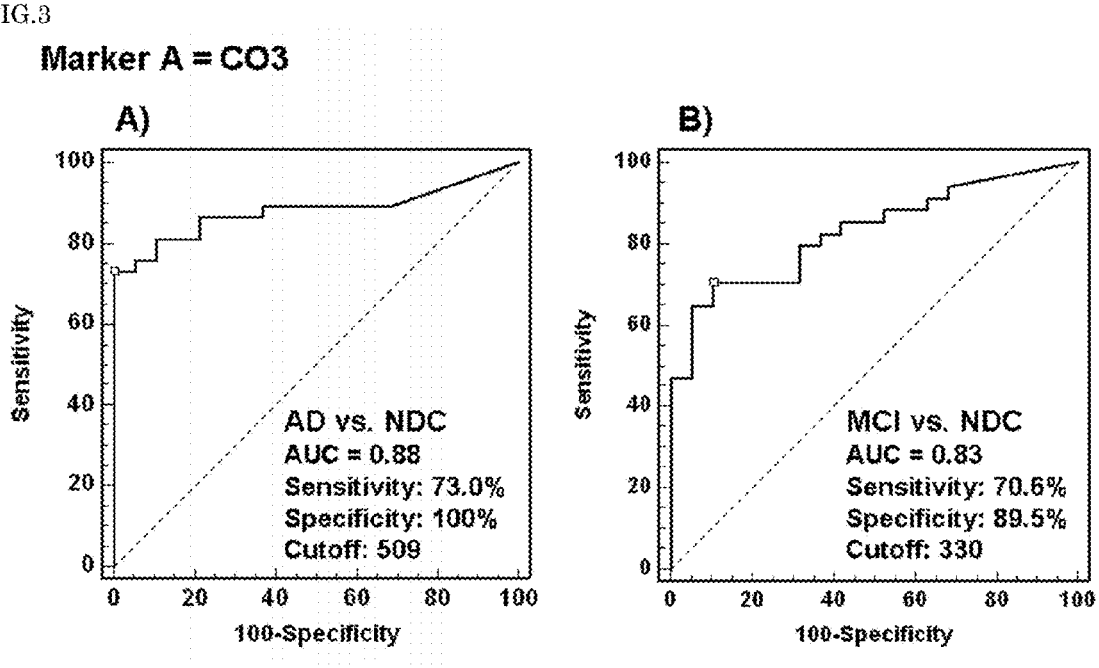

Marker A = CO3
A)
Sensitivity
100-Specificity
AD vs. NDC
AUC = 0.88
Sensitivity: 73.0%
Specificity: 100%
Cutoff: 509
B)
Sensitivity
100-Specificity
MCI vs. NDC
AUC = 0.83
Sensitivity: 70.6%
Specificity: 89.5%
Cutoff: 330

FIG.4

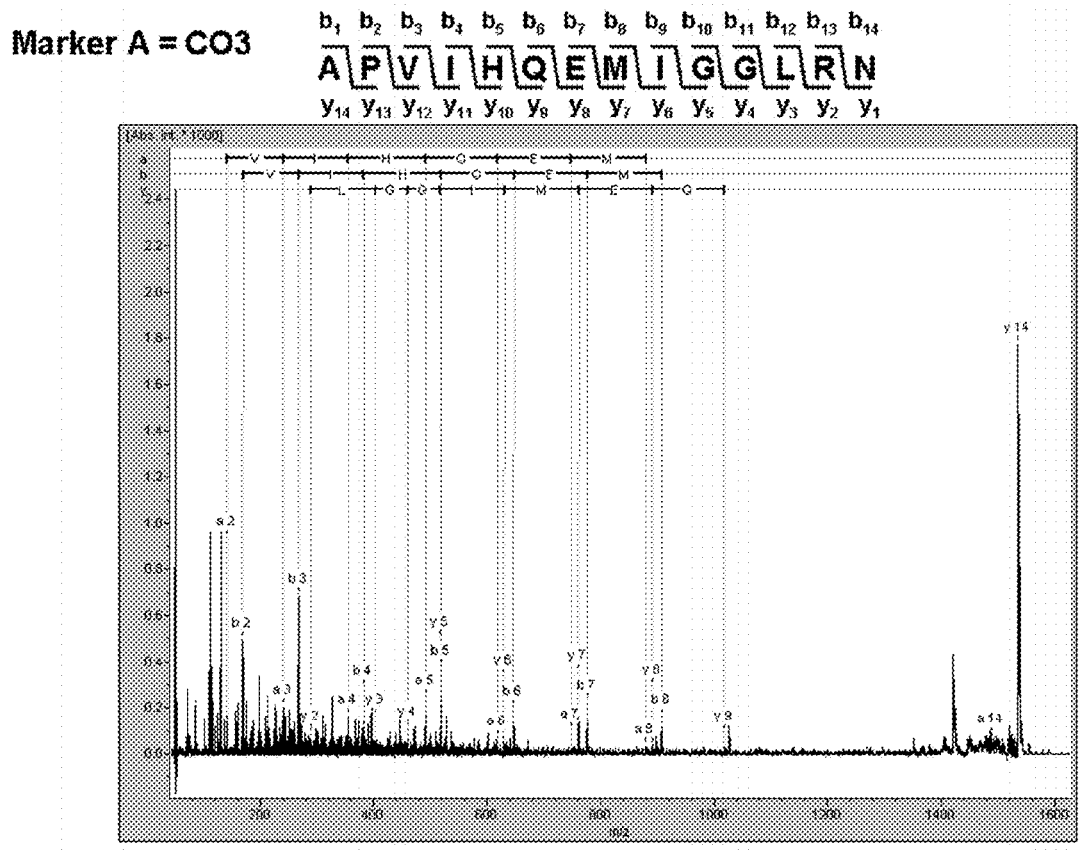

Marker A = CO3
b1 b2 b3 b4 b5 b6 b7 b8 b9 b10 b11 b12 b13 b14
A P V I H Q E M I G G L R N
y14 y13 y12 y11 y10 y9 y8 y7 y6 y5 y4 y3 y2 y1
y14
b2
b3
y5
b5
b4
y6
b6
y7
b7
b8
y8
y9
a14
m/z

FIG.5

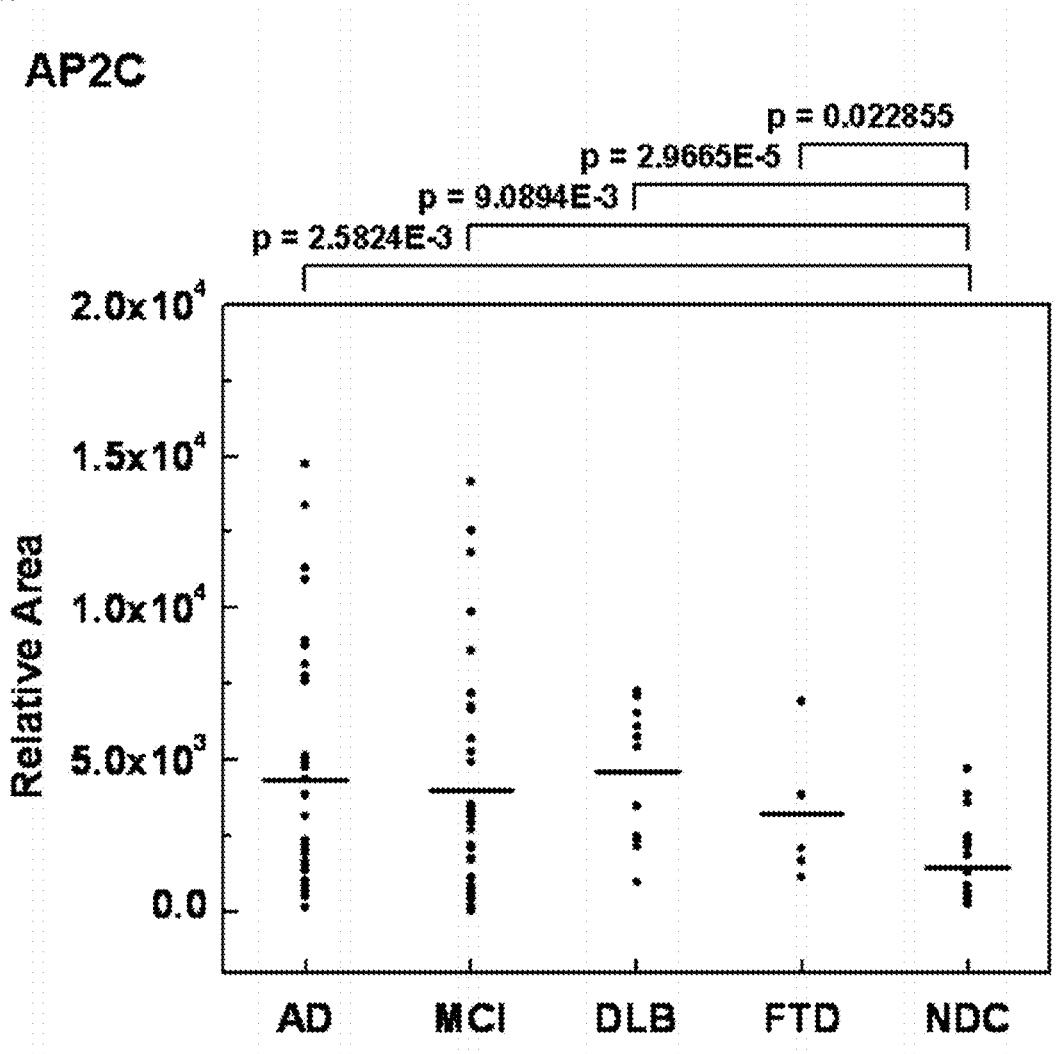

AP2C
p = 0.022855
p = 2.9665E-5
p = 9.0894E-3
p = 2.5824E-3
2.0x10^4
1.5x10^4
1.0x10^4
5.0x10^3
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.6

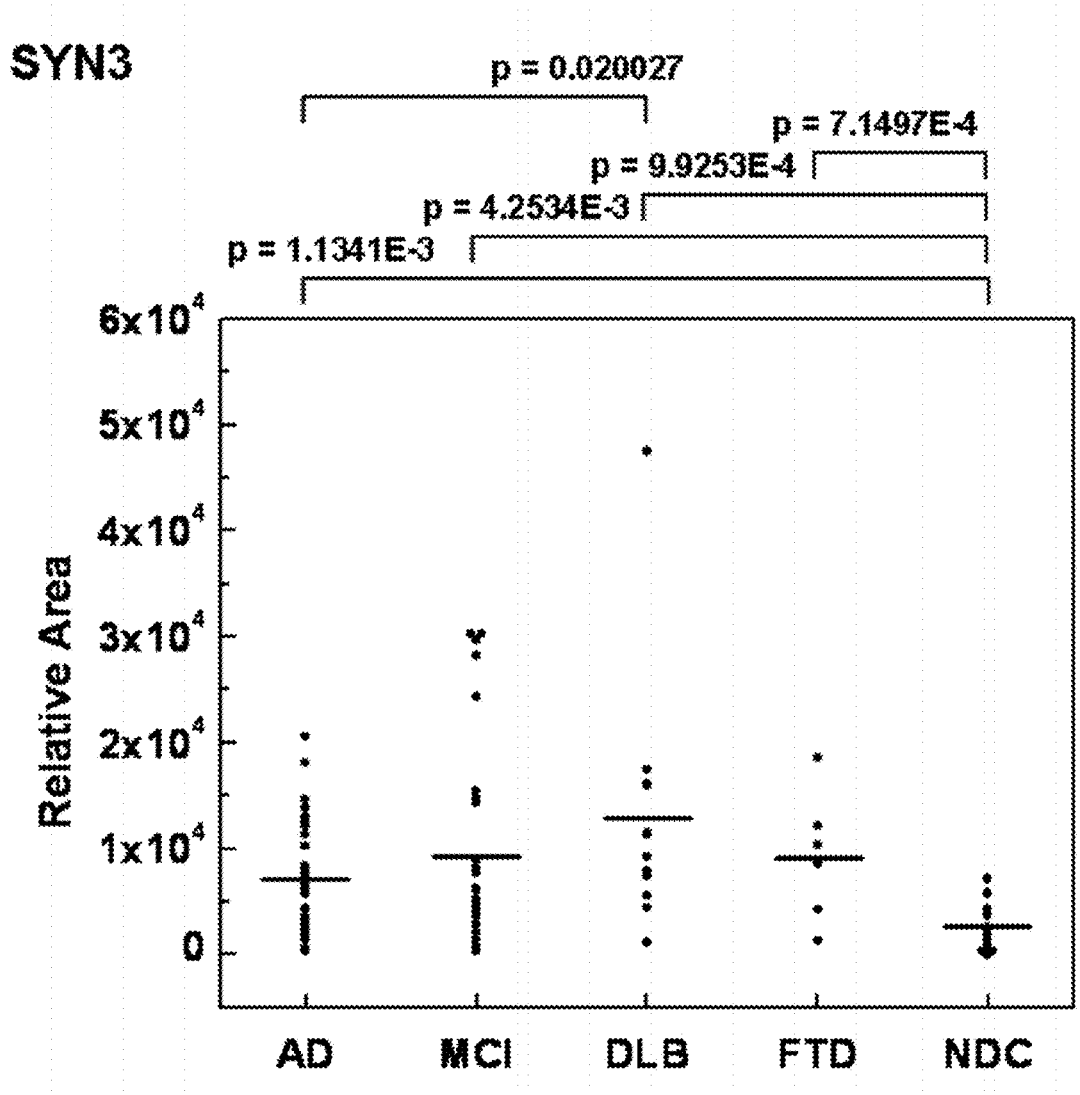

SYN3
p = 0.020027
p = 7.1497E-4
p = 9.9253E-4
p = 4.2534E-3
p = 1.1341E-3
Relative Area
6x10^4
5x10^4
4x10^4
3x10^4
2x10^4
1x10^4
0
AD
MCI
DLB
FTD
NDC

FIG.7

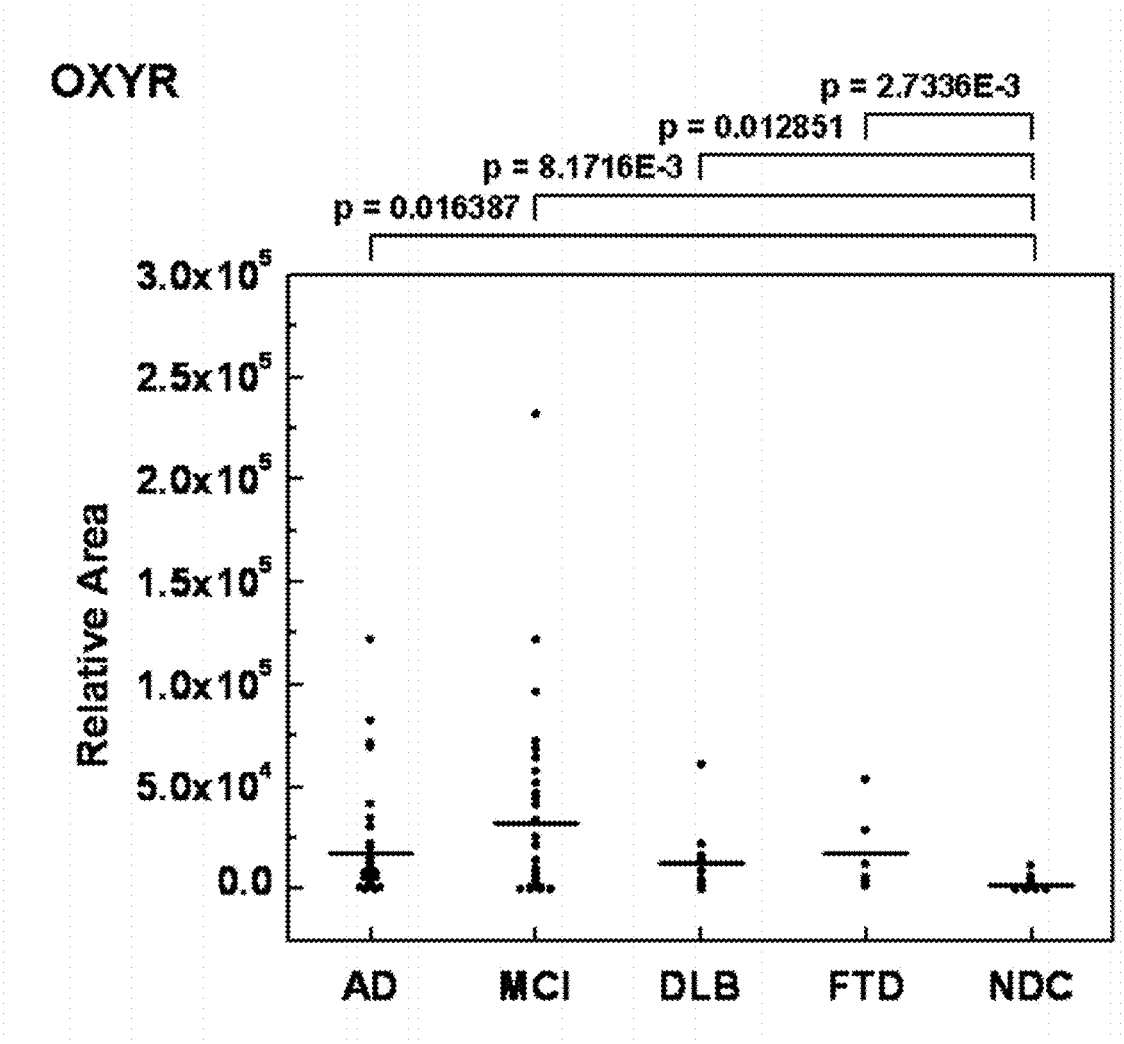

OXYR
p = 2.7336E-3
p = 0.012851
p = 8.1716E-3
p = 0.016387
3.0x10^5
2.5x10^5
2.0x10^5
1.5x10^5
1.0x10^5
5.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.8

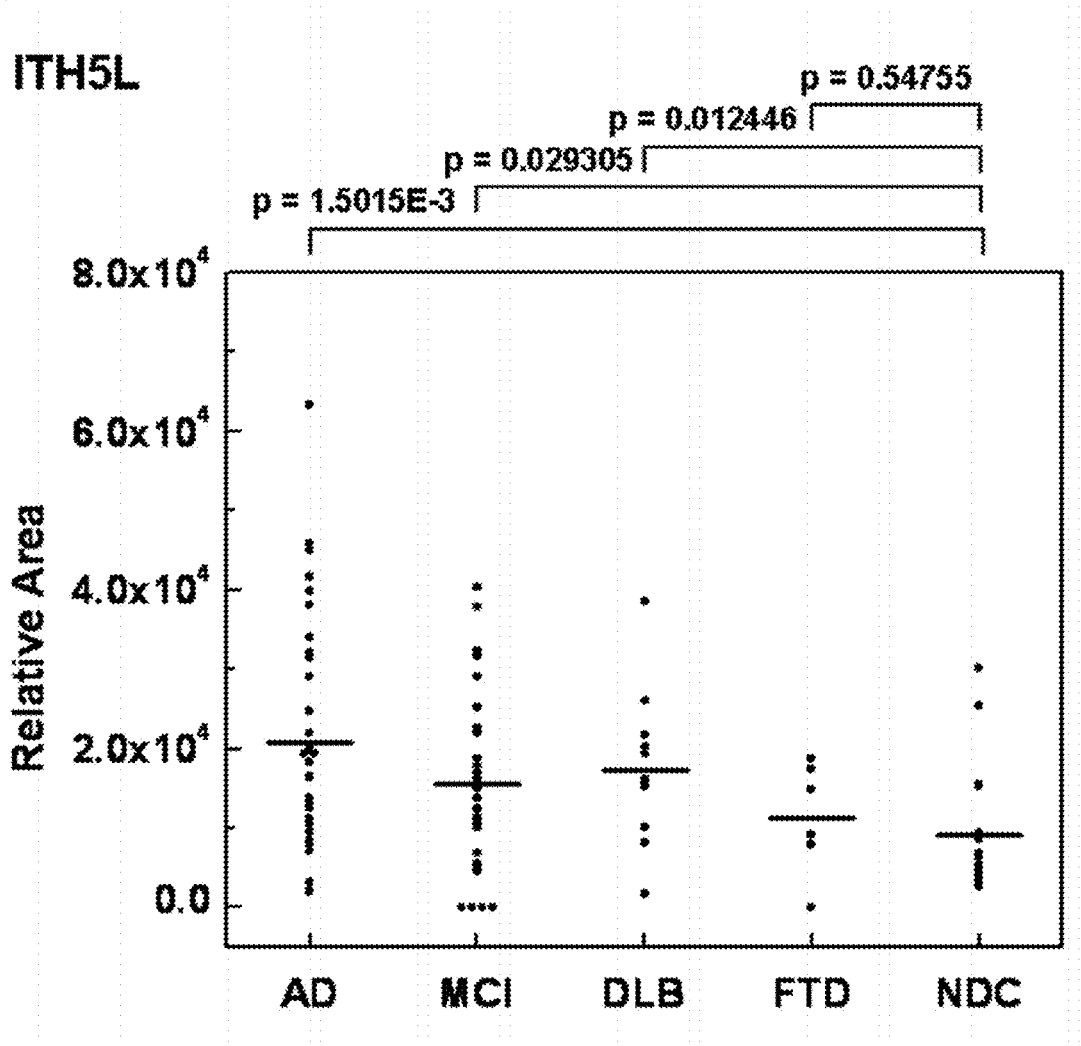

ITH5L
p = 0.54755
p = 0.012446
p = 0.029305
p = 1.5015E-3
8.0x10^4
6.0x10^4
4.0x10^4
2.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.9

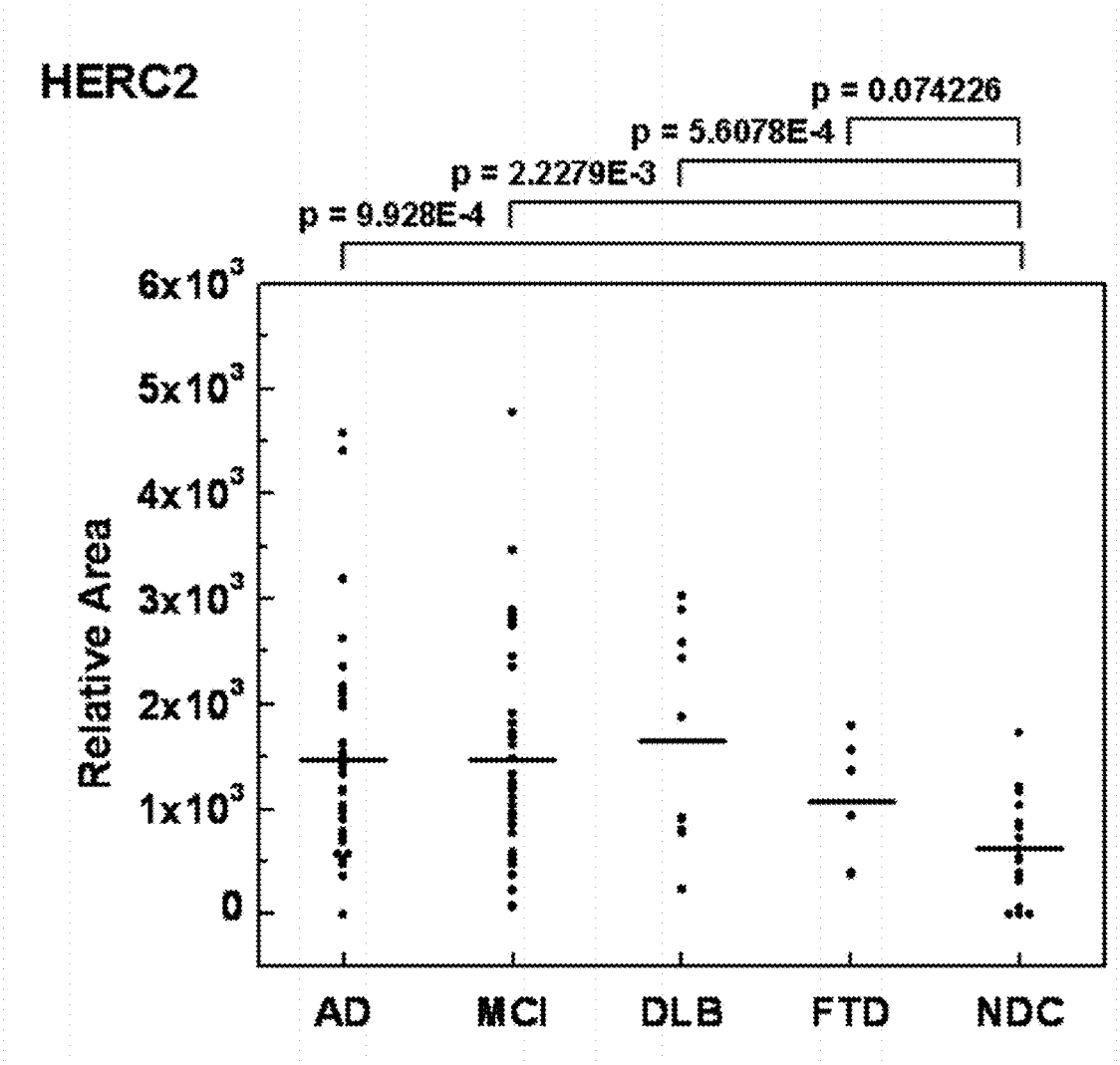

HERC2
p = 0.074226
p = 5.6078E-4
p = 2.2279E-3
p = 9.928E-4
6x10^3
5x10^3
4x10^3
3x10^3
2x10^3
1x10^3
0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.10

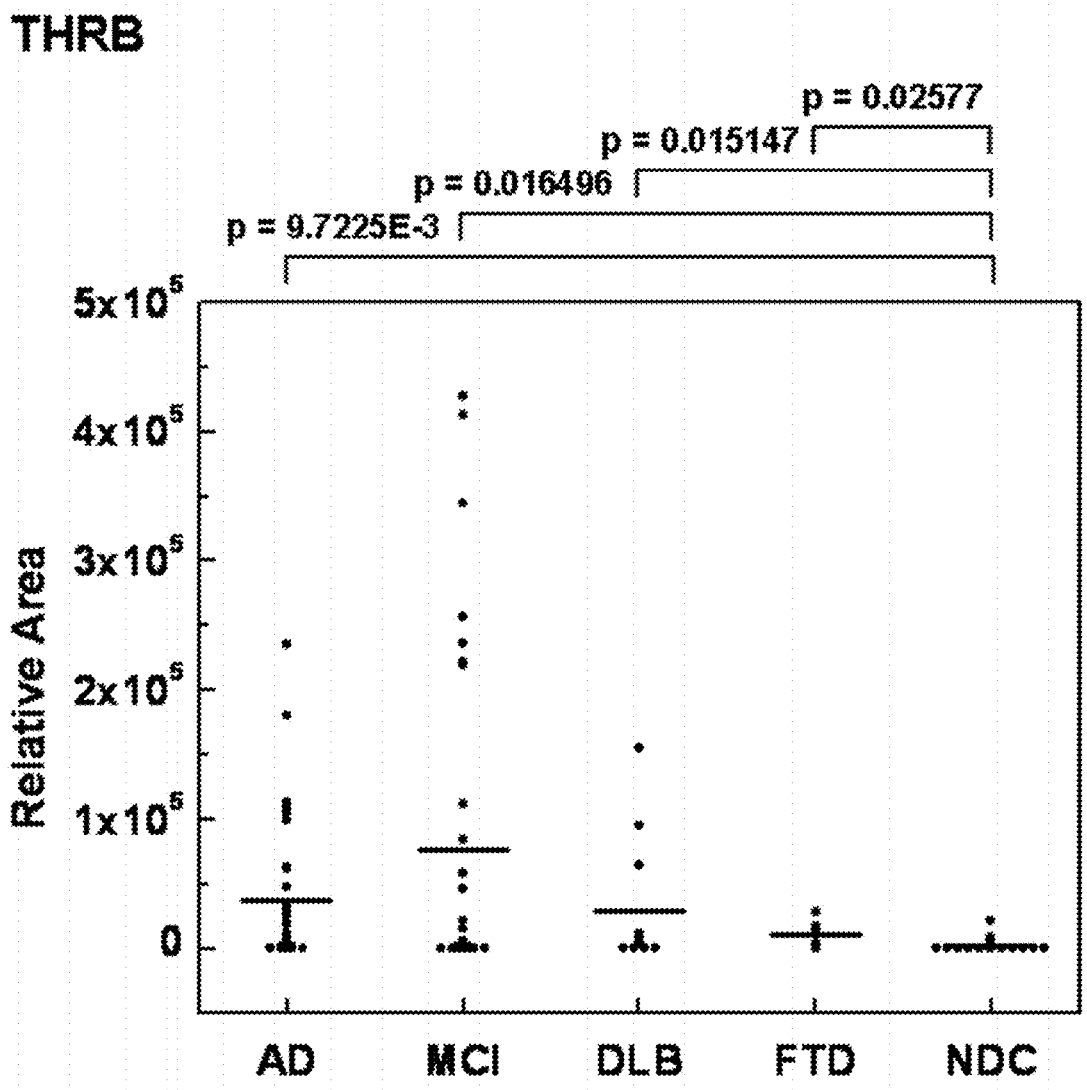

THRB
p = 0.02577
p = 0.015147
p = 0.016496
p = 9.7225E-3
Relative Area
5x10^5
4x10^5
3x10^5
2x10^5
1x10^5
0
AD
MCI
DLB
FTD
NDC

FIG.11

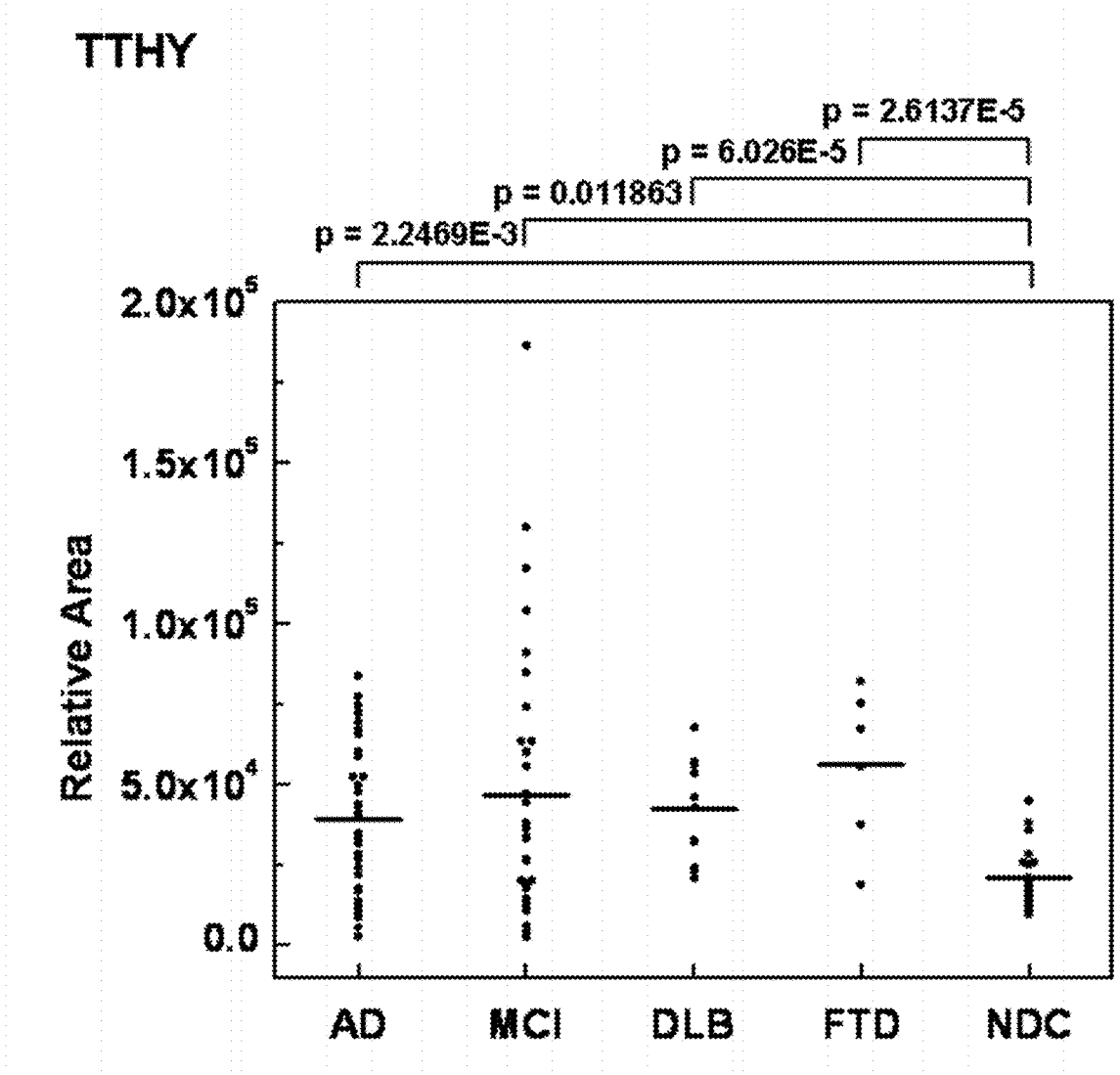

TTHY
p = 2.6137E-5
p = 6.026E-5
p = 0.011863
p = 2.2469E-3
2.0x10^5
1.5x10^5
1.0x10^5
5.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.12

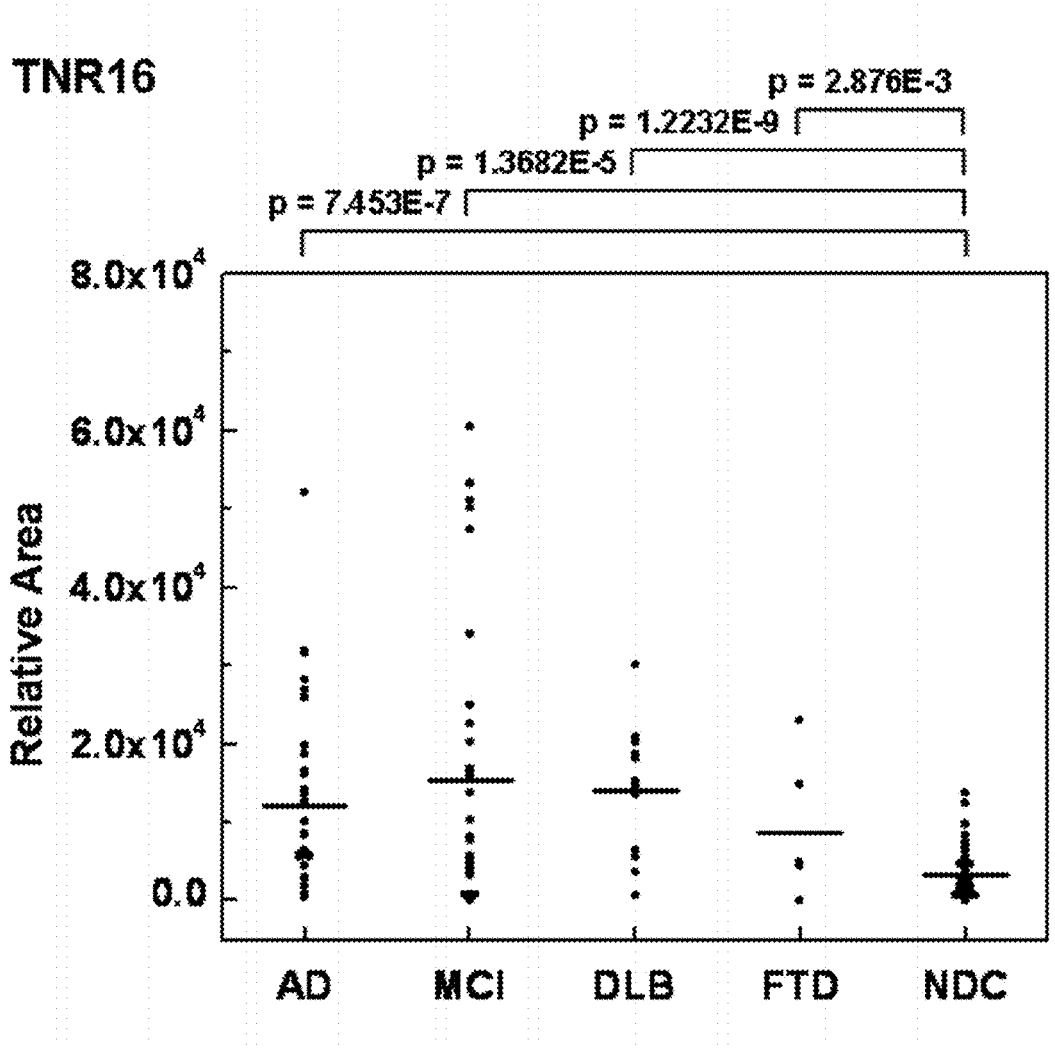

TNR16
p = 2.876E-3
p = 1.2232E-9
p = 1.3682E-5
p = 7.453E-7
8.0x10^4
6.0x10^4
4.0x10^4
2.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.13

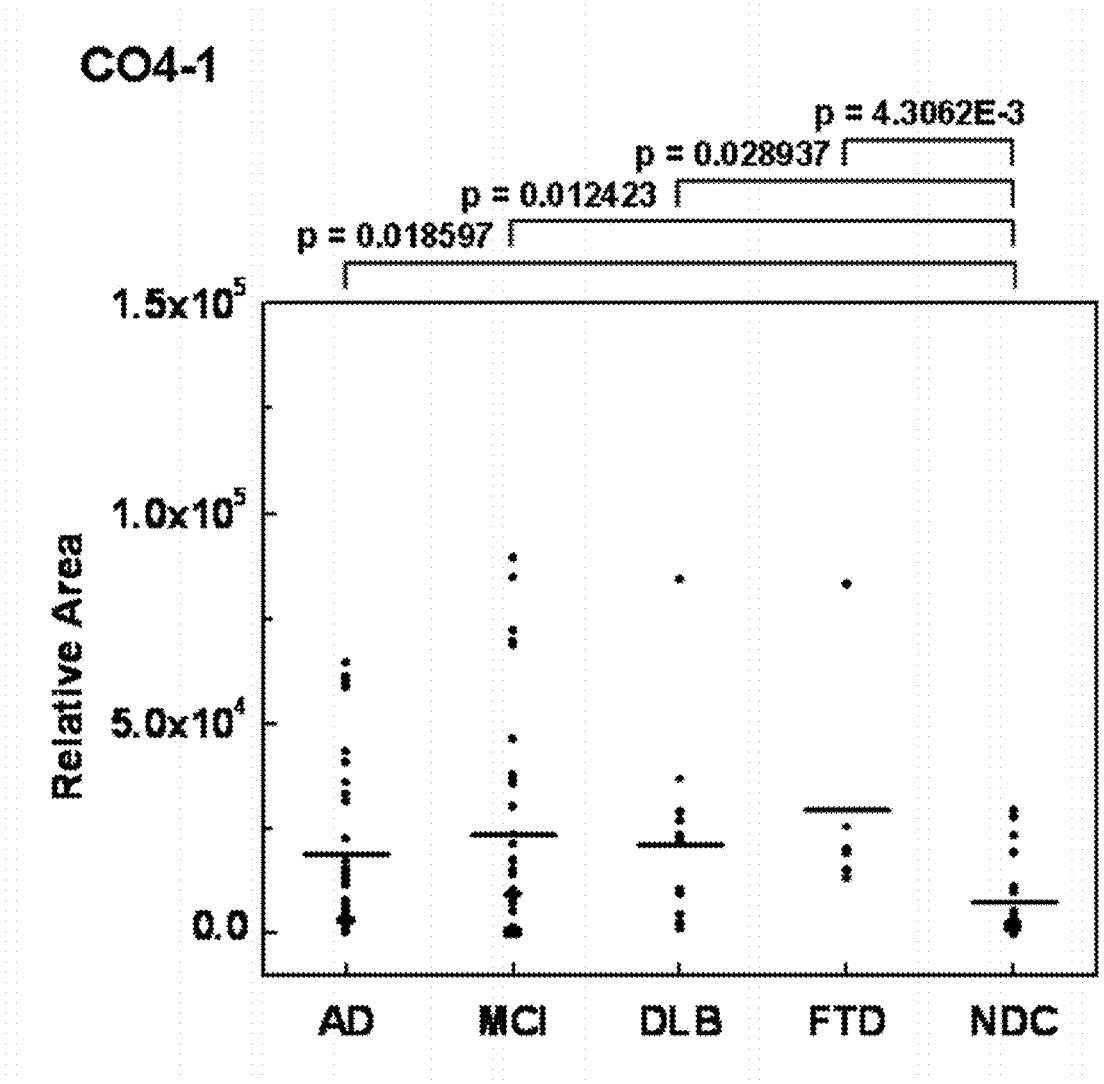

CO4-1
p = 4.3062E-3
p = 0.028937
p = 0.012423
p = 0.018597
1.5x10^5
1.0x10^5
5.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.14

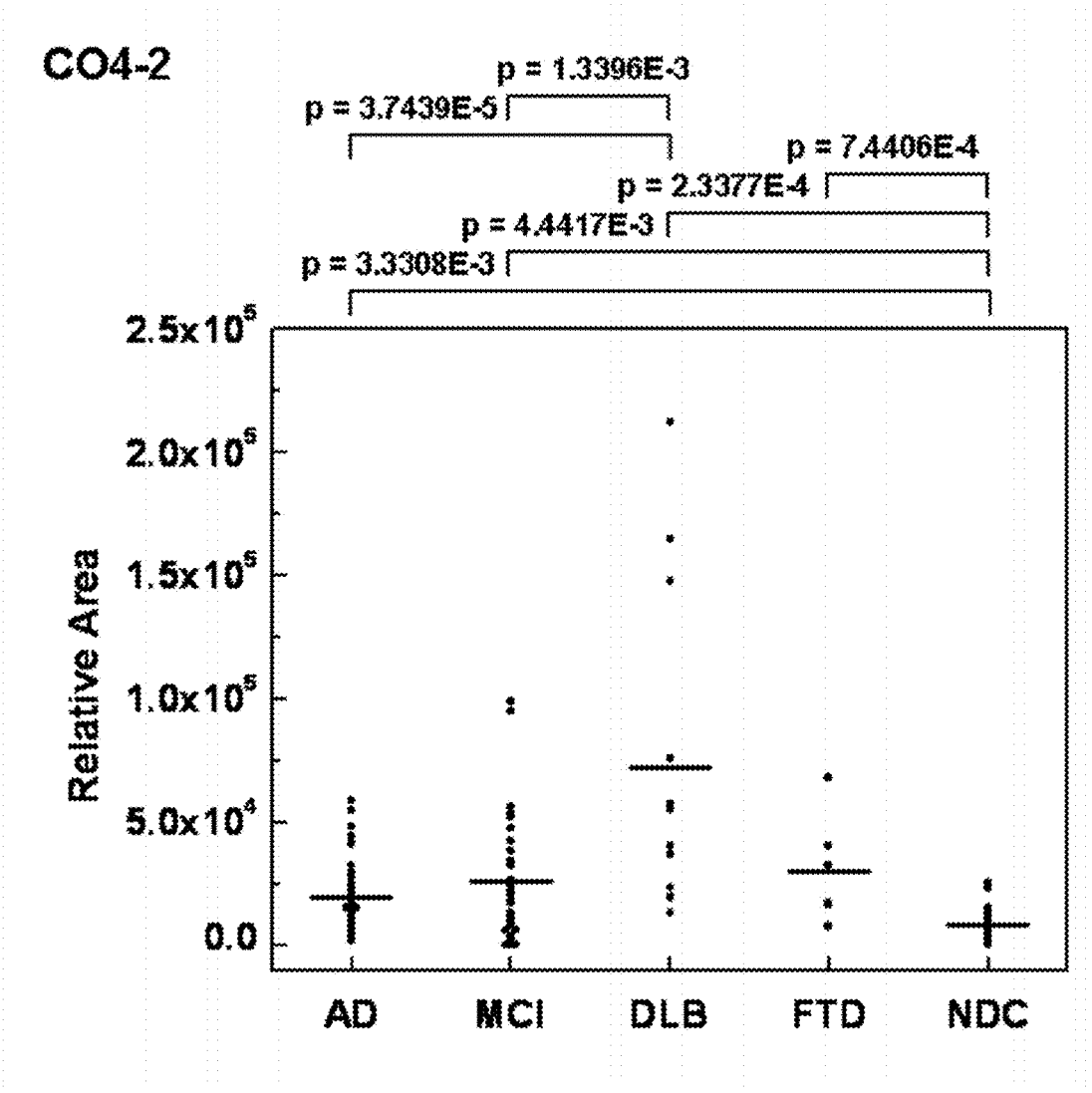

CO4-2
p = 1.3396E-3
p = 3.7439E-5
p = 7.4406E-4
p = 2.3377E-4
p = 4.4417E-3
p = 3.3308E-3
2.5x10^5
2.0x10^5
1.5x10^5
1.0x10^5
5.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.15

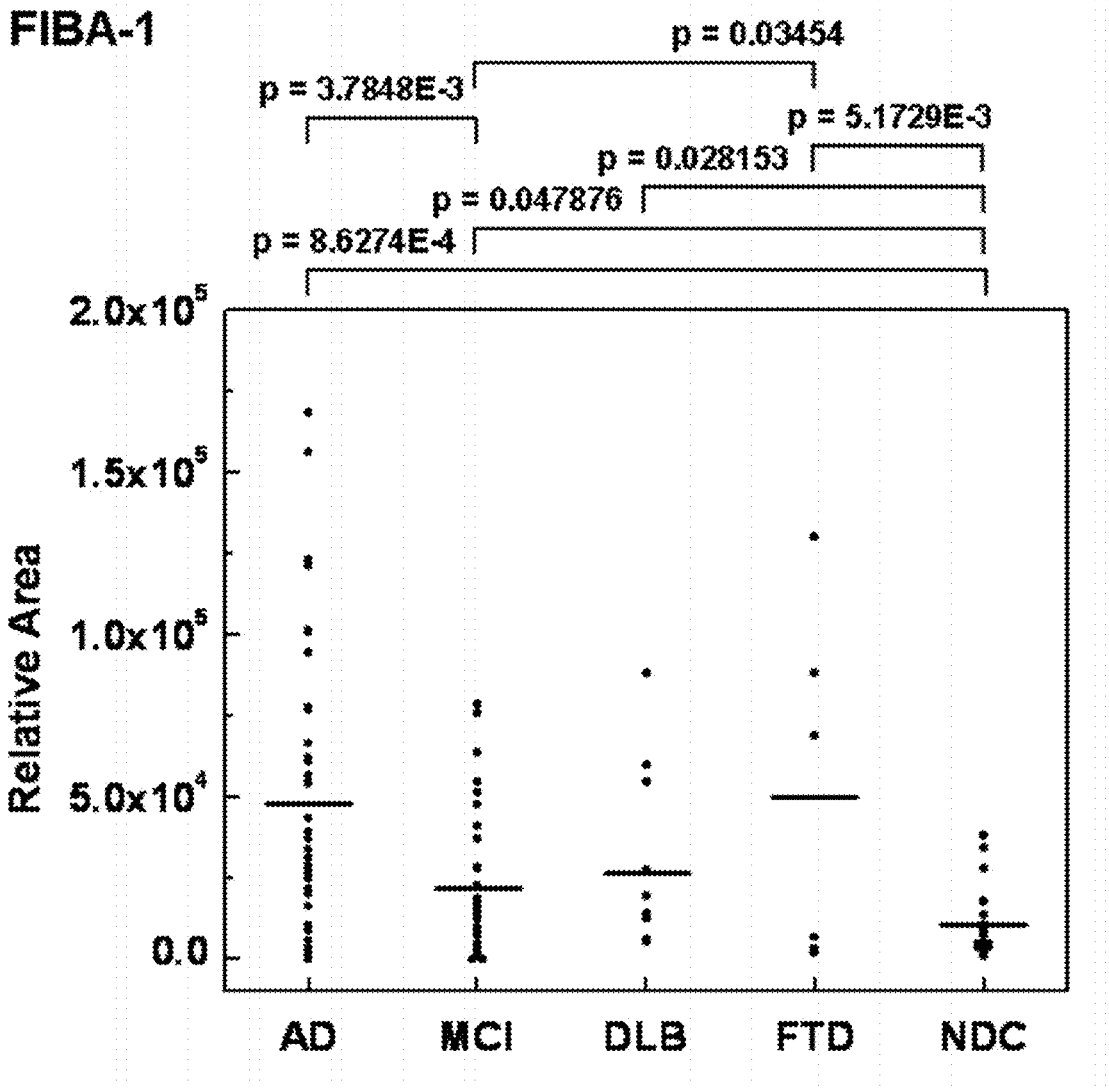

FIBA-1
p = 0.03454
p = 3.7848E-3
p = 5.1729E-3
p = 0.028153
p = 0.047876
p = 8.6274E-4
2.0x10^5
1.5x10^5
1.0x10^5
5.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.16

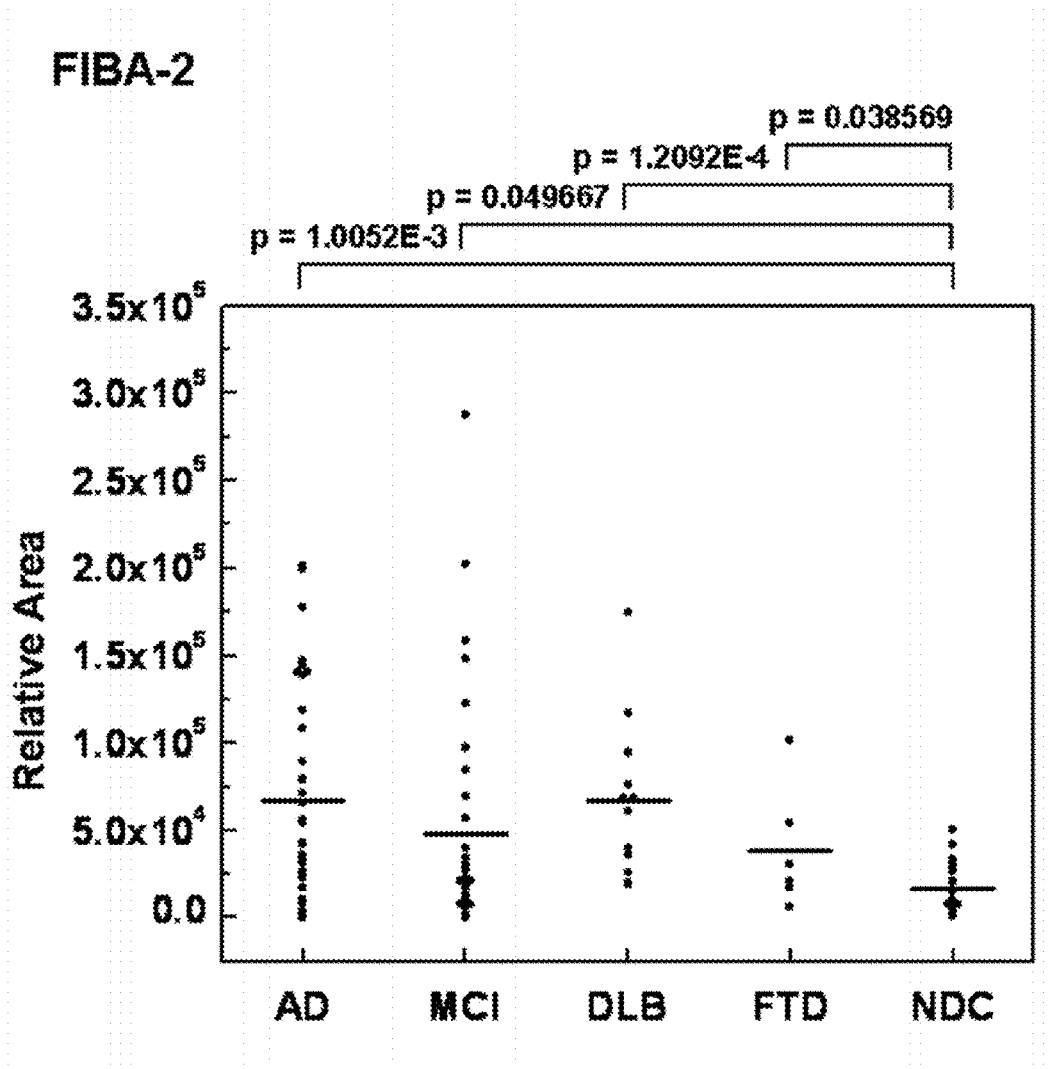
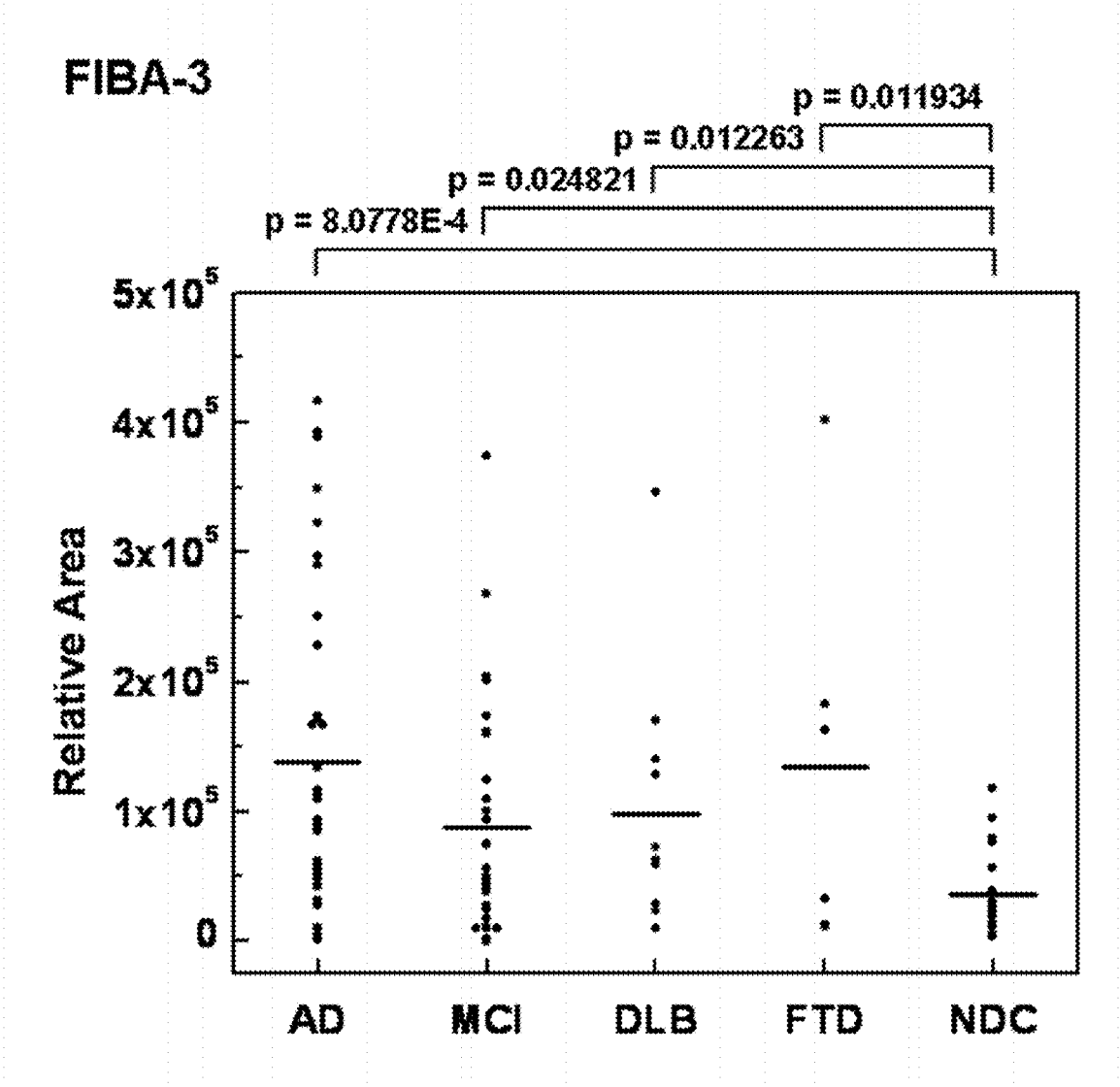

FIBA-2
p = 0.038569
p = 1.2092E-4
p = 0.049667
p = 1.0052E-3
3.5x10^5
3.0x10^5
2.5x10^5
2.0x10^5
1.5x10^5
1.0x10^5
5.0x10^4
0.0
Relative Area
AD
MCI
DLB
FTD
NDC

FIG.17


FIBA-3
p = 0.011934
p = 0.012263
p = 0.024821
p = 8.0778E-4
5x10^5
4x10^5
3x10^5
2x10^5
1x10^5
0
Relative Area
AD
MCI
DLB
FTD
NDC

NOVEL BIOMARKERS FOR COGNITIVE IMPAIRMENT AND METHODS FOR DETECTING COGNITIVE IMPAIRMENT USING SUCH BIOMARKERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of copending application Ser. No. 15/467,646, filed on Mar. 23, 2017, which is a Continuation of Ser. No. 14/582,778, filed on Dec. 24, 2014, which is a Continuation of Application No. 13/995,682, filed on Sep. 3, 2013 (now abandoned), which was filed as PCT International Application No. PCT/JP2011/007150 on Dec. 21, 2011, which claims the benefit under 35 U.S.C. §119(a) to Patent Application No. 2010-285726, filed in JAPAN on Dec. 22, 2010, all of which are hereby expressly incorporated by reference into the present application.

FIELD OF THE INVENTION

[0002] The present invention relates to novel biomarkers for mild cognitive impairment or cognitive impairment including Alzheimer disease, and methods for detecting cognitive impairment using such biomarkers.

BACKGROUND OF THE INVENTION

[0003] The commonly used means to differentiate between normal and non-normal states of a human subject using his or her biological materials are mainly those which have been used in the field of diagnostics. Most frequently used are those methods which target biomarkers in blood. It has been practiced in this field to comparatively measure the amount of a specific protein or a peptide that is less than 10,000 in molecular weight or, in the case of enzyme protein, enzyme activities in samples from normal (healthy) subjects and those from diseased individuals to help diagnosis. Here, prior to testing real samples, measurements are done on a fixed number each of samples from healthy controls and patients with certain disease with respect to the amount (s) or activity (activities) of single or multiple specific proteins or peptides and the ranges of abnormal and normal values are respectively determined. The sample to be evaluated is then analyzed by the same method and the resultant value is judged with respect to whether it is in normal or abnormal range.

[0004] In the actual measurements, the amount(s) of specified protein(s) or peptide(s) in test samples, as such or after dilution, are determined by the use of enzyme-linked immmunosorbent assay (ELISA) which uses a primary, or secondary, antibody labeled with an enzyme reacting with a substrate that yields a color upon reaction, chemiluminescent immunoassay (CLIA), radioimmunoassay (RIA) which uses a primary, or secondary, antibody labeled with a radioisotope, and, if the protein is an enzyme, the measurement of the activity of the enzyme by adding its substrate and determining the intensity of produced color, etc. These antibody-based methods are called as enzyme-, fluorescence- or radioisotope-labeled methods, respectively. In addition, there is a method where an enzyme reaction product derived from the corresponding substrate is determined by high performance liquid chromatography (HPLC). In further addition, there is a method where HPLC is combined with mass spectrometer, called LC-MS/MS, and there is a method called selected reaction monitoring (SRM)/multiple reaction monitoring (MRM) that utilizes LC-MS/MS. In another method to determine the concentration in a sample, it is appropriately pretreated, and separation of proteins or peptides is attained by 2-dimensional polyacrylamide gel electrophoresis (2D-PAGE), and target protein or peptide is determined by silver staining, Coomassie blue staining or immunological staining (Western blotting) that uses an antibody to target protein or peptide. In still further addition, there is a method which utilizes mass spectrometry to determine the amount of target protein or peptide in samples fractionated by column chromatography. Instead of column chromatography, protein chips and magnetic beads may also be utilized for purpose of pretreatment.

[0005] Furthermore, these inventors have developed an immunoMS method, where target protein or peptide is captured by beads (including magnetic ones) with linked antibody to the protein or peptide, eluted from the beads, and determined by mass spectrometry. Further, intact proteins have been reported to be analyzed by mass spectrometry using above-mentioned methods after digestion with trypsin etc. (Patent Document 1). Here, intact target proteins are selected either by fractionation or by adsorption to an adsorbant specific to them and then determined by mass spectrometry.

[0006] Number of patients suffered from cognitive impairment like Alzheimer disease is increasing rapidly along with increasing of old-age population in Japan. It is estimated that number of patients is 1.3 million in 1995 and it will be 1.9 million in 2005 and will reach to about 3.0 million in 2020. It is reported that 60-90% of cognitive impairment is Alzheimer disease. As manifestation of Alzheimer disease is not only loss of memory but several disturbance in daily life, increase of patients of this disease is becoming an important social issue to be solved. In Japan, Donepezil-hydrochloride, anti-acetylcholine esterase inhibitor has been available for medical treatment for Alzheimer disease since 1999, and it let progress of cognitive impairment in these patients be 'slow-down' efficiently, if the patient is diagnosed at early stage. Thus, in medication of Alzheimer disease, most important issue is 'early diagnosis' to treat the patients effectively by drug available at present and new coming drug.

[0007] Followings are major criteria for diagnosis of Alzheimer disease described in DSM-IV, which is published by American Psychiatric Association.

[0008] A. The development of multiple cognitive deficits manifested by both

[0009] (1) memory impairment (impaired ability to learn new information or to recall previously learned information)

[0010] (2) one (or more) of the following cognitive disturbances:

[0011] a) aphasia (language disturbance)

[0012] b) apraxia (impaired ability to carry out motor activities despite intact motor function)

[0013] c) agnosia (failure to recognize or identify objects despite intact sensory function)

[0014] d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

[0015] B. The cognitive deficits in Criteria A 1 and A2 each cause significant impairment in social or occupa-

tional functioning and represent a significant decline from a previous level of functioning. (Non-patent reference 1)

[0016] There are several types of neurological disorders related to Alzheimer disease (AD). As cognitive dysfunction appears gradually in dementia including AD, there is a disease status of pre-stage of dementia. This stage is called as mild cognitive impairment (MCI). In United States, 10% MCI develops to AD within 1 year, and 50% of MCI develops to AD within 4 years. MCI is defined as a condition characterized by newly acquired cognitive decline to an extent that is beyond that expected for age or educational background, yet not causing significant functional impairment, and not showing disturbance in daily life. Frontotemporal dementia (frontotemporal lobar degeneration) (FTD) shows loss of personal awareness, loss of social awareness, hyperorality, and stereotyped, perseverative behavior. These clinical characteristics are different from AD. FTD includes Pick's disease, which is characterized by microscopically Pick bodies usually found in limbic, paralimbic, and ventral temporal lobe cortex. Dementia with Lewy bodies (DLB) is characterized by progressive disease and psychiatric symptoms include anxiety, depression, hallucinations (usually visual) and delusions (false beliefs). DLB is thought to be the second most common subtype and 10-30% of dementia is DLB. The symptoms of DLB are caused by the build-up of Lewy bodies. FTD and DLB belong to demented neurological disease as they also lose of memory, their ability to solve problems and maintain emotional control. (Non-patent reference 1)

[0017] In description in present patent, cognitive impairment includes AD, MCI and the demented neurological disease.

[0018] The screening tests for dementia widely used are the Hasegawa Dementia Scale-revised (HDS-R) and Mini-Mental State Examination (MMSE). In these screening tests, inspector asks several questions and evaluates level of cognitive impairment of each subject by scores. HDS-R is revised version of HDS published in 1991. In HDS-R, test consists of 9 questions to analyses orientation, remembrance, calculation, retain and recall ability, and common sense. Full score is 30 and a person whose score is less than 23 is suspected as dementia. MMSE has been developed in United States to screen and diagnose dementia, and analyses global cognitive function, with items assessing orientation, word recall, attention and calculation, language abilities, and visuospatial (drawing) ability. This test consists of 11 questions, and full score is 30 and a person who has score less than 23 is suspected as dementia. The results of HDS-R and MMSE coincide with each other. Both are used for screening, not for diagnosis and not for staging of disease progression. (Non-patent reference 1).

[0019] Neuroimaging test for dementia are Computed tomography (CT) and Magnetic resonance imaging (MRI) which evaluate morphological changes like brain atrophy and ventricular dilation and single-photon emission computed tomography (SPECT) which analyses regional cerebral blood flow and PET which shows brain metabolism by measurement of consumption of oxygen and sugar. SPECT and PET, nuclear imaging technologies, can identify neuronal dysfunction at preclinical stage. However, these neuroimaging cannot be widely used in hospitals because they need special facilities to perform nuclear imaging, and neuroimaging may not be objective test as imaging diagnosis is completely depend on the skill of physician who analyses the mages.

[0020] Thus, methods for screening and diagnosis of dementia including AD that are available at present is dependent on tests lacking objectivity and is dependent on expensive instruments, and so it is very difficult to use these tests for screening of early stage-cognitive impairment. If we get blood (serum/plasma) biomarker for cognitive impairment, which enables us objective test using specimens we can easily obtain, we can identify cognitive impairment at early stage (preclinical stage) by blood test using such biomarker. Present patent provides novel biomarkers and a novel and potent diagnostic method for cognitive impairment by using such biomarkers and biomarkers described here.

CITATION LIST

Patent Document

[0021] Patent Document 1, JP-A-2004-333274
[0022] Patent Document 2, JP-A-2006-308533

Non-Patent Document

[0023] Non-Patent Document 1, "The better understanding of Alzheimer's disease.," edited by Imaharu Nakano and Hldehiro Mizusawa., Nagai Shoten Co., Ltd., 2004 (in Japanese) Non-Patent Document 2, Benkirane, N. et al., J. Biol. Chem. Vol. 268, 26279-26285, 1993

SUMMARY OF THE INVENTION

[0024] Technical Problem

[0025] The present invention aims to present methods to detect mild cognitive impairment or cognitive impairment including Alzheimer disease by using a protein or its partial peptide that differs in presence or absence, or in quantity between non-cognitive impairment subjects (including healthy people, the human subjects that may be affected with any disease and unaffected with psychiatry disease including cognitive impairment. These human subjects are allowed to match the age and gender of patient with cognitive impairment. And, these human subjects are called non-demented control, hereinafter abbreviated to NDC.) and patients with cognitive impairment and further aims to present biomarkers comprising said proteins and said partial peptides to be used to detect mild cognitive impairment or cognitive impairment including Alzheimer disease.

Solution to Problem

[0026] These inventors investigated to find out means to detect cognitive impairment and found a peptide capable of detecting mild cognitive impairment or cognitive impairment including Alzheimer disease in the serum. Said peptides found in the present invention are those with significance as a biomarker to detecting in the case of serum not only other biological materials such as blood, plasma, cerebrospinal fluid, and urine. Simultaneously, protein or peptide is the origin of these peptides (hereinafter referred to as intact proteins or peptides) also has significance as biomarkers.

[0027] Specifically, these inventors found that a biomarker comprising at least one protein or peptide selected from the group consisting of Complement C3 consisting of amino

acid sequence expressed by SEQ ID NO: 1, Transcription factor AP-2 gamma consisting of amino acid sequence expressed by SEQ ID NO: 3, Synapsin-3 consisting of amino acid sequence expressed by SEQ ID NO: 5, Oxytocin receptor consisting of amino acid sequence expressed by SEQ ID NO: 7, Inter-alpha-trypsin inhibitor heavy chain H5-like protein consisting of amino acid sequence expressed by SEQ ID NO: 9, E3 ubiquitin-protein ligase HERC2 consisting of amino acid sequence expressed by SEQ ID NO: 11, Prothrombin consisting of amino acid sequence expressed by SEQ ID NO: 13, Transthyretin consisting of amino acid sequence expressed by SEQ ID NO: 15, Tumor necrosis factor receptor superfamily member 16 consisting of amino acid sequence expressed by SEQ ID NO: 17, Complement C4-A consisting of amino acid sequence expressed by SEQ ID NO: 19, Complement C4-B consisting of amino acid sequence expressed by SEQ ID NO: 21, Fibrinogen alpha chain (isoform 1) consisting of amino acid sequence expressed by-SEQ ID NO: 23, and Fibrinogen alpha chain (isoform 2) consisting of amino acid sequence expressed by SEQ ID NO: 25; or a biomarker comprising protein fragment or peptide of not less than 5 amino acid residues arising from at least one protein or peptide selected from the group consisting of them, could be used as biomarkers to detect cognitive impairment.

[0028] Furthermore, these inventors found that a biomarker comprising from the group consisting of Complement C3-derived peptide CO3 consisting of amino acid sequence expressed by SEQ ID NO: 2, Transcription factor AP-2 gamma-derived peptide AP2C consisting of amino acid sequence expressed by SEQ ID NO: 4, Synapsin-3-derived peptide SYN3 consisting of amino acid sequence expressed by SEQ ID NO: 6, Oxytocin receptor-derived peptide OXYR consisting of amino acid sequence expressed by SEQ ID NO: 8, Inter-alpha-trypsin inhibitor heavy chain H5-like protein-derived peptide ITH5L consisting of amino acid sequence expressed by SEQ ID NO: 10, E3 ubiquitin-protein ligase HERC2-derived peptide HERC2 consisting of amino acid sequence expressed by SEQ ID NO: 12, Prothrombin-derived peptide THRB consisting of amino acid sequence expressed by SEQ ID NO: 14, Transthyretin-derived peptide TTHY consisting of amino acid sequence expressed by SEQ ID NO: 16, Tumor necrosis factor receptor superfamily member 16-derived peptide TNR16 consisting of amino acid sequence expressed by SEQ ID NO: 18, Complement C4-derived peptide CO4-1 consisting of amino acid sequence expressed by SEQ ID NO: 20, Complement C4-derived peptide CO4-2 consisting of amino acid sequence expressed by SEQ ID NO: 22, Fibrinogen alpha chain-derived peptide FIBA-1 consisting of amino acid sequence expressed by SEQ ID NO: 24, Fibrinogen alpha chain-derived peptide FIBA-2 consisting of amino acid sequence expressed by SEQ ID NO: 26, and Fibrinogen alpha chain-derived peptide FIBA-3 consisting of amino acid sequence expressed by SEQ ID NO: 27 could be used as biomarkers to detect cognitive impairment.

[0029] These inventors brought the present invention to perfection by further succeeding in determining simultaneously these many proteins and its partial peptides by using two-dimensional high performance liquid chromatography-MALDI TOF-MS method (mass spectrometry) and immunoMS method.

[0030] The features of the present invention are shown below.

[0031] [1] A biomarker for detection of cognitive impairment comprising protein fragment or peptide of not less than 5 amino acid residues arising from at least one protein or peptide selected from the group consisting of Complement C3 consisting of amino acid sequence expressed by SEQ ID NO: 1, Transcription factor AP-2 gamma consisting of amino acid sequence expressed by SEQ ID NO: 3, Synapsin-3 consisting of amino acid sequence expressed by SEQ ID NO: 5, Oxytocin receptor consisting of amino acid sequence expressed by SEQ ID NO: 7, Inter-alpha-trypsin inhibitor heavy chain H5-like protein consisting of amino acid sequence expressed by SEQ ID NO: 9, E3 ubiquitin-protein ligase HERC2 consisting of amino acid sequence expressed by SEQ ID NO: 11, Prothrombin consisting of amino acid sequence expressed by SEQ ID NO: 13, Transthyretin consisting of amino acid sequence expressed by SEQ ID NO: 15, Tumor necrosis factor receptor superfamily member 16 consisting of amino acid sequence expressed by SEQ ID NO: 17, Complement C4-A consisting of amino acid sequence expressed by SEQ ID NO: 19, Complement C4-B consisting of amino acid sequence expressed by SEQ ID NO: 21, Fibrinogen alpha chain (isoform 1) consisting of amino acid sequence expressed by SEQ ID NO: 23, and Fibrinogen alpha chain (isoform 2) consisting of amino acid sequence expressed by SEQ ID NO: 25, or a biomarker for detection of cognitive impairment comprising at least one protein or peptide selected from the group consisting of them.

[0032] [2] A biomarker for detection of cognitive impairment comprising the peptide selected from the group consisting of Complement C3-derived peptide CO3 consisting of amino acid sequence expressed by SEQ ID NO: 2, Transcription factor AP-2 gamma-derived peptide AP2C consisting of amino acid sequence expressed by SEQ ID NO: 4, Synapsin-3-derived peptide SYN3 consisting of amino acid sequence expressed by-SEQ ID NO: 6, Oxytocin receptor-derived peptide OXYR consisting of amino acid sequence expressed by SEQ ID NO: 8, Inter-alpha-trypsin inhibitor heavy chain H5-like protein-derived peptide ITI-I5L consisting of amino acid sequence expressed by SEQ ID NO: 10, E3 ubiquitin-protein ligase HERC2-derived peptide HERC2 consisting of amino acid sequence expressed by SEQ ID NO: 12, Prothrombin-derived peptide THRB consisting of amino acid sequence expressed by SEQ ID NO: 14, Transthyretin-derived peptide TTHY consisting of amino acid sequence expressed by SEQ ID NO: 16, Tumor necrosis factor receptor superfamily member 16-derived peptide TNR16 consisting of amino acid sequence expressed by SEQ ID NO: 18, Complement C4-derived peptide CO4-1 consisting of amino acid sequence expressed by SEQ ID NO: 20, Complement C4-derived peptide CO4-2 consisting of amino acid sequence expressed by SEQ ID NO: 22, Fibrinogen alpha chain-derived peptide FIBA-1 consisting of amino acid sequence expressed by SEQ ID NO: 24, Fibrinogen alpha chain-derived peptide FIBA-2 consisting of amino acid sequence expressed by SEQ ID NO: 26, and Fibrinogen alpha chain-derived peptide FIBA-3 consisting of amino acid sequence expressed by SEQ ID NO: 27, or a biomarker for detection of cognitive impairment comprising at least one protein or peptide selected from the group consisting of them.

[0033] [3] A biomarker of cognitive impairment comprising the peptides selected from the group consisting of amino acid sequence expressed by SEQ ID NOS: 2, 4, 6, 8, 10, 12,

14, 16, 18, 20, 22, 24, 26, and 27 that is appeared or increased in biological material of patients of cognitive impairment as compared to biological material of subjects not suffering from psychiatry disease.

[0034] [4] A biomarker of Alzheimer disease comprising the peptides selected from the group consisting of amino acid sequence expressed by SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 27 that is appeared or increased in biological material of patients of Alzheimer disease as compared to biological material of subjects not suffering from psychiatry disease.

[0035] [5] A biomarker of mild cognitive impairment comprising the peptides selected from the group consisting of amino acid sequence expressed by SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 27 that is appeared or increased in biological material of patients of mild cognitive impairment as compared to biological material of subjects not suffering from psychiatry disease.

[0036] [6] Method for detection of cognitive impairment involving determination in biological material of at least one biomarker for cognitive impairment described in any of [1] to [5].

[0037] [7] Method for detection of psychiatry disease described in [6] wherein detection is made either by immunoblot procedure, Western blotting, enzyme-, fluorescence-, or radioisotope-labeled antibody method, mass spectrometry, immunoMS method or surface plasmon resonance method.

[0038] [8] A kit for detection of cognitive impairment to determine at least one biomarker described in any of [1] to [5].

[0039] [9] A kit for detection of psychiatry disease containing antibody or aptamer to at least one biomarker described in any of [1] to [5].

Advantageous Effect of the Invention

[0040] According to the present invention, it is possible to diagnose the subject such as suffering from mild cognitive impairment or cognitive impairment including Alzheimer's disease, when to increase or appear compared to the biological sample of subjects not suffering from psychiatry disease by determining amount of at least one biomarker comprising protein fragment or peptide of not less than 5 amino acid residues arising from at least one protein or peptide selected from the group consisting of Complement C3 consisting of amino acid sequence expressed by SEQ ID NO: 1, Transcription factor AP-2 gamma consisting of amino acid sequence expressed by SEQ ID NO: 3, Synapsin-3 consisting of amino acid sequence expressed by SEQ ID NO: 5, Oxytocin receptor consisting of amino acid sequence expressed by SEQ ID NO: 7, Inter-alpha-trypsin inhibitor heavy chain H5-like protein consisting of amino acid sequence expressed by SEQ ID NO: 9, E3 ubiquitin-protein ligase HERC2 consisting of amino acid sequence expressed by SEQ ID NO: 11, Prothrombin consisting of amino acid sequence expressed by SEQ ID NO: 13, Transthyretin consisting of amino acid sequence expressed by SEQ ID NO: 15, Tumor necrosis factor receptor superfamily member 16 consisting of amino acid sequence expressed by SEQ ID NO: 17, Complement C4-A consisting of amino acid sequence expressed by SEQ ID NO: 19, Complement C4-B consisting of amino acid sequence expressed by SEQ ID NO: 21, Fibrinogen alpha chain (isoform 1) consisting of amino acid sequence expressed by SEQ ID NO: 23, and Fibrinogen alpha chain (isoform 2) consisting of amino acid sequence expressed by SEQ ID NO: 25.

[0041] In addition, according to the present invention, it is possible to diagnose the subject such as suffering from mild cognitive impairment or cognitive impairment including Alzheimer's disease, when to increase or appear compared to the biological sample of subjects not suffering from psychiatry disease by determining kind or amount at least one peptide selected from the group consisting of Complement C3-derived peptide CO3 consisting of amino acid sequence expressed by SEQ ID NO: 2, Transcription factor AP-2 gamma-derived peptide AP2C consisting of amino acid sequence expressed by SEQ ID NO: 4, Synapsin-3-derived peptide SYN3 consisting of amino acid sequence expressed by SEQ ID NO: 6, Oxytocin receptor-derived peptide OXYR consisting of amino acid sequence expressed by SEQ ID NO: 8, Inter-alpha-trypsin inhibitor heavy chain H5-like protein-derived peptide ITH5L consisting of amino acid sequence expressed by SEQ ID NO: 10, E3 ubiquitin-protein ligase HERC2-derived peptide HERC2 consisting of amino acid sequence expressed by SEQ ID NO: 12, Prothrombin-derived peptide THRB consisting of amino acid sequence expressed by SEQ ID NO: 14, Transthyretin-derived peptide TTHY consisting of amino acid sequence expressed by SEQ ID NO: 16, Tumor necrosis factor receptor superfamily member 16-derived peptide TNR16 consisting of amino acid sequence expressed by SEQ ID NO: 18, Complement C4-derived peptide CO4-1 consisting of amino acid sequence expressed by SEQ ID NO: 20, Complement C4-derived peptide CO4-2 consisting of amino acid sequence expressed by SEQ ID NO: 22, Fibrinogen alpha chain-derived peptide FIBA-1 consisting of amino acid sequence expressed by SEQ ID NO: 24, Fibrinogen alpha chain-derived peptide FIBA-2 consisting of amino acid sequence expressed by SEQ ID NO: 26, and Fibrinogen alpha chain-derived peptide FIBA-3 consisting of amino acid sequence expressed by SEQ ID NO: 27.

[0042] The present invention provides a diagnostic system that is high in both accuracy and specificity. The present invention enables highly accurate diagnosis of cognitive impairment in which there have been no specific test methods for such biological materials as blood. Furthermore, the biomarkers disclosed in the present invention are highly useful in judgment of drug efficacy.

BRIEF DESCRIPTION OF DRAWINGS

[0043] FIG. **1** illustrates the cluster map of Marker A. The dots within the rectangle indicated by (A) are m/z and retention time of the mass peak of Marker A detected from the serum of the individual subject using reverse phase chromatography. The dots in a cluster can be regarded as the same retention time and the same m/z in the error range, and the dots in a cluster are defined to be derived from the same peptide.

[0044] FIG. **2** illustrates the results of differential analysis in the case of Marker A. As shown in the amino acid sequences resulting of MS/MS analysis in FIG. **4**, Marker A is Complement C3-derived peptides CO3. FIG. **2** shows the comparison between NDC and cognitive impairment (AD, MCI, DLB and FTD) related to CO3.

[0045] FIG. **3** illustrates the ROC curves of CO3 expressed by SEQ ID NO: 2. Definition of the ROC curve, see the section on the results of Example. FIG. **3**A) shows

the ROC curve of the comparison of AD vs. NDC. FIG. **3**B) shows the ROC curve of the comparison of MCI vs. NDC.

[0046] FIG. **4** illustrates the MS/MS spectrum of CO3 by TOF/TOF mass spectrometer. In FIG. **4** top, it was shown the amino acid sequence of CO3, and it was shown y-ions and b-ions that appear in the MS/MS spectrum.

[0047] FIG. **5** illustrates the results of differential analysis of AP2C expressed by SEQ ID NO: 4. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0048] FIG. **6** illustrates the results of differential analysis of SYN3 expressed by SEQ ID NO: 6. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0049] FIG. **7** illustrates the results of differential analysis of OXYR expressed by SEQ ID NO: 8. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0050] FIG. **8** illustrates the results of differential analysis of ITH5L expressed by SEQ ID NO: 10. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0051] FIG. **9** illustrates the results of differential analysis of HERC2 expressed by SEQ ID NO: 12. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0052] FIG. **10** illustrates the results of differential analysis of THRB expressed by SEQ ID NO: 14. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0053] FIG. **11** illustrates the results of differential analysis of TTHY expressed by SEQ ID NO: 16. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0054] FIG. **12** illustrates the results of differential analysis of TNR16 expressed by SEQ ID NO: 18. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0055] FIG. **13** illustrates the results of differential analysis of CO4-1 expressed by SEQ ID NO: 20. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0056] FIG. **14** illustrates the results of differential analysis of CO4-2 expressed by SEQ ID NO: 22. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0057] FIG. **15** illustrates the results of differential analysis of FIBA-1 expressed by SEQ ID NO: 24. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0058] FIG. **16** illustrates the results of differential analysis of FIBA-2 expressed by SEQ ID NO: 26. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

[0059] FIG. **17** illustrates the results of differential analysis of FIBA-3 expressed by SEQ ID NO: 27. This figure shows a comparison between cognitive impairment patients (AD, MCI, DLB, FTD) and subjects not suffering from psychiatry disease (NDC).

DESCRIPTION OF EMBODIMENTS

[0060] The present invention is a method for determining the kind and the amount of intact protein and/or its partial peptide when test subject is suffering from cognitive impairment as well as for diagnosing whether test subject is suffering from cognitive impairment. A peptide is generally said to be a chemical entity, made by polymerizing a number of amino acids, of less than 10,000 in molecular weight or by polymerizing several to less than about 50 amino acid residues. While in the present invention a partial peptide of an intact protein can be used as a biomarker for detection of cognitive impairment, such partial peptide is defined as a peptide of less than 10,000 in molecular weight consisting of a part of the amino acid sequence of the intact protein. Such peptide may arise as a partial peptide during the expression by transcription followed by synthesis by translation before maturing into an intact protein or as a peptide produced by enzyme digestion in the body after the intact protein has been synthesized. It is possible that, when the body is in abnormal state suffering from such disease as cognitive impairment, the mechanism for protein synthesis and regulation is de-regulated. In other words, the present invention is also a method for determining if test subject is in normal state or is suffering from cognitive impairment by using the degree of protein synthesis and/or protein digestion as an indicator. The detection of cognitive impairment in the present invention means evaluation and differentiation, i.e., diagnosis of test subject as to whether the subject is suffering from cognitive impairment. The present invention can also include the evaluation of patient's risk of suffering from more serious cognitive impairment.

[0061] Specifically, in the method of the present invention, the examples of intact protein that can be used as a cognitive impairment include Complement C3 consisting of amino acid sequence expressed by SEQ ID NO: 1, Transcription factor AP-2 gamma consisting of amino acid sequence expressed by SEQ ID NO: 3, Synapsin-3 consisting of amino acid sequence expressed by SEQ ID NO: 5, Oxytocin receptor consisting of amino acid sequence expressed by SEQ ID NO: 7, Inter-alpha-trypsin inhibitor heavy chain H5-like protein consisting of amino acid sequence expressed by SEQ ID NO: 9, E3 ubiquitin-protein ligase HERC2 consisting of amino acid sequence expressed by SEQ ID NO: 11, Prothrombin consisting of amino acid sequence expressed by SEQ ID NO: 13, Transthyretin consisting of amino acid sequence expressed by SEQ ID NO: 15, Tumor necrosis factor receptor superfamily member 16 consisting of amino acid sequence expressed by SEQ ID NO: 17, Complement C4-A consisting of amino acid sequence expressed by SEQ ID NO: 19, Complement C4-B consisting of amino acid sequence expressed by SEQ ID NO: 21, Fibrinogen alpha chain (isoform 1) consisting of amino acid sequence expressed by SEQ ID NO: 23, and Fibrinogen alpha chain (isoform 2) consisting of amino acid sequence expressed by SEQ ID NO: 25, and further, the peptide

fragments that comprise of partial peptides of not less than 5 amino acid residues of these intact proteins can be used as same purpose.

[0062] Still further, an example of biomarkers for cognitive impairment of the present invention includes the partial peptides consisting of amino acid sequence expressed by SEQ ID NO: 2 of Complement C3-derived peptide CO3, SEQ ID NO: 4 of Transcription factor AP-2 gamma-derived peptide AP2C, SEQ ID NO: 6 of Synapsin-3-derived peptide SYN3, SEQ ID NO: 8 of Oxytocin receptor-derived peptide OXYR, SEQ ID NO: 10 of Inter-alpha-trypsin inhibitor heavy chain H5-like protein-derived peptide ITH5L, SEQ ID NO: 12 of E3 ubiquitin-protein ligase HERC2-derived peptide HERC2, SEQ ID NO: 14 of Prothrombin-derived peptide THRB, SEQ ID NO: 16 of Transthyretin-derived peptide TTHY, SEQ ID NO: 18 of Tumor necrosis factor receptor superfamily member 16-derived peptide TNR16, SEQ ID NO: 20 of Complement C4-derived peptide CO4-1, SEQ ID NO: 22 of Complement C4-derived peptide CO4-2, SEQ ID NO: 24 of Fibrinogen alpha chain-derived peptide FIBA-1, SEQ ID NO: 26 of Fibrinogen alpha chain-derived peptide FIBA-2, and SEQ ID NO: 27 of Fibrinogen alpha chain-derived peptide FIBA-3. In the present invention, proteins and peptides consisting of amino acid sequences derived from SEQ ID NOS: 1 through 27 by deletion, exchange, and/or addition of one or a few amino acids can be used as biomarkers and are included in the present invention. '"One or a few" herein means "one or three," "one or two," or "one." Furthermore, the partial peptides that can be used as biomarkers in the present invention include those peptide fragments consisting of not less than 5 amino acid residues arising respectively from SEQ ID NOS: 1 through 27. The basis for the limitation of peptide fragments consisting of not less than 5 amino acid residues is in the description below in Non-patent Document 2. The document reported that an antibody obtained by using the peptide IRGERA as immunogen, which was the C-terminus (130-135) of histone H3, recognized the peptide IKGERA derived by exchange of K for R and the peptide CGGGERA which was derived by deletion of IR followed by addition of CGG. This demonstrates that the immunogenicity (antigenicity) is recognized by a peptide of not less than 4 amino acid residues. In order to expand this finding to other peptides than the C-terminus of histone H3, the number of amino acid residue is defined as not less than 5 instead of 4 in the present invention. To make such a low molecular weight peptide as the subject of the present invention is important when the method of detection and differentiation uses immunological means including immunoblot, ELISA and immunoMS.

[0063] It is to be noted that there are cases where a sugar chain or sugar chains have been added to an intact protein or its partial peptide to form glycated entities. Proteins and partial peptides in glycated form can also be used as biomarkers for detection of cognitive impairment.

[0064] It is also to be noted that, in the present invention, biomarker can be quantified or its presence or absence can be determined qualitatively.

[0065] Two-dimensional electrophoresis (2-DE) or 2-dimensional chromatography (2-DC) can be used in the present invention to separate biomarkers in biological materials including serum. Known chromatographic methods can be selected from ion-exchange chromatography, reverse-phase chromatography and gel-filtration chromatography. It is also possible to make quantification with the SRM/MRM method in LC-MS/MS technology. Furthermore, the immunoMS method which these inventors have developed, where target protein or peptide is captured by beads (including magnetic ones) with antibody linked to the protein or peptide, eluted from the beads, and determined by mass spectrometry enables convenient determination of presence or absence or the amount of target protein, protein fragment or peptide without the use of 2-DE or chromatography.

[0066] It is possible with the use of the method disclosed in the present invention to evaluate at the stage of mild of cognitive dysfunction in test subject and therefore it can be useful in prophylactic medicine. Further, when psychotherapy and/or drug therapy is given to patients with cognitive impairment, it is reflected in the amount of proteins and partial peptides in biological materials such as serum if the progression of the disorder has been inhibited. Therefore, by measuring these proteins and partial peptides, it is possible to evaluate and determine therapeutic effect.

[0067] The kind and amount of a protein in biological materials can be determined by various methods. If target protein (including protein fragment and partial peptide) has been characterized and when an antibody (primary antibody) to it has already been obtained, the following methods can be used:

1. Immunoblot

[0068] This is one of the simplest methods. Test serum in a fixed amount (about 1 microliter) after stepwise dilution is dropped onto an appropriate membrane such as of nitrocellulose and dried in air. The membrane is treated with a blocking solution containing a protein such as BSA, washed, reacted with primary antibody, and washed. Thereafter, the membrane is reacted with labeled secondary antibody to detect the primary antibody. The membrane is washed and the label is visualized to measure its density.

2. Western Blotting

[0069] After separation with one-dimensional or two-dimensional electrophoresis involving isoelectric focusing or SDS-PAGE, proteins are transferred onto such an appropriate membrane as of PVDF and their amounts are determined, as in above-mentioned immunoblot, using primary antibody and labeled secondary antibody.

3. ELISA

[0070] Antibody to protein or its partial peptide is fixed to such a plate as a chemically modified microtiter plate. Appropriate amounts of samples after stepwise dilution are applied to the plate and incubated. Proteins and peptides not captured are removed by washing. Next, the plate is incubated with secondary antibody labeled with fluorescent or chemiluminescent substance or enzyme. After addition of respective substrate, fluorescence, chemiluminescence or visible light due to enzyme reaction is measured for evaluation and judgment.

[0071] Additional examples of methods are illustrated below (see Patent Document 2) but the invention is not limited by these examples.

4. Methods that use Microarray (Microchip)

[0072] A microarray is a general term for devices where solidified materials with affinity for target substances are arrayed on solid support (plate). In the present invention, antibodies or aptamer to proteins and partial peptides are

arrayed. A sample of biological material is placed on the microarray for fixation of target proteins or partial peptides and the microarray is then incubated with secondary antibody labeled with fluorescent or chemiluminescent substance or enzyme. After addition of respective substrate, fluorescence, chemiluminescence or visible light due to enzyme reaction is measured.

5. Mass Spectrometry

[0073] In mass spectrometry, for example, antibody to a specified protein or partial peptide is attached to chemically modified microbeads or plate (protein chip). The microbeads could be magnetic beads. There are no requirements for the material of the plate. The antibody to be used could be (1) an antibody which recognizes the full length form of the specified protein only, (2) an antibody which recognizes a partial peptide only, (3) all of antibodies which recognizes both the specified protein and its partial peptide, or a combination of (1) and (2), (1) and (3), or (2) and (3). Samples after stepwise dilution with original solvent or buffer are added to the microbeads or plate carrying antibody or antibodies and incubated. Those proteins and partial peptides not captured are removed by washing. The protein or partial peptide captured by microbeads or plate is eluted, and analyzed by mass spectrometry with MALDI-TOF-MS, SELDI-TOF-MS, etc. Measurements are made with respect to the mass and intensity of the peak due to the protein, protein fragment or partial peptide. Prior to the measurements a fixed amount of substance serving as the internal standard is added to the original biological material and the intensity of its peak is also measured. The concentration of the target in the original biological material can be calculated from the ratio of peak intensity of the target to the peak intensity of the internal standard. This is called immunoMS method. Further, it is possible to make quantification, after the sample is diluted with original solvent or buffer, or after part of proteins are removed, by separation with HPLC followed by mass spectrometry with electrospray ionization (ESI) method. Therein the SRM/MRM method can be utilized for absolute quantification with the use of an isotope-labeled internal standard peptide.

[0074] Furthermore, in addition to the above-mentioned methods, it is possible to analyze proteins and partial peptides by using 2-DE, surface plasmon resonance, etc.

[0075] The present invention includes the method to detect cognitive impairment from the presence or absence or amount of the above-mentioned biomarker after applying biological material obtained from test subject to 2-DE or surface plasmon resonance.

EXAMPLES

[0076] Discovery of a marker peptide for detection of cognitive impairment using two-dimensional liquid chromatography-mass spectrometry (2D-LC-MALDI TOF-MS).

(1) Serum Samples.

[0077] Followings, the characters before the parenthesis are an abbreviation.

[0078] A sera obtained from 40 AD (Alzheimer's disease), 35MCI (mild cognitive impairment), 13 DLB (Dementia with Lewy bodies), 7 FTD (frontotemporal lobar degeneration), and 21 NDC (subjects not suffering from psychiatry disease) were used.

(2) Methods

[0079] After 475 μl of 0.1% trifluoroacetic acid (TFA) were added in each of 25 μl of sera, samples were boiled for 15 min at 100 degrees. Subsequently, in order to recover peptides of molecular weight of 10,000 or less, ultrafiltration were performed by using YM-10 filter unit (Millipore Corp.). Then the analysis using 2D-LC-MALDI TOF-MS were performed as follows. In other words, recovering samples were fractionated to 382 fractions per sample by using two-dimensional HPLC (SCX cation exchange column at one-dimension and C18 reverse-phase column at two-dimension). The samples were fractionated into two fractions by SCX cation exchange column, namely, SCX 1 fraction is through fraction, SCX 2 fraction is the fraction that eluted with 100% salt solution. Two fractions that were fractionated by SCX, respectively, were fractionated 191 fractions by C18 reverse phase column chromatography. It was eluted with 6 seconds in one fraction, and the retention times were calculated by multiplying the number of minus 1 from number of eluted fractions to 6 seconds. All fractionated samples were spotted on MALDI target plate (MTP AnchorChip™600/384 plate, BRUKER DALTONICS) for MALDI TOF/TOF mass spectrometer (ultraflex TOF/TOF, BRUKER DALTONICS) using a spotting robot (AccuSpot, SHIMADZU) that is connected online, and matrix solution (alpha-cyano-hydroxycinnamic acid, CHCA) were mixed and crystallized. After mounting MALDI target plate into ultraflex TOF/TOF, the mass and the peak area of the mass were measured automatically in reflectron mode by irradiating to crystallized sample by laser. Peak area was normalized with 250 fmole of per each well of bradykinin 1-7 fragment that was added into matrix solution in advance. In other words, the area value was calculated dividing the peak area of specific mass in sample by the peak area obtained from bradykinin1-7 fragment. This area value is corresponding in 25 μl of sample serum. Detection of difference in abundance of peptides in serum between groups (called differential analysis) was performed using multi-group statistical analysis software Parnassum™ (MCBI) developed by us. Peptide that was observed to difference in abundance was directly determined amino acid sequence in MS/MS analysis by ultraflex TOF/TOF, and intact proteins or peptides of their origin were identified.

(3) Results

[0080] The following shows the result of differential analysis by Parnassum software for data of serum individual subjects obtained using 2D-LC MALDI TOF-MS. FIG. **1** shows the result that was obtained from sample that was applied to 2D-LC-MALDI TOF-MS. Sample was fractionated into 2 fractions by SCX cation exchange column in the first dimension, then first fractions from SCX column (SCX 1) were fractionated into 191 fractions by C18 reverse-phase column. Mass spectra of 191 fractions were obtained by MALDI TOF-MS measuring. As the horizontal axis is the m/z and the vertical axis is the fractions of reverse-phase column chromatography, FIG. **1** was visualized by Parnassum software developed by present inventors. The dots in FIG. **1** shows respectively TOF-MS peak derived from the individual subject. The sections that dots are gathered can be regarded as the same retention time and the same m/z in the error range, and the dots in the sections are defined to be

derived from the same peptide. These sections are referred to as clusters. Section (A) of FIG. **1** shows cluster of Marker A.

[0081] FIG. **2** shows the results of differential analysis in the case of Marker A. As shown in FIG. **4**, Marker A is Complement C3-derived peptides CO3. FIG. **2** shows the comparison between subjects not suffering from psychiatry disease (NDC) and cognitive impairment (AD, MCI, DLB and FTD) related to CO3. In the results of t-test, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC ($p<0.05$).

[0082] From the results of FIG. **2**, in order to evaluate the extent to which the Marker A is useful as biomarker, the analysis by receiver operating characteristic (ROC) curve was performed. A) and B) in FIG. **3** shows respectively the ROC curve of the comparison of AD vs. NDC and MCI vs. NDC. If the area value (hereinafter referred to as the AUC value) of under the ROC curve is close to 1, the usefulness as biomarker of Marker A will be higher. In A) and B) of FIG. **3**, the typical values of sensitivity and specificity are the values of the point (open square in the figure) of the coordinate on ROC curve that the distance is minimized when a straight line was drawn to ROC curve from the point of 100% on y-axis. The value of cut-off giving this point becomes a useful threshold to distinguish between the different groups, and the values of sensitivity and specificity at that time (i.e., above the typical values) becomes an indicator of the usefulness of biomarkers together with AUC values. In A) of FIG. **3**, as typical values in AD vs. NDC, the sensitivity was 73.0%, the specificity was 100%, and the AUC value was 0.88. In B) of FIG. **3**, as typical values in MCI vs. NDC, the sensitivity was 70.6%, the specificity was 89.5%, and the AUC value was 0.83.

[0083] Thus, it was revealed that Marker A was useful to distinguish AD and MCI with NDC. In particular, since MCI is the state of previous stage of AD, Marker A is considered to be an extremely useful marker to detect MCI for early diagnosis of potential subjects to migrate to AD.

[0084] FIG. **4**, for Marker A, illustrates the results of MS/MS spectrum using ultraflex TOF/TOF. The signals that show y-ions and b-ions have enough appeared, and the amino acid sequence could be readily identified. Mascot search was performed on this result and the protein of origin or the peptide (hereinafter referred to as intact proteins or peptides) is Complement C3, and the detected peptide was found that the sequence is APVIHQEMIGGLRN (SEQ ID NO: 2). CO3 of entry name of Swiss-Prot against Complement C3 will use as an abbreviation of the peptide name. Followings, for peptides other than CO3, entry name will use as peptide name, similarly.

[0085] Including the Marker A, the peptides that have difference in abundance between the groups in serum were measured MS/MS spectra using ultraflex TOF/TOF, and in addition to determining the amino acid sequence, the results identified intact proteins or peptides were shown below. For peptides other than Marker A, the signals that show y-ions and b-ions has enough appeared, and the amino acid sequence could be readily identified. The following amino acid sequence that shows a set of two sequences, the first sequence shows the amino acid sequence of intact proteins, and the second sequence shows the amino acid sequence of peptide detected by 2D-LC MALDI TOF-MS. The peptide comprising of the underlined portion in the first sequence correspond to the sequence of peptide detected by 2D-LC MALDI TOF-MS. The amino acid sequence starting at 0001 in the sequence shows the sequence of the N-terminus side.

(1) Complement C3-Derived Peptide CO3

[0086] CO3 shown as SEQ ID NO: 2 had formed a cluster by clustering using Parnassum software.

[0087] As shown in FIG. **2**, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC (t-test, $p<0.05$). Thus, it was revealed that CO3 shown as SEQ ID NO: 2 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See FIG. **3**A), **3**B) and Table 1).

Intact Protein/Peptide

[0088]

(SEQ ID NO: 1)

```
0001 SPMYSIITPN ILRLESEETM VLEAHDAQGD VPVTVTVHDF PGKKLVLSSE

0051 KTVLTPATNH MGNVTFTIPA NREFKSEKGR NKFVTVQATF GTQVVEKVVL

0101 VSLQSGYLFI QTDKTIYTPG STVLYRIFTV NHKLLPVGRT VMVNIENPEG

0151 IPVKQDSLSS QNQLGVLPLS WDIPELVNMG QWKIRAYYEN SPQQVFSTEF

0201 EVKEYVLPSF EVIVEPTEKF YYIYNEKGLE VTITARFLYG KKVEGTAFVI

0251 FGIQDGEQRI SLPESLKRIP IEDGSGEVVL SRKVLLDGVQ NPRAEDLVGK

0301 SLYVSATVIL HSGSDMVQAE RSGIPIVTSP YQIHFTKTPK YFKPGMPFDL

0351 MVFVTNPDGS PAYRVPVAVQ GEDTVQSLTQ GDGVAKLSIN THPSQKPLSI

0401 TVRTKKQELS EAEQATRTMQ ALPYSTVGNS NNYLHLSVLR TELRPGETLN

0451 VNFLLRMDRA HEAKIRYYTY LIMNKGRLLK AGRQVREPGQ DLVVLPLSIT

0501 TDFIPSFRLV AYYTLIGASG QREVVADSVW VDVKDSCVGS LVVKSGQSED

0551 RQPVPGQQMT LKIEGDHGAR VVLVAVDKGV FVLNKKNKLT QSKIWDVVEK
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-continued

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0601 ADIGCTPGSG KDYAGVFSDA GLTFTSSSGQ QTAQRAELQC PQPAARRRRS

0651 VQLTEKRMDK VGKYPKELRK CCEDGMRENP MRFSCQRRTR FISLGEACKK

0701 VFLDCCNYIT ELRRQHARAS HLGLARSNLD EDIIAEENIV SRSEFPESWL

0751 WNVEDLKEPP KNGISTKLMN IFLKDSITTW EILAVSMSDK KGICVADPFE

0801 VTVMQDFFID LRLPYSVVRN EQVEIRAVLY NYRQNQELKV RVELLHNPAF

0851 CSLATTKRRH QQTVTIPPKS SLSVPYVIVP LKTGLQEVEV KAAVYHHFIS

0901 DGVRKSLKVV PEGIRMNKTV AVRTLDPERL GREGVQKEDI PPADLSDQVP

0951 DTESETRILL QGTPVAQMTE DAVDAERLKH LIVTPSGCGE QNMIGMTPTV

1001 IAVHYLDETE QWEKFGLEKR QGALELIKKG YTQQLAFRQP SSAFAAFVKR

1051 APSTWLTAYV VKVFSLAVNL IAIDSQVLCG AVKWLILEKQ KPDGVFQEDA

1101 PVIHQEMIGG LRNNNEKDMA LTAFVLISLQ EAKDICEEQV NSLPGSITKA

1151 GDFLEANYMN LQRSYTVAIA GYALAQMGRL KGPLLNKFLT TAKDKNRWED

1201 PGKQLYNVEA TSYALLALLQ LKDFDFVPPV VRWLNEQRYY GGGYGSTQAT

1251 FMVFQALAQY QKDAPDHQEL NLDVSLQLPS RSSKITHRIH WESASLLRSE

1301 ETKENEGFTV TAEGKGQGTL SVVTMYHAKA KDQLTCNKFD LKVTIKPAPE

1351 TEKRPQDAKN TMILEICTRY RGDQDATMSI LDISMMTGFA PDTDDLKQLA

1401 NGVDRYISKY ELDKAFSDRN TLIIYLDKVS HSEDDCLAFK VHQYFNVELI

1451 QPGAVKVYAY YNLEESCTRF YHPEKEDGKL NKLCRDELCR CAEENCFIQK

1501 SDDKVTLEER LDKACEPGVD YVYKTRLVKV QLSNDFDEYI MAIEQTIKSG

1551 SDEVQVGQQR TFISPIKCRE ALKLEEKKHY LMWGLSSDFW GEKPNLSYII

1601 GKDTWVEHWP EEDECQDEEN QKQCQDLGAF TESMVVFGCP N
```

Complement C3-Derived Peptide CO3

[0089]

(SEQ ID NO: 2)

APVIHQEMIGGLRN

(2) Transcription Factor AP-2 Gamma-Derived Peptide AP2C

[0090] For AP2C shown as SEQ ID NO: 4, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **5**).

[0091] Thus, it was revealed that AP2C shown as SEQ ID NO: 4 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0092]

(SEQ ID NO: 3)

```
0001 MLWKITDNVK YEEDCEDRHD GSSNGNPRVP HLSSAGQHLY SPAPPLSHTG

0051 VAEYQPPPYF PPPYQQLAYS QSADPYSHLG EAYAAAINPL HQPAPTGSQQ

0101 QAWPGRQSQE GAGLPSHHGR PAGLLPHLSG LEAGAVSARR DAYRRSDLLL

0151 PHAHALDAAG LAENLGLHDM PHQMDEVQNV DDQHLLLHDQ TVIRKGPISM

0201 TKNPLNLPCQ KELVGAVMNP TEVFCSVPGR LSLLSSTSKY KVTVAEVQRR

0251 LSPPECLNAS LLGGVLRRAK SKNGGRSLRE KLDKIGLNLP AGRRKAAHVT

0301 LLTSLVEGEA VHLARDFAYV CEAEFPSKPV AEYLTRPHLG GRNEMAARKN

0351 MLLAAQQLCK EFTELLSQDR TPHGTSRLAP VLETNIQNCL SHFSLITHGF

0401 GSQAICAAVS ALQNYIKEAL IVIDKSYMNP GDQSPADSNK TLEKMEKHRK
```

Transcription Factor AP-2 Gamma-Derived Peptide AP2C

[0093]

(SEQ ID NO: 4)

PGRQSQEGAGLPSHHG

(3) Synapsin-3-Derived Peptide SYN3

[0094] For SYN3 shown as SEQ ID NO: 6, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **6**).

[0095] Thus, it was revealed that SYN3 shown as SEQ ID NO: 6 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0096]

(SEQ ID NO: 5)

0001 MNFLRRRLSD SSFMANLPNG YMTDLQRPDS STSSPASPAM ERRHPQPLAA

0051 SFSSPGSSLF SSLSSAMKQA PQATSGLMEP PGPSTPIVQR PRILLVIDDA

0101 HTDWSKYFHG KKVNGEIEIR VEQAEFSELN LAAYVTGGCM VDMQVVRNGT

0151 KVVSRSFKPD FILVRQHAYS MALGEDYRSL VIGLQYGGLP AVNSLYSVYN

0201 FCSKPWVFSQ LIKIFHSLGP EKFPLVEQTF FPNHKPMVTA PHFPVVVKLG

0251 HAHAGMGKIK VENQLDFQDI TSVVAMAKTY ATTEAFIDSK YDIRIQKIGS

0301 NYKAYMRTSI SGNWKANTGS AMLEQVAMTE RYRLWVDSCS EMFGGLDICA

0351 VKAVHSKDGR DYIIEVMDSS MPLIGEHVEE DRQLMADLVV SKMSQLPMPG

0401 GTAPSPLRPW APQIKSAKSP GQAQLGPQLG QPQPRPPPQG GPRQAQSPQP

0451 QRSGSPSQQR LSPQGQQPLS PQSGSPQQQR SPGSPQLSRA SSGSSPNQAS

0501 KPGATLASQP RPPVQGRSTS QQGEESKKPA PPHPHLNKSQ SLTNSLSTSD

0551 TSQRGTPSED EAKAETIRNL RKSFASLFSD

Synapsin-3-Derived Peptide SYN3

[0097]

(SEQ ID NO: 6)

EMFGGLDICAVKAVHSK

(4) Oxytocin Receptor-Derived Peptide OXYR

[0098] For OXYR shown as SEQ ID NO: 8, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **7**). Thus, it was revealed that OXYR shown as SEQ ID NO: 8 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0099]

(SEQ ID NO: 7)

0001 MEGALAANWS AEAANASAAP PGAEGNRTAG PPRRNEALAR VEVAVLCLIL

0051 LLALSGNACV LLALRTTRQK HSRLFFFMKH LSIADLVVAV FQVLPQLLWD

0101 ITFRFYGPDL LCRLVKYLQV VGMFASTYLL LLMSLDRCLA ICQPLRSLRR

-continued

0151 RTDRLAVLAT WLGCLVASAP QVHIFSLREV ADGVFDCWAV FIQPWGPKAY

0201 ITWITLAVYI VPVIVLAACY GLISFKIWQN LRLKTAAAAA AEAPEGAAAG

0251 DGGRVALARV SSVKLISKAK IRTVKMTFII VLAFIVCWTP FFFVQMWSVW

0301 DANAPKEASA FIIVMLLASL NSCCNPWIYM LFTGHLFHEL VQRFLCCSAS

0351 YLKGRRLGET SASKKSNSSS FVLSHRSSSQ RSCSQPSTA

Oxytocin Receptor-Derived Peptide OXYR

[0100]

(SEQ ID NO: 8)

AAPPGAEGNRT

(5) Inter-Alpha-Trypsin Inhibitor Heavy Chain H5-Like Protein-Derived Peptide ITH5L

[0101] For ITH5L shown as SEQ ID NO: 10, area values of cognitive impairment (AD, MCI and DLB) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **8**).

[0102] Thus, it was revealed that ITH5L shown as SEQ ID NO: 10 was useful to distinguish patient of cognitive impairment (AD, MCI and DLB) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0103]

(SEQ ID NO: 9)

0001 GPPVPASSST KLLMTSYSMR STVVSRYAHT LVTSVLFNPH AEAHEAIFDL

0051 DLPHLAFISN FTMTINNKVY IAEVKEKHQA KKIYEEAHQQ GKTAAHVGIR

0101 DRESEKFRIS TSLAAGTEVT FSLAYEELLQ RHQGQYQLVV SLRPGQLVKR

0151 LSIEVTVSER TGISYVHIPP LRTGRLRTNA HASEVDSPPS TRIERGETCV

0201 RITYCPTLQD QSSISGSGIM ADFLVQYDVV MEDIIGDVQI YDDYFIHYFA

0251 PRGLPPMEKN VVFVIDVSSS MFGTKMEQTK TAMNVILSDL QANDYFNIIS

0301 FSDTVNVWKA GGSIQATIQN VHSAKDYLHC MEADGWTDVN SALLAAASVL

0351 NHSNQEPGRG PSVGRIPLII FLTDGEPTAG VTTPSVILSN VRQALGHRVS

0401 LFSLAFGDDA DFTLLRRLSL ENRGIARRIY EDTDAALQLK GLYEEISMPL

0451 LADVRLNYLG GLVGASPWAV FPNYFGGSEL VVAGQVQPGK QELGIHLAAR

0501 GPKDQLLVAH HSEGATNNSQ KAFGCPGEPA PNVAHFIRRL WAYVTIGELL

0551 DAHFQARDTT TRHLLAAKVL NLSLEYNFVT PLTSLVMVQP KQASEETRRQ

0601 TSTSAGPDTI MPSSSSRHGL GVSTAQPALV PKVISPKSRP VKPKFYLSST

0651 TTASTKKMLS SKELEPLGES PHTLSMPTYP KAKIPAQQDS GTLAQPTLRT

0701 KPTILVPSNS GTLLPLKPGS LSHQNPDILP TNSRTQVPPV KPGIPASPKA

0751 DTVKCVTPLH SKPGAPSHPQ LGALTSQAPK GLPQSRPGVS TLQVPKYPLH

0801 TRPRVPAPKT RNNMPHLGPG ILLSKTPKIL LSLKPSAPPH QISTSISLSK

0851 PETPNPHMPQ TPLPPRPDRP RPPLPESLST FPNTISSSTG PSSTTTTSVL

0901 GEPLPMPFTP TLPPGRFWHQ YDLLPGPQRT RQVLGPSRPG VPTMSLLNSS

0951 RPTPEGSPPN LPILLPSSIL PEAISLLLLP EELELLSESM VESKFVESLN

1001 PPAFYTFLTP DEDGSPNWDG NSEEILGGAG GSMESQGSSV GLAKGTLPSI

1051 FTFSSSVDGD PHFVIQIPHS EEKICFTLNG HPGDLLQLIE DPKAGLHVSG

1101 KLLGAPPRPG HKDQTRTYFQ IITVTTDKPR AYTITISRSS ISLRGEGTLR

1151 LSWDQPALLK RPQLELYVAA AARLTLRLGP YLEFLVLRHR YRHPSTLQLP

-continued

1201 HLGFYVANGS GLSPSARGLI GQFQHADIRL VTGPMGPCLR RHHGPDVPVI

1251 LGKRLLKDSP RLLPRWASCW LVKRSHVELL LGHPYLSYVL

Inter-Alpha-Trypsin Inhibitor Heavy Chain H5-Like Protein-Derived Peptide ITH5L

[0104]

(SEQ ID NO: 10)

RVSLFSLAFGDDAD

(6) E3 Ubiquitin-Protein Ligase HERC2-Derived Peptide HERC2

[0105] For HERC2 shown as SEQ ID NO: 12, area values of cognitive impairment (AD, MCI and DLB) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **9**).

[0106] Thus, it was revealed that HERC2 shown as SEQ ID NO: 12 was useful to distinguish patient of cognitive impairment (AD, MCI and DLB) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0107]

(SEQ ID NO: 11)

0001 MPSESFCLAA QARLDSKWLK TDIQLAFTRD GLCGLWNEMV KDGEIVYTGT

0051 ESTQNGELPP RKDDSVEPSG TKKEDLNDKE KKDEEETPAP IYRAKSILDS

0101 WVWGKQPDVN ELKECLSVLV KEQQALAVQS ATTTLSALRL KQRLVILERY

0151 FIALNRTVFQ ENVKVKWKSS GISLPPVDKK SSRPAGKGVE GLARVGSRAA

0201 LSFAFAFLRR AWRSGEDADL CSELLQESLD ALRALPEASL FDESTVSSVW

0251 LEVVERATRF LRSVVTGDVH GTPATKGPGS IPLQDQHLAL AILLELAVQR

0301 GTLSQMLSAI LLLLQLWDSG AQETDNERSA QGTSAPLLPL LQRFQSIICR

0351 KDAPHSEGDM HLLSGPLSPN ESFLRYLTLP QDNELAIDLR QTAVVVMAHL

0401 DRLATPCMPP LCSSPTSHKG SLQEVIGWGL IGWKYYANVI GPIQCEGLAN

0451 LGVTQIACAE KRFLILSRNG RVYTQAYNSD TLAPQLVQGL ASRNIVKIAA

0501 HSDGHHYLAL AATGEVYSWG CGDGGRLGHG DTVPLEEPKV ISAFSGKQAG

0551 KHVVHIACGS TYSAAITAEG ELYTWGRGNY GRLGHGSSED EAIPMLVAGL

0601 KGLKVIDVAC GSGDAQTLAV TENGQVWSWG DGDYGKLGRG GSDGCKTPKL

0651 IEKLQDLDVV KVRCGSQFSI ALTKDGQVYS WGKGDNQRLG HGTEEHVRYP

0701 KLLEGLQGKK VIDVAAGSTH CLALTEDSEV HSWGSNDQCQ HFDTLRVTKP

0751 EPAALPGLDT KHIVGIACGP AQSFAWSSCS EWSIGLRVPF VVDICSMTFE

0801 QLDLLLRQVS EGMDGSADWP PPQEKECVAV ATLNLLRLQL HAAISHQVDP

0851 EFLGLGLGSI LLNSLKQTVV TLASSAGVLS TVQSAAQAVL QSGWSVLLPT

0901 AEERARALSA LLPCAVSGNE VNISPGRRFM IDLLVGSLMA DGGLESALHA

0951 AITAEIQDIE AKKEAQKEKE IDEQEANAST FHRSRTPLDK DLINTGICES

1001 SGKQCLPLVQ LIQQLLRNIA SQTVARLKDV ARRISSCLDF EQHSRERSAS

1051 LDLLLRFQRL LISKLYPGES IGQTSDISSP ELMGVGSLLK KYTALLCTHI

1101 GDILPVAASI ASTSWRHFAE VAYIVEGDFT GVLLPELVVS IVLLLSKNAG

1151 LMQEAGAVPL LGGLLEHLDR FNHLAPGKER DDHEELAWPG IMESFFTGQN

1201 CRNNEEVTLI RKADLENHNK DGGFWTVIDG KVYDIKDFQT QSLTGNSILA

1251 QFAGEDPVVA LEAALQFEDT RESMHAFCVG QYLEPDQEIV TIPDLGSLSS

1301 PLIDTERNLG LLLGLHASYL AMSTPLSPVE IECAKWLQSS IFSGGLQTSQ

-continued

1351 IHYSYNEEKD EDHCSSPGGT PASKSRLCSH RRALGDHSQA FLQAIADNNI

1401 QDHNVKDFLC QIERYCRQCH LTTPIMFPPE HPVEEVGRLL LCCLLKHEDL

1451 GHVALSLVHA GALGIEQVKH RTLPKSVVDV CRVVYQAKCS LIKTHQEQGR

1501 SYKEVCAPVI ERLRFLFNEL RPAVCNDLSI MSKFKLLSSL PRWRRIAQKI

1551 IRERRKKRVP KKPESTDDEE KIGNEESDLE EACILPHSPI NVDKRPIAIK

1601 SPKDKWQPLL STVTGVHKYK WLKQNVQGLY PQSPLLSTIA EFALKEEPVD

1651 VEKMRKCLLK QLERAEVRLE GIDTILKLAS KNFLLPSVQY AMFCGWQRLI

1701 PEGIDIGEPL TDCLKDVDLI PPFNRMLLEV TFGKLYAWAV QNIRNVLMDA

1751 SAKFKELGIQ PVPLQTITNE NPSGPSLGTI PQARFLLVML SMLTLQHGAN

1801 NLDLLLNSGM LALTQTALRL IGPSCDNVEE DMNASAQGAS ATVLEETRKE

1851 TAPVQLPVSG PELAAMMKIG TRVMRGVDWK WGDQDGPPPG LGRVIGELGE

1901 DGWIRVQWDT GSTNSYRMGK EGKYDLKLAE LPAAAQPSAE DSDTEDDSEA

1951 EQTERNIHPT AMMFTSTINL LQTLCLSAGV HAEIMQSEAT KTLCGLLRML

2001 VESGTTDKTS SPNRLVYREQ HRSWCTLGFV RSIALTPQVC GALSSPQWIT

2051 LLMKVVEGHA PFTATSLQRQ ILAVHLLQAV LPSWDKTERA RDMKCLVEKL

2101 FDFLGSLLTT CSSDVPLLRE STLRRRRVRP QASLTATHSS TLAEEVVALL

2151 RTLHSLTQWN GLINKYINSQ LRSITHSFVG RPSEGAQLED YFPDSENPEV

2201 GGLMAVLAVI GGIDGRLRLG GQVMHDEFGE GTVTRITPKG KITVQFSDMR

2251 TCRVCPLNQL KPLPAVAFNV NNLPFTEPML SVWAQLVNLA GSKLEKHKIK

2301 KSTKQAFAGQ VDLDLLRCQQ LKLYILKAGR ALLSHQDKLR QILSQPAVQE

2351 TGTVHTDDGA VVSPDLGDMS PEGPQPPMIL LQQLLASATQ PSPVKAIFDK

2401 QELEAAALAV CQCLAVESTH PSSPGFEDCS SSEATTPVAV QHIRPARVKR

2451 RKQSPVPALP IVVQLMEMGF SRRNIEFALK SLTGASGNAS SLPGVEALVG

2501 WLLDHSDIQV TELSDADTVS DEYSDEEVVE DVDDAAYSMS TGAVVTESQT

2551 YKKRADFLSN DDYAVYVREN IQVGMMVRCC RAYEEVCEGD VGKVIKLDRD

2601 GLHDLNVQCD WQQKGGTYWV RYIHVELIGY PPPSSSSHIK IGDKVRVKAS

2651 VTTPKYKWGS VTHQSVGVVK AFSANGKDII VDFPQQSHWT GLLSEMELVP

2701 SIHPGVTCDG CQMFPINGSR FKCRNCDDFD FCETCFKTKK HNTRHTFGRI

2751 NEPGQSAVFC GRSGKQLKRC HSSQPGMLLD SWSRMVKSLN VSSSVNQASR

2801 LIDGSEPCWQ SSGSQGKHWI RLEIFPDVLV HRLKMIVDPA DSSYMPSLVV

2851 VSGGNSLNNL IELKTININP SDTTVPLLND CTEYHRYIEI AIKQCRSSGI

2901 DCKIHGLILL GRIRAEEEDL AAVPFLASDN EEEEDEKGNS GSLIRKKAAG

2951 LESAATIRTK VFVWGLNDKD QLGGLKGSKI KVPSFSETLS ALNVVQVAGG

3001 SKSLFAVTVE GKVYACGEAT NGRLGLGISS GTVPIPRQIT ALSSYVVKKV

3051 AVHSGGRHAT ALTVDGKVFS WGEGDDGKLG HFSRMNCDKP RLIEALKTKR

3101 IRDIACGSSH SAALTSSGEL YTWGLGEYGR LGHGDNTTQL KPKMVKVLLG

3151 HRVIQVACGS RDAQTLALTD EGLVFSWGDG DFGKLGRGGS EGCNIPQNIE

3201 RLNGQGVCQI ECGAQFSLAL TKSGVVWTWG KGDYFRLGHG SDVHVRKPQV

3251 VEGLRGKKIV HVAVGALHCL AVTDSGQVYA WGDNDHGQQG NGTTTVNRKP

-continued

3301 TLVQGLEGQK ITRVACGSSH SVAWTTVDVA TPSVHEPVLF QTARDPLGAS

3351 YLGVPSDADS SAASNKISGA SNSKPNRPSL AKILLSLDGN LAKQQALSHI

3401 LTALQIMYAR DAVVGALMPA AMIAPVECPS FSSAAPSDAS AMASPMNGEE

3451 CMLAVDIEDR LSPNPWQEKR EIVSSEDAVT PSAVTPSAPS ASARPFIPVT

3501 DDLGAASIIA ETMTKTKEDV ESQNKAAGPE PQALDEFTSL LIADDTRVVV

3551 DLLKLSVCSR AGDRGRDVLS AVLSGMGTAY PQVADMLLEL CVTELEDVAT

3601 DSQSGRLSSQ PVVVESSHPY TDDTSTSGTV KIPGAEGLRV EFDRQCSTER

3651 RHDPLTVMDG VNRIVSVRSG REWSDWSSEL RIPGDELKWK FISDGSVNGW

3701 GWRFTVYPIM PAAGPKELLS DRCVLSCPSM DLVTCLLDFR LNLASNRSIV

3751 PRLAASLAAC AQLSALAASH RMWALQRLRK LLTTEFGQSI NINRLLGEND

3801 GETRALSFTG SALAALVKGL PEALQRQFEY EDPIVRGGKQ LLHSPFFKVL

3851 VALACDLELD TLPCCAETHK WAWFRRYCMA SRVAVALDKR TPLPRLFLDE

3901 VAKKIRELMA DSENMDVLHE SHDIFKREQD EQLVQWMNRR PDDWTLSAGG

3951 SGTIYGWGHN HRGQLGGIEG AKVKVPTPCE ALATLRPVQL IGGEQTLFAV

4001 TADGKLYATG YGAGGRLGIG GTESVSTPTL LESIQHVFIK KVAVNSGGKH

4051 CLALSSEGEV YSWGEAEDGK LGHGNRSPCD RPRVIESLRG IEVVDVAAGG

4101 AHSACVTAAG DLYTWGKGRY GRLGHSDSED QLKPKLVEAL QGHRVVDIAC

4151 GSGDAQTLCL TDDDTVWSWG DGDYGKLGRG GSDGCKVPMK IDSLTGLGVV

4201 KVECGSQFSV ALTKSGAVYT WGKGDYHRLG HGSDDHVRRP RQVQGLQGKK

4251 VIAIATGSLH CVCCTEDGEV YTWGDNDEGQ LGDGTTNAIQ RPRLVAALQG

4301 KKVNRVACGS AHTLAWSTSK PASAGKLPAQ VPMEYNHLQE IPIIALRNRL

4351 LLLHHLSELF CPCIPMFDLE GSLDETGLGP SVGFDTLRGI LISQGKEAAF

4401 RKVVQATMVR DRQHGPVVEL NRIQVKRSRS KGGLAGPDGT KSVFGQMCAK

4451 MSSFGPDSLL LPHRVWKVKF VGESVDDCGG GYSESIAEIC EELQNGLTPL

4501 LIVTPNGRDE SGANRDCYLL SPAARAPVHS SMFRFLGVLL GIAIRTGSPL

4551 SLNLAEPVWK QLAGMSLTIA DLSEVDKDFI PGLMYIRDNE ATSEEFEAMS

4601 LPFTVPSASG QDIQLSSKHT HITLDNRAEY VRLAINYRLH EFDEQVAAVR

4651 EGMARVVPVP LLSLFTGYEL ETMVCGSPDI PLHLLKSVAT YKGIEPSASL

4701 IQWFWEVMES FSNTERSLFL RFVWGRTRLP RTIADFRGRD FVIQVLDKYN

4751 PPDHFLPESY TCFFLLKLPR YSCKQVLEEK LKYAIHFCKS IDTDDYARIA

4801 LTGEPAADDS SDDSDNEDVD SFASDSTQDY LTGH

E3 Ubiquitin-Protein Ligase HERC2-Derived Peptide HERC2

[0108]

(SEQ ID NO: 12)

KLAELPAAAQPSAEDSD

(7) Prothrombin-Derived Peptide THRB

[0109] For THRB shown as SEQ ID NO: 14, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **10**).

[0110] Thus, it was revealed that THRB shown as SEQ ID NO: 14 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0111]

(SEQ ID NO: 13)

0001 ANTFLEEVRK GNLERECVEE TCSYEEAFEA LESSTATDVF WAKYTACETA

0051 RTPRDKLAAC LEGNCAEGLG TNYRGHVNIT RSGIECQLWR SRYPHKPEIN

0101 STTHPGADLQ ENFCRNPDSS TTGPWCYTTD PTVRRQECSI PVCGQDQVTV

0151 AMTPRSEGSS VNLSPPLEQC VPDRGQQYQG RLAVTTHGLP CLAWASAQAK

0201 ALSKHQDFNS AVQLVENFCR NPDGDEEGVW CYVAGKPGDF GYCDLNYCEE

0251 AVEEETGDGL DEDSDRAIEG RTATSEYQTF FNPRTFGSGE ADCGLRPLFE

0301 KKSLEDKTER ELLESYIDGR IVEGSDAEIG MSPWQVMLFR KSPQELLCGA

0351 SLISDRWVLT AAHCLLYPPW DKNFTENDLL VRIGKHSRTR YERNIEKISM

0401 LEKIYIHPRY NWRENLDRDI ALMKLKKPVA FSDYIHPVCL PDRETAASLL

0451 QAGYKGRVTG WGNLKETWTA NVGKGQPSVL QVVNLPIVER PVCKDSTRIR

0501 ITDNMFCAGY KPDEGKRGDA CEGDSGGPFV MKSPFNNRWY QMGIVSWGEG

0551 CDRDGKYGFY THVFRLKKWI QKVIDQFGE

Prothrombin-Derived Peptide THRB

[0112]

(SEQ ID NO: 14)

TATSEYQTFFNPRTFGSGEAD

(8) Transthyretin-Derived Peptide TTHY

[0113] For TTHY shown as SEQ ID NO: 16, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **11**).

[0114] Thus, it was revealed that TTHY shown as SEQ ID NO: 16 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0115]

(SEQ ID NO: 15)

0001 GPTGTGESKC PLMVKVLDAV RGSPAINVAV HVFRKAADDT WEPFASGKTS

0051 ESGELHGLTT EEEFVEGIYK VEIDTKSYWK ALGISPFHEH AEVVFTANDS

0101 GPRRYTIAAL LSPYSYSTTA VVTNPKE

Transthyretin-Derived Peptide TTHY

[0116]

(SEQ ID NO: 16)

AVRGSPAINVAVHVFRKAAD

(9) Tumor Necrosis Factor Receptor Superfamily Member 16-Derived Peptide TNR16

[0117] For TNR16 shown as SEQ ID NO: 18, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **12**).

[0118] Thus, it was revealed that TNR16 shown as SEQ ID NO: 18 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0119]

(SEQ ID NO: 17)

```
0001  KEACPTGLYT HSGECCKACN LGEGVAQPCG ANQTVCEPCL DSVTFSDVVS

0051  ATEPCKPCTE CVGLQSMSAP CVEADDAVCR CAYGYYQDET TGRCEACRVC

0101  EAGSGLVFSC QDKQNTVCEE CPDGTYSDEA NHVDPCLPCT VCEDTERQLR

0151  ECTRWADAEC EEIPGRWITR STPPEGSDST APSTQEPEAP PEQDLIASTV

0201  AGVVTTVMGS SQPVVTRGTT DNLIPVYCSI LAAVVVGLVA YIAFKRWNSC

0251  KQNKQGANSR PVNQTPPPEG EKLHSDSGIS VDSQSLHDQQ PHTQTASGQA

0301  LKGDGGLYSS LPPAKREEVE KLLNGSAGDT WRHLAGELGY QPEHIDSFTH

0351  EACPVRALLA SWATQDSATL DALLAALRRI QRADLVESLC SESTATSPV
```

Tumor Necrosis Factor Receptor Superfamily Member 16-Derived Peptide TNR16

[0120]

(SEQ ID NO: 18)

QTASGQALKGDGGLYS

(10) Complement C4-A-Derived Peptide CO4-1

[0121] For CO4-1 shown as SEQ ID NO: 20, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **13**).

[0122] Thus, it was revealed that CO4-1 shown as SEQ ID NO: 20 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

[0123] After Biosynthesis, Complement C4-A protein is divided into C4 beta chain, Complement C4-A alpha chain and Complement C4 gamma chain by processing.

[0124] SEQ ID NO: 19 is amino acid sequence of intact Complement C4-A protein containing all of these processed peptides.

Intact Protein/Peptide

[0125]

(SEQ ID NO: 19)

```
0001  KPRLLLFSPS VVHLGVPLSV GVQLQDVPRG QVVKGSVFLR NPSRNNVPCS

0051  PKVDFTLSSE RDFALLSLQV PLKDAKSCGL HQLLRGPEVQ LVAHSPWLKD

0101  SLSRTTNIQG INLLFSSRRG HLFLQTDQPI YNPGQRVRYR VFALDQKMRP

0151  STDTITVMVE NSHGLRVRKK EVYMPSSIFQ DDFVIPDISE PGTWKISARF

0201  SDGLESNSST QFEVKKYVLP NFEVKITPGK PYILTVPGHL DEMQLDIQAR

0251  YIYGKPVQGV AYVRFGLLDE DGKKTFFRGL ESQTKLVNGQ SHISLSKAEF

0301  QDALEKLNMG ITDLQGLRLY VAAAIIESPG GEMEEAELTS WYFVSSPFSL

0351  DLSKTKRHLV PGAPFLLQAL VREMSGSPAS GIPVKVSATV SSPGSVPEVQ

0401  DIQQNTDGSG QVSIPIIIPQ TISELQLSVS AGSPHPAIAR LTVAAPPSGG

0451  PGFLSIERPD SRPPRVGDTL NLNLRAVGSG ATFSHYYYMI LSRGQIVFMN

0501  REPKRTLTSV SVFVDHHLAP SFYFVAFYYH GDHPVANSLR VDVQAGACEG

0551  KLELSVDGAK QYRNGESVKL HLETDSLALV ALGALDTALY AAGSKSHKPL

0601  NMGKVFEAMN SYDLGCGPGG GDSALQVFQA AGLAFSDGDQ WTLSRKRLSC

0651  PKEKTTRKKR NVNFQKAINE KLGQYASPTA KRCCQDGVTR LPMMRSCEQR

0701  AARVQQPDCR EPFLSCCQFA ESLRKKSRDK GQAGLQRALE ILQEEDLIDE

0751  DDIPVRSFFP ENWLWRVETV DRFQILTLWL PDSLTTWEIH GLSLSKTKGL

0801  CVATPVQLRV FREFHLHLRL PMSVRRFEQL ELRPVLYNYL DKNLTVSVHV

0851  SPVEGLCLAG GGGLAQQVLV PAGSARPVAF SVVPTAAAAV SLKVVARGSF
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0901 EFPVGDAVSK VLQIEKEGAI HREELVYELN PLDHRGRTLE IPGNSDPNMI

0951 PDGDFNSYVR VTASDPLDTL GSEGALSPGG VASLLRLPRG CGEQTMIYLA

1001 PTLAASRYLD KTEQWSTLPP ETKDHAVDLI QKGYMRIQQF RKADGSYAAW

1051 LSRDSSTWLT AFVLKVLSLA QEQVGGSPEK LQETSNWLLS QQQADGSFQD

1101 PCPVLDRSMQ GGLVGNDETV ALTAFVTIAL HHGLAVFQDE GAEPLKQRVE

1151 ASISKANSFL GEKASAGLLG AHAAAITAYA LSLTKAPVDL LGVAHNNLMA

1201 MAQETGDNLY WGSVTGSQSN AVSPTPAPRN PSDPMPQAPA LWIETTAYAL

1251 LHLLLHEGKA EMADQASAWL TRQGSFQGGF RSTQDTVIAL DALSAYWIAS

1301 HTTEERGLNV TLSSTGRNGF KSHALQLNNR QIRGLEEELQ FSLGSKINVK

1351 VGGNSKGTLK VLRTYNVLDM KNTTCQDLQI EVTVKGHVEY TMEANEDYED

1401 YEYDELPAKD DPDAPLQPVT PLQLFEGRRN RRRREAPKVV EEQESRVHYT

1451 VCIWRNGKVG LSGMAIADVT LLSGFHALRA DLEKLTSLSD RYVSHFETEG

1501 PHVLLYFDSV PTSRECVGFE AVQEVPVGLV QPASATLYDY YNPERRCSVF

1551 YGAPSKSRLL ATLCSAEVCQ CAEGKCPRQR RALERGLQDE DGYRMKFACY

1601 YPRVEYGFQV KVLREDSRAA FRLFETKITQ VLHFTKDVKA AANQMRNFLV

1651 RASCRLRLEP GKEYLIMGLD GATYDLEGHP QYLLDSNSWI EEMPSERLCR

1701 STRQRAACAQ LNDFLQEYGT QGCQV
```

Complement C4-Derived Peptide CO4-1

[0126]

(SEQ ID NO: 20)

NGFKSHALQLNNRQIR

(11) Complement C4-B-Derived Peptide CO4-1

[0127] From the results of MS/MS analysis and MASCOT database search, A sequence of CO4-1 peptide as shown SEQ ID NO: 20 is an amino acid sequence present in the part of topological region that is common to Complement C4-A protein (SEQ ID NO: 19) and Complement C4-B protein. After Biosynthesis, Complement C4-B protein is divided into C4 beta chain, Complement C4-B alpha chain and Complement C4 gamma chain by processing.

[0128] SEQ ID NO: 21 is amino acid sequence of intact Complement C4-B protein containing all of these processed peptides.

Intact Protein/Peptide

[0129]

(SEQ ID NO: 21)

```
0001 KPRLLLFSPS VVHLGVPLSV GVQLQDVPRG QVVKGSVFLR NPSRNNVPCS

0051 PKVDFTLSSE RDFALLSLQV PLKDAKSCGL HQLLRGPEVQ LVAHSPWLKD

0101 SLSRTTNIQG INLLFSSRRG HLFLQTDQPI YNPGQRVRYR VFALDQKMRP

0151 STDTITVMVE NSHGLRVRKK EVYMPSSIFQ DDFVIPDISE PGTWKISARF

0201 SDGLESNSST QFEVKKYVLP NFEVKITPGK PYILTVPGHL DEMQLDIQAR

0251 YIYGKPVQGV AYVRFGLLDE DGKKTFFRGL ESQTKLVNGQ SHISLSKAEF

0301 QDALEKLNMG ITDLQGLRLY VAAAIIESPG GEMEEAELTS WYFVSSPFSL

0351 DLSKTKRHLV PGAPFLLQAL VREMSGSPAS GIPVKVSATV SSPGSVPEVQ

0401 DIQQNTDGSG QVSIPIIIPQ TISELQLSVS AGSPHPAIAR LTVAAPPSGG

0451 PGFLSIERPD SRPPRVGDTL NLNLRAVGSG ATFSHYYYMI LSRGQIVFMN

0501 REPKRTLTSV SVFVDHHLAP SFYFVAFYYH GDHPVANSLR VDVQAGACEG

0551 KLELSVDGAK QYRNGESVKL HLETDSLALV ALGALDTALY AAGSKSHKPL
```

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```
0601 NMGKVFEAMN SYDLGCGPGG GDSALQVFQA AGLAFSDGDQ WTLSRKRLSC

0651 PKEKTTRKKR NVNFQKAINE KLGQYASPTA KRCCQDGVTR LPMMRSCEQR

0701 AARVQQPDCR EPFLSCCQFA ESLRKKSRDK GQAGLQRALE ILQEEDLIDE

0751 DDIPVRSFFP ENWLWRVETV DRFQILTLWL PDSLTTWEIH GLSLSKTKGL

0801 CVATPVQLRV FREFHLHLRL PMSVRRFEQL ELRPVLYNYL DKNLTVSVHV

0851 SPVEGLCLAG GGGLAQQVLV PAGSARPVAF SVVPTAAAAV SLKVVARGSF

0901 EFPVGDAVSK VLQIEKEGAI HREELVYELN PLDHRGRTLE IPGNSDPNMI

0951 PDGDFNSYVR VTASDPLDTL GSEGALSPGG VASLLRLPRG CGEQTMIYLA

1001 PTLAASRYLD KTEQWSTLPP ETKDHAVDLI QKGYMRIQQF RKADGSYAAW

1051 LSRDSSTWLT AFVLKVLSLA QEQVGGSPEK LQETSNWLLS QQQADGSFQD

1101 LSPVIHRSMQ GGLVGNDETV ALTAFVTIAL HHGLAVFQDE GAEPLKQRVE

1151 ASISKANSFL GEKASAGLLG AHAAAITAYA LSLTKAPVDL LGVAHNNLMA

1201 MAQETGDNLY WGSVTGSQSN AVSPTPAPRN PSDPMPQAPA LWIETTAYAL

1251 LHLLLHEGKA EMADQASAWL TRQGSFQGGF RSTQDTVIAL DALSAYWIAS

1301 HTTEERGLNV TLSSTGRNGF KSHALQLNNR QIRGLEEELQ FSLGSKINVK

1351 VGGNSKGTLK VLRTYNVLDM KNTTCQDLQI EVTVKGHVEY TMEANEDYED

1401 YEYDELPAKD DPDAPLQPVT PLQLFEGRRN RRRREAPKVV EEQESRVHYT

1451 VCIWRNGKVG LSGMAIADVT LLSGFHALRA DLEKLTSLSD RYVSHFETEG

1501 PHVLLYFDSV PTSRECVGFE AVQEVPVGLV QPASATLYDY YNPERRCSVF

1551 YGAPSKSRLL ATLCSAEVCQ CAEGKCPRQR RALERGLQDE DGYRMKFACY

1601 YPRVEYGFQV KVLREDSRAA FRLFETKITQ VLHFTKDVKA AANQMRNFLV

1651 RASCRLRLEP GKEYLIMGLD GATYDLEGHP QYLLDSNSWI EEMPSERLCR

1701 STRQRAACAQ LNDFLQEYGT QGCQV
```

Just in case, following shows the sequence of CO4-1.

Complement C4-Derived Peptide CO4-1

[0130]

(SEQ ID NO: 20)

NGFKSHALQLNNRQIR

(12) Complement C4-A-Derived Peptide CO4-2

[0131] For CO4-2 shown as SEQ ID NO: 22, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **14**).

[0132] Thus, it was revealed that CO4-2 shown as SEQ ID NO: 22 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1) After Biosynthesis, Complement C4-A protein is divided into C4 beta chain, Complement C4-A alpha chain and Complement C4 gamma chain by processing.

[0133] SEQ ID NO: 19 is amino acid sequence of intact Complement C4-A protein containing all of these processed peptides.

Intact Protein/Peptide

[0134]

(SEQ ID NO: 19)

```
0001 KPRLLLFSPS VVHLGVPLSV GVQLQDVPRG QVVKGSVFLR NPSRNNVPCS

0051 PKVDFTLSSE RDFALLSLQV PLKDAKSCGL HQLLRGPEVQ LVAHSPWLKD

0101 SLSRTTNIQG INLLFSSRRG HLFLQTDQPI YNPGQRVRYR VFALDQKMRP

0151 STDTITVMVE NSHGLRVRKK EVYMPSSIFQ DDFVIPDISE PGTWKISARF

0201 SDGLESNSST QFEVKKYVLP NFEVKITPGK PYILTVPGHL DEMQLDIQAR
```

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0251 YIYGKPVQGV AYVRFGLLDE DGKKTFFRGL ESQTKLVNGQ SHISLSKAEF

0301 QDALEKLNMG ITDLQGLRLY VAAAIIESPG GEMEEAELTS WYFVSSPFSL

0351 DLSKTKRHLV PGAPFLLQAL VREMSGSPAS GIPVKVSATV SSPGSVPEVQ

0401 DIQQNTDGSG QVSIPIIIPQ TISELQLSVS AGSPHPAIAR LTVAAPPSGG

0451 PGFLSIERPD SRPPRVGDTL NLNLRAVGSG ATFSHYYYMI LSRGQIVFMN

0501 REPKRTLTSV SVFVDHHLAP SFYFVAFYYH GDHPVANSLR VDVQAGACEG

0551 KLELSVDGAK QYRNGESVKL HLETDSLALV ALGALDTALY AAGSKSHKPL

0601 NMGKVFEAMN SYDLGCGPGG GDSALQVFQA AGLAFSDGDQ WTLSRKRLSC

0651 PKEKTTRKKR NVNFQKAINE KLGQYASPTA KRCCQDGVTR LPMMRSCEQR

0701 AARVQQPDCR EPFLSCCQFA ESLRKKSRDK GQAGLQRALE ILQEEDLIDE

0751 DDIPVRSFFP ENWLWRVETV DRFQILTLWL PDSLTTWEIH GLSLSKTKGL

0801 CVATPVQLRV FREFHLHLRL PMSVRRFEQL ELRPVLYNYL DKNLTVSVHV

0851 SPVEGLCLAG GGGLAQQVLV PAGSARPVAF SVVPTAAAAV SLKVVARGSF

0901 EFPVGDAVSK VLQIEKEGAI HREELVYELN PLDHRGRTLE IPGNSDPNMI

0951 PDGDFNSYVR VTASDPLDTL GSEGALSPGG VASLLRLPRG CGEQTMIYLA

1001 PTLAASRYLD KTEQWSTLPP ETKDHAVDLI QKGYMRIQQF RKADGSYAAW

1051 LSRDSSTWLT AFVLKVLSLA QEQVGGSPEK LQETSNWLLS QQQADGSFQD

1101 PCPVLDRSMQ GGLVGNDETV ALTAFVTIAL HHGLAVFQDE GAEPLKQRVE

1151 ASISKANSFL GEKASAGLLG AHAAAITAYA LSLTKAPVDL LGVAHNNLMA

1201 MAQETGDNLY WGSVTGSQSN AVSPTPAPRN PSDPMPQAPA LWIETTAYAL

1251 LHLLLHEGKA EMADQASAWL TRQGSFQGGF RSTQDTVIAL DALSAYWIAS

1301 HTTEERGLNV TLSSTGRNGF KSHALQLNNR QIRGLEEELQ FSLGSKINVK

1351 VGGNSKGTLK VLRTYNVLDM KNTTCQDLQI EVTVKGHVEY TMEANEDYED

1401 YEYDELPAKD DPDAPLQPVT PLQLFEGRRN RRRREAPKVV EEQESRVHYT

1451 VCIWRNGKVG LSGMAIADVT LLSGFHALRA DLEKLTSLSD RYVSHFETEG

1501 PHVLLYFDSV PTSRECVGFE AVQEVPVGLV QPASATLYDY YNPERRCSVF

1551 YGAPSKSRLL ATLCSAEVCQ CAEGKCPRQR RALERGLQDE DGYRMKFACY

1601 YPRVEYGFQV KVLREDSRAA FRLFETKITQ VLHFTKDVKA AANQMRNFLV

1651 RASCRLRLEP GKEYLIMGLD GATYDLEGHP QYLLDSNSWI EEMPSERLCR

1701 STRQRAACAQ LNDFLQEYGT QGCQV

Complement C4-Derived Peptide CO4-2

[0135]

(SEQ ID NO: 22)

APLQPVTPLQLFEGRRN

(13) Complement C4-B-Derived Peptide CO4-2

[0136] From the results of MS/MS analysis and MASCOT database search, A sequence of CO4-2 peptide as shown SEQ ID NO: 22 is an amino acid sequence present in the part of topological region that is common to Complement C4-A protein (SEQ ID NO: 19) and Complement C4-B protein. After Biosynthesis, Complement C4-B protein is divided into C4 beta chain, Complement C4-B alpha chain and Complement C4 gamma chain by processing. SEQ ID NO: 21 is amino acid sequence of intact Complement C4-B protein containing all of these processed peptides.

Intact Protein/Peptide

[0137]

(SEQ ID NO: 21)

```
0001 KPRLLLFSPS VVHLGVPLSV GVQLQDVPRG QVVKGSVFLR NPSRNNVPCS

0051 PKVDFTLSSE RDFALLSLQV PLKDAKSCGL HQLLRGPEVQ LVAHSPWLKD

0101 SLSRTTNIQG INLLFSSRRG HLFLQTDQPI YNPGQRVRYR VFALDQKMRP

0151 STDTITVMVE NSHGLRVRKK EVYMPSSIFQ DDFVIPDISE PGTWKISARF

0201 SDGLESNSST QFEVKKYVLP NFEVKITPGK PYILTVPGHL DEMQLDIQAR

0251 YIYGKPVQGV AYVRFGLLDE DGKKTFFRGL ESQTKLVNGQ SHISLSKAEF

0301 QDALEKLNMG ITDLQGLRLY VAAAIIESPG GEMEEAELTS WYFVSSPFSL

0351 DLSKTKRHLV PGAPFLLQAL VREMSGSPAS GIPVKVSATV SSPGSVPEVQ

0401 DIQQNTDGSG QVSIPIIIPQ TISELQLSVS AGSPHPAIAR LTVAAPPSGG

0451 PGFLSIERPD SRPPRVGDTL NLNLRAVGSG ATFSHYYYMI LSRGQIVFMN

0501 REPKRTLTSV SVFVDHHLAP SFYFVAFYYH GDHPVANSLR VDVQAGACEG

0551 KLELSVDGAK QYRNGESVKL HLETDSLALV ALGALDTALY AAGSKSHKPL

0601 NMGKVFEAMN SYDLGCGPGG GDSALQVFQA AGLAFSDGDQ WTLSRKRLSC

0651 PKEKTTRKKR NVNFQKAINE KLGQYASPTA KRCCQDGVTR LPMMRSCEQR

0701 AARVQQPDCR EPFLSCCQFA ESLRKKSRDK GQAGLQRALE ILQEEDLIDE

0751 DDIPVRSFFP ENWLWRVETV DRFQILTLWL PDSLTTWEIH GLSLSKTKGL

0801 CVATPVQLRV FREFHLHLRL PMSVRRFEQL ELRPVLYNYL DKNLTVSVHV

0851 SPVEGLCLAG GGGLAQQVLV PAGSARPVAF SVVPTAAAAV SLKVVARGSF

0901 EFPVGDAVSK VLQIEKEGAI HREELVYELN PLDHRGRTLE IPGNSDPNMI

0951 PDGDFNSYVR VTASDPLDTL GSEGALSPGG VASLLRLPRG CGEQTMIYLA

1001 PTLAASRYLD KTEQWSTLPP ETKDHAVDLI QKGYMRIQQF RKADGSYAAW

1051 LSRDSSTWLT AFVLKVLSLA QEQVGGSPEK LQETSNWLLS QQQADGSFQD

1101 LSPVIHRSMQ GGLVGNDETV ALTAFVTIAL HHGLAVFQDE GAEPLKQRVE

1151 ASISKANSFL GEKASAGLLG AHAAAITAYA LSLTKAPVDL LGVAHNNLMA

1201 MAQETGDNLY WGSVTGSQSN AVSPTPAPRN PSDPMPQAPA LWIETTAYAL

1251 LHLLLHEGKA EMADQASAWL TRQGSFQGGF RSTQDTVIAL DALSAYWIAS

1301 HTTEERGLNV TLSSTGRNGF KSHALQLNNR QIRGLEEELQ FSLGSKINVK

1351 VGGNSKGTLK VLRTYNVLDM KNTTCQDLQI EVTVKGHVEY TMEANEDYED

1401 YEYDELPAKD DPDAPLQPVTPLQLFEGRRN RRRREAPKVV EEQESRVHYT

1451 VCIWRNGKVG LSGMAIADVT LLSGFHALRA DLEKLTSLSD RYVSHFETEG

1501 PHVLLYFDSV PTSRECVGFE AVQEVPVGLV QPASATLYDY YNPERRCSVF

1551 YGAPSKSRLL ATLCSAEVCQ CAEGKCPRQR RALERGLQDE DGYRMKFACY

1601 YPRVEYGFQV KVLREDSRAA FRLFETKITQ VLHFTKDVKA AANQMRNFLV
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1651 RASCRLRLEP GKEYLIMGLD GATYDLEGHP QYLLDSNSWI EEMPSERLCR

1701 STRQRAACAQ LNDFLQEYGT QGCQV

[0138] Just in case, following shows the sequence of CO4-2.

Complement C4-Derived Peptide CO4-2

[0139]

(SEQ ID NO: 22)

APLQPVTPLQLFEGRRN

(14) Fibrinogen Alpha Chain (isoform 1)-Derived Peptide FIBA-1

[0140] For FIBA-1 shown as SEQ ID NO: 24, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **15**).

[0141] Thus, it was revealed that FIBA-1 shown as SEQ ID NO: 24 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0142]

(SEQ ID NO: 23)

0001 GPRVVERHQS ACKDSDWPFC SDEDWNYKCP SGCRMKGLID EVNQDFTNRI

0051 NKLKNSLFEY QKNNKDSHSL TTNIMEILRG DFSSANNRDN TYNRVSEDLR

0101 SRIEVLKRKV IEKVQHIQLL QKNVRAQLVD MKRLEVDIDI KIRSCRGSCS

0151 RALAREVDLK DYEDQQKQLE QVIAKDLLPS RDRQHLPLIK MKPVPDLVPG

0201 NFKSQLQKVP PEWKALTDMP QMRMELERPG GNEITRGGST SYGTGSETES

0251 PRNPSSAGSW NSGSSGPGST GNRNPGSSGT GGTATWKPGS SGPGSTGSWN

0301 SGSSGTGSTG NQNPGSPRPG STGTWNPGSS ERGSAGHWTS ESSVSGSTGQ

0351 WHSESGSFRP DSPGSGNARP NNPDWGTFEE VSGNVSPGTR REYHTEKLVT

0401 SKGDKELRTG KEKVTSGSTT TTRRSCSKTV TKTVIGPDGH KEVTKEVVTS

0451 EDGSDCPEAM DLGTLSGIGT LDGFRHRHPD EAAFFDTAST GKTFPGFFSP

0501 MLGEFVSETE SRGSESGIFT NTKESSSHHP GIAEFPSRGK SSSYSKQFTS

0551 STSYNRGDSTFESKSYKMAD EAGSEADHEG THSTKRGHAK SRPVRDCDDV

0601 LQTHPSGTQS GIFNIKLPGS SKIFSVYCDQ ETSLGGWLLI QQRMDGSLNF

0651 NRTWQDYKRG FGSLNDEGEG EFWLGNDYLH LLTQRGSVLR VELEDWAGNE

0701 AYAEYHFRVG SEAEGYALQV SSYEGTAGDA LIEGSVEEGA EYTSHNNMQF

0751 STFDRDADQW EENCAEVYGG GWWYNNCQAA NLNGIYYPGG SYDPRNNSPY

0801 EIENGVVWVS FRGADYSLRA VRMKIRPLVT Q

Fibrinogen Alpha Chain-Derived Peptide FIBA-1

[0143]

(SEQ ID NO: 24)

SSSYSKQFTSSTSYNRGDSTFES

(15) Fibrinogen Alpha Chain (isoform 2)-Derived Peptide FIBA-1

[0144] From the results of MS/MS analysis and MASCOT database search, A sequence of FIBA-1 peptide as shown SEQ ID NO: 24 is an amino acid sequence present in the part of topological region that is common to Fibrinogen alpha chain (isoform 1) (SEQ ID NO: 23) and Fibrinogen alpha chain (isoform 2). Followings, as SEQ ID NO: 25, an amino acid sequence of intact protein of Fibrinogen alpha chain (isoform 2) were shown.

Intact Protein/Peptide

[0145]

(SEQ ID NO: 25)

```
0001 GPRVVERHQS ACKDSDWPFC SDEDWNYKCP SGCRMKGLID EVNQDFTNRI

0051 NKLKNSLFEY QKNNKDSHSL TTNIMEILRG DFSSANNRDN TYNRVSEDLR

0101 SRIEVLKRKV IEKVQHIQLL QKNVRAQLVD MKRLEVDIDI KIRSCRGSCS

0151 RALAREVDLK DYEDQQKQLE QVIAKDLLPS RDRQHLPLIK MKPVPDLVPG

0201 NFKSQLQKVP PEWKALTDMP QMRMELERPG GNEITRGGST SYGTGSETES

0251 PRNPSSAGSW NSGSSGPGST GNRNPGSSGT GGTATWKPGS SGPGSTGSWN

0301 SGSSGTGSTG NQNPGSPRPG STGTWNPGSS ERGSAGHWTS ESSVSGSTGQ

0351 WHSESGSFRP DSPGSGNARP NNPDWGTFEE VSGNVSPGTR REYHTEKLVT

0401 SKGDKELRTG KEKVTSGSTT TTRRSCSKTV TKTVIGPDGH KEVTKEVVTS

0451 EDGSDCPEAM DLGTLSGIGT LDGFRHRHPD EAAFFDTAST GKTFPGFFSP

0501 MLGEFVSETE SRGSESGIFT NTKESSSHHP GIAEFPSRGK SSSYSKQFTS

0551 STSYNRGDSTFESKSYKMAD EAGSEADHEG THSTKRGHAK SRPVRGIHTS

0601 PLGKPSLSP
```

[0146] Just in case, following shows the sequence of FIBA-1.

Fibrinogen Alpha Chain-Derived Peptide FIBA-1

[0147]

(SEQ ID NO: 24)

```
SSSYSKQFTSSTSYNRGDSTFES
```

(16) Fibrinogen Alpha Chain (isoform 1)-Derived Peptide FIBA-2

[0148] For FIBA-2 shown as SEQ ID NO: 26, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **16**).

[0149] Thus, it was revealed that FIBA-2 shown as SEQ ID NO: 26 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1)

Intact Protein/Peptide

[0150]

(SEQ ID NO: 23)

```
0001 GPRVVERHQS ACKDSDWPFC SDEDWNYKCP SGCRMKGLID EVNQDFTNRI

0051 NKLKNSLFEY QKNNKDSHSL TTNIMEILRG DFSSANNRDN TYNRVSEDLR

0101 SRIEVLKRKV IEKVQHIQLL QKNVRAQLVD MKRLEVDIDI KIRSCRGSCS

0151 RALAREVDLK DYEDQQKQLE QVIAKDLLPS RDRQHLPLIK MKPVPDLVPG

0201 NFKSQLQKVP PEWKALTDMP QMRMELERPG GNEITRGGST SYGTGSETES

0251 PRNPSSAGSW NSGSSGPGST GNRNPGSSGT GGTATWKPGS SGPGSTGSWN

0301 SGSSGTGSTG NQNPGSPRPG STGTWNPGSS ERGSAGHWTS ESSVSGSTGQ

0351 WHSESGSFRP DSPGSGNARP NNPDWGTFEE VSGNVSPGTR REYHTEKLVT

0401 SKGDKELRTG KEKVTSGSTT TTRRSCSKTV TKTVIGPDGH KEVTKEVVTS

0451 EDGSDCPEAM DLGTLSGIGT LDGFRHRHPD EAAFFDTAST GKTFPGFFSP

0501 MLGEFVSETE SRGSESGIFT NTKESSSHHP GIAEFPSRGK SSSYSKQFTS

0551 STSYNRGDSTFESKSYKMAD EAGSEADHEG THSTKRGHAK SRPVRDCDDV

0601 LQTHPSGTQS GIFNIKLPGS SKIFSVYCDQ ETSLGGWLLI QQRMDGSLNF
```

-continued

```
0651 NRTWQDYKRG FGSLNDEGEG EFWLGNDYLH LLTQRGSVLR VELEDWAGNE

0701 AYAEYHFRVG SEAEGYALQV SSYEGTAGDA LIEGSVEEGA EYTSHNNMQF

0751 STFDRDADQW EENCAEVYGG GWWYNNCQAA NLNGIYYPGG SYDPRNNSPY

0801 EIENGVVWVS FRGADYSLRA VRMKIRPLVT Q
```

Fibrinogen Alpha Chain-Derived Peptide FIBA-2

[0151]

(SEQ ID NO: 26)
SSSYSKQFTSSTSYNRGDSTFESKS

(17) Fibrinogen Alpha Chain (isoform 2)-Derived Peptide FIBA-2

[0152] From the results of MS/MS analysis and MASCOT database search, A sequence of FIBA-2 peptide as shown SEQ ID NO: 26 is an amino acid sequence present in the part of topological region that is common to Fibrinogen alpha chain (isoform 1) (SEQ ID NO: 23) and Fibrinogen alpha chain (isoform 2). Followings, as SEQ ID NO: 25, an amino acid sequence of intact protein of Fibrinogen alpha chain (isoform 2) were shown.

Intact Protein/Peptide

[0153]

(SEQ ID NO: 25)

```
0001 GPRVVERHQS ACKDSDWPFC SDEDWNYKCP SGCRMKGLID EVNQDFTNRI

0051 NKLKNSLFEY QKNNKDSHSL TTNIMEILRG DFSSANNRDN TYNRVSEDLR

0101 SRIEVLKRKV IEKVQHIQLL QKNVRAQLVD MKRLEVDIDI KIRSCRGSCS

0151 RALAREVDLK DYEDQQKQLE QVIAKDLLPS RDRQHLPLIK MKPVPDLVPG

0201 NFKSQLQKVP PEWKALTDMP QMRMELERPG GNEITRGGST SYGTGSETES

0251 PRNPSSAGSW NSGSSGPGST GNRNPGSSGT GGTATWKPGS SGPGSTGSWN

0301 SGSSGTGSTG NQNPGSPRPG STGTWNPGSS ERGSAGHWTS ESSVSGSTGQ

0351 WHSESGSFRP DSPGSGNARP NNPDWGTFEE VSGNVSPGTR REYHTEKLVT

0401 SKGDKELRTG KEKVTSGSTT TTRRSCSKTV TKTVIGPDGH KEVTKEVVTS

0451 EDGSDCPEAM DLGTLSGIGT LDGFRHRHPD EAAFFDTAST GKTFPGFFSP

0501 MLGEFVSETE SRGSESGIFT NTKESSSHHP GIAEFPSRGK SSSYSKQFTS

0551 STSYNRGDSTFESKSYKMAD EAGSEADHEG THSTKRGHAK SRPVRGIHTS

0601 PLGKPSLSP
```

[0154] Just in case, following shows the sequence of FIBA-2.

Fibrinogen Alpha Chain-Derived Peptide FIBA-2

[0155]

(SEQ ID NO: 26)
SSSYSKQFTSSTSYNRGDSTFESKS

(18) Fibrinogen Alpha Chain (isoform 1)-Derived Peptide FIBA-3

[0156] For FIBA-3 shown as SEQ ID NO: 27, area values of cognitive impairment (AD, MCI, DLB and FTD) were significantly higher than NDC. (t-test, $p<0.05$) (see FIG. **17**).

[0157] Thus, it was revealed that FIBA-3 shown as SEQ ID NO: 27 was useful to distinguish patient of cognitive impairment (AD, MCI, DLB and FTD) with subjects not suffering from psychiatry disease (NDC). According to the analysis by receiver operating characteristic (ROC) curve, CO3 was clearly useful to distinguish AD and MCI with NDC. (See Table 1).

Intact Protein/Peptide

[0158]

(SEQ ID NO: 23)

```
0001 GPRVVERHQS ACKDSDWPFC SDEDWNYKCP SGCRMKGLID EVNQDFTNRI

0051 NKLKNSLFEY QKNNKDSHSL TTNIMEILRG DFSSANNRDN TYNRVSEDLR

0101 SRIEVLKRKV IEKVQHIQLL QKNVRAQLVD MKRLEVDIDI KIRSCRGSCS

0151 RALAREVDLK DYEDQQKQLE QVIAKDLLPS RDRQHLPLIK MKPVPDLVPG

0201 NFKSQLQKVP PEWKALTDMP QMRMELERPG GNEITRGGST SYGTGSETES

0251 PRNPSSAGSW NSGSSGPGST GNRNPGSSGT GGTATWKPGS SGPGSTGSWN

0301 SGSSGTGSTG NQNPGSPRPG STGTWNPGSS ERGSAGHWTS ESSVSGSTGQ

0351 WHSESGSFRP DSPGSGNARP NNPDWGTFEE VSGNVSPGTR REYHTEKLVT

0401 SKGDKELRTG KEKVTSGSTT TTRRSCSKTV TKTVIGPDGH KEVTKEVVTS

0451 EDGSDCPEAM DLGTLSGIGT LDGFRHRHPD EAAFFDTAST GKTFPGFFSP

0501 MLGEFVSETE SRGSESGIFT NTKESSSHHP GIAEFPSRGK SSSYSKQFTS

0551 STSYNRGDSTFESKSYKMAD EAGSEADHEG THSTKRGHAK SRPVRDCDDV

0601 LQTHPSGTQS GIFNIKLPGS SKIFSVYCDQ ETSLGGWLLI QQRMDGSLNF

0651 NRTWQDYKRG FGSLNDEGEG EFWLGNDYLH LLTQRGSVLR VELEDWAGNE

0701 AYAEYHFRVG SEAEGYALQV SSYEGTAGDA LIEGSVEEGA EYTSHNNMQF

0751 STFDRDADQW EENCAEVYGG GWWYNNCQAA NLNGIYYPGG SYDPRNNSPY

0801 EIENGVVWVS FRGADYSLRA VRMKIRPLVT Q
```

Fibrinogen Alpha Chain-Derived Peptide FIBA-3

[0159]

(SEQ ID NO: 27)

```
SSSYSKQFTSSTSYNRGDSTFESKSY
```

(19) Fibrinogen Alpha Chain (isoform 2)-Derived Peptide FIBA-3

[0160] From the results of MS/MS analysis and MASCOT database search, A sequence of FIBA-3 peptide as shown SEQ ID NO: 27 is an amino acid sequence present in the part of topological region that is common to Fibrinogen alpha chain (isoform 1) (SEQ ID NO: 23) and Fibrinogen alpha chain (isoform 2). Followings, as SEQ ID NO: 25, an amino acid sequence of intact protein of Fibrinogen alpha chain (isoform 2) were shown.

Intact Protein/Peptide

[0161]

(SEQ ID NO: 25)

```
0001 GPRVVERHQS ACKDSDWPFC SDEDWNYKCP SGCRMKGLID EVNQDFTNRI

0051 NKLKNSLFEY QKNNKDSHSL TTNIMEILRG DFSSANNRDN TYNRVSEDLR

0101 SRIEVLKRKV IEKVQHIQLL QKNVRAQLVD MKRLEVDIDI KIRSCRGSCS

0151 RALAREVDLK DYEDQQKQLE QVIAKDLLPS RDRQHLPLIK MKPVPDLVPG

0201 NFKSQLQKVP PEWKALTDMP QMRMELERPG GNEITRGGST SYGTGSETES

0251 PRNPSSAGSW NSGSSGPGST GNRNPGSSGT GGTATWKPGS SGPGSTGSWN

0301 SGSSGTGSTG NQNPGSPRPG STGTWNPGSS ERGSAGHWTS ESSVSGSTGQ

0351 WHSESGSFRP DSPGSGNARP NNPDWGTFEE VSGNVSPGTR REYHTEKLVT

0401 SKGDKELRTG KEKVTSGSTT TTRRSCSKTV TKTVIGPDGH KEVTKEVVTS

0451 EDGSDCPEAM DLGTLSGIGT LDGFRHRHPD EAAFFDTAST GKTFPGFFSP

0501 MLGEFVSETE SRGSESGIFT NTKESSSHHP GIAEFPSRGK SSSYSKQFTS
```

-continued

0551 STSYNRGDSTFESKSYKMAD EAGSEADHEG THSTKRGHAK SRPVRGIHTS

0601 PLGKPSLSP

[0162] Just in case, following shows the sequence of FIBA-3.

Fibrinogen Alpha Chain-Derived Peptide FIBA-3

[0163]

(SEQ ID NO: 27)

SSSYSKQFTSSTSYNRGDSTFESKSY

TABLE 1

Marker Peptide			
Sequence No.	Sequence name	AD vs. NDC AUC value	MCI vs. NDC AUC value
2	CO3	0.88	0.83
4	AP2C	0.78	0.70
6	SYN3	0.77	0.77
8	OXYR	0.81	0.77
10	ITH5L	0.79	0.70
12	HERC2	0.76	0.73
14	THRB	0.85	0.79
16	TTHY	0.73	0.69
18	TNR16	0.75	0.74
20	CO4-1	0.73	0.67
22	CO4-2	0.76	0.74
24	FIBA-1	0.77	0.64

TABLE 1-continued

Marker Peptide			
Sequence No.	Sequence name	AD vs. NDC AUC value	MCI vs. NDC AUC value
26	FIBA-2	0.74	0.61
27	FIBA-3	0.80	0.64

[0164] Table 1 shows AUC values obtained by the analysis by receiver operating characteristic (ROC) curve in the detection of cognitive impairment of each marker peptides.

[0165] Using these marker peptides in singly or in combination, using or without using liquid chromatography and/or any other suitable separation methods, directly measuring the abundance in serum using other methods such as mass spectrometry or immunological methods or enzymatic methods, on the diagnosis, it is possible to distinguish between non-psychiatry disease subjects including normal healthy subjects and subjects of cognitive impairment like AD, MCI, DLB and FTD.

INDUSTRIAL APPLICABILITY

[0166] By using the biomarkers disclosed in the present invention, mild cognitive impairment and cognitive impairment including Alzheimer disease can be detected. This invention is applicable to the field of medical diagnostics including diagnostic reagent.

SEQUENCE LIST

[0167] 10P01009_Sequence.txt

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 27

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<211> LENGTH: 1641
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

Ser Pro Met Tyr Ser Ile Ile Thr Pro Asn Ile Leu Arg Leu Glu Ser
1 5 10 15

Glu Glu Thr Met Val Leu Glu Ala His Asp Ala Gln Gly Asp Val Pro
20 25 30

Val Thr Val Thr Val His Asp Phe Pro Gly Lys Lys Leu Val Leu Ser
35 40 45

Ser Glu Lys Thr Val Leu Thr Pro Ala Thr Asn His Met Gly Asn Val
50 55 60

Thr Phe Thr Ile Pro Ala Asn Arg Glu Phe Lys Ser Glu Lys Gly Arg
65 70 75 80

Asn Lys Phe Val Thr Val Gln Ala Thr Phe Gly Thr Gln Val Val Glu
85 90 95

Lys Val Val Leu Val Ser Leu Gln Ser Gly Tyr Leu Phe Ile Gln Thr
100 105 110

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Asp Lys Thr Ile Tyr Thr Pro Gly Ser Thr Val Leu Tyr Arg Ile Phe
        115                 120                 125

Thr Val Asn His Lys Leu Leu Pro Val Gly Arg Thr Val Met Val Asn
    130                 135                 140

Ile Glu Asn Pro Glu Gly Ile Pro Val Lys Gln Asp Ser Leu Ser Ser
145                 150                 155                 160

Gln Asn Gln Leu Gly Val Leu Pro Leu Ser Trp Asp Ile Pro Glu Leu
                165                 170                 175

Val Asn Met Gly Gln Trp Lys Ile Arg Ala Tyr Tyr Glu Asn Ser Pro
            180                 185                 190

Gln Gln Val Phe Ser Thr Glu Phe Glu Val Lys Glu Tyr Val Leu Pro
        195                 200                 205

Ser Phe Glu Val Ile Val Glu Pro Thr Glu Lys Phe Tyr Tyr Ile Tyr
    210                 215                 220

Asn Glu Lys Gly Leu Glu Val Thr Ile Thr Ala Arg Phe Leu Tyr Gly
225                 230                 235                 240

Lys Lys Val Glu Gly Thr Ala Phe Val Ile Phe Gly Ile Gln Asp Gly
                245                 250                 255

Glu Gln Arg Ile Ser Leu Pro Glu Ser Leu Lys Arg Ile Pro Ile Glu
            260                 265                 270

Asp Gly Ser Gly Glu Val Val Leu Ser Arg Lys Val Leu Leu Asp Gly
        275                 280                 285

Val Gln Asn Pro Arg Ala Glu Asp Leu Val Gly Lys Ser Leu Tyr Val
    290                 295                 300

Ser Ala Thr Val Ile Leu His Ser Gly Ser Asp Met Val Gln Ala Glu
305                 310                 315                 320

Arg Ser Gly Ile Pro Ile Val Thr Ser Pro Tyr Gln Ile His Phe Thr
                325                 330                 335

Lys Thr Pro Lys Tyr Phe Lys Pro Gly Met Pro Phe Asp Leu Met Val
            340                 345                 350

Phe Val Thr Asn Pro Asp Gly Ser Pro Ala Tyr Arg Val Pro Val Ala
        355                 360                 365

Val Gln Gly Glu Asp Thr Val Gln Ser Leu Thr Gln Gly Asp Gly Val
    370                 375                 380

Ala Lys Leu Ser Ile Asn Thr His Pro Ser Gln Lys Pro Leu Ser Ile
385                 390                 395                 400

Thr Val Arg Thr Lys Lys Gln Glu Leu Ser Glu Ala Glu Gln Ala Thr
                405                 410                 415

Arg Thr Met Gln Ala Leu Pro Tyr Ser Thr Val Gly Asn Ser Asn Asn
            420                 425                 430

Tyr Leu His Leu Ser Val Leu Arg Thr Glu Leu Arg Pro Gly Glu Thr
        435                 440                 445

Leu Asn Val Asn Phe Leu Leu Arg Met Asp Arg Ala His Glu Ala Lys
    450                 455                 460

Ile Arg Tyr Tyr Thr Tyr Leu Ile Met Asn Lys Gly Arg Leu Leu Lys
465                 470                 475                 480

Ala Gly Arg Gln Val Arg Glu Pro Gly Gln Asp Leu Val Val Leu Pro
                485                 490                 495

Leu Ser Ile Thr Thr Asp Phe Ile Pro Ser Phe Arg Leu Val Ala Tyr
            500                 505                 510

Tyr Thr Leu Ile Gly Ala Ser Gly Gln Arg Glu Val Val Ala Asp Ser
```

-continued

```
        515                 520                 525

Val Trp Val Asp Val Lys Asp Ser Cys Val Gly Ser Leu Val Val Lys
    530                 535                 540

Ser Gly Gln Ser Glu Asp Arg Gln Pro Val Pro Gly Gln Gln Met Thr
545                 550                 555                 560

Leu Lys Ile Glu Gly Asp His Gly Ala Arg Val Val Leu Val Ala Val
                565                 570                 575

Asp Lys Gly Val Phe Val Leu Asn Lys Lys Asn Lys Leu Thr Gln Ser
            580                 585                 590

Lys Ile Trp Asp Val Val Glu Lys Ala Asp Ile Gly Cys Thr Pro Gly
        595                 600                 605

Ser Gly Lys Asp Tyr Ala Gly Val Phe Ser Asp Ala Gly Leu Thr Phe
    610                 615                 620

Thr Ser Ser Ser Gly Gln Gln Thr Ala Gln Arg Ala Glu Leu Gln Cys
625                 630                 635                 640

Pro Gln Pro Ala Ala Arg Arg Arg Arg Ser Val Gln Leu Thr Glu Lys
                645                 650                 655

Arg Met Asp Lys Val Gly Lys Tyr Pro Lys Glu Leu Arg Lys Cys Cys
            660                 665                 670

Glu Asp Gly Met Arg Glu Asn Pro Met Arg Phe Ser Cys Gln Arg Arg
        675                 680                 685

Thr Arg Phe Ile Ser Leu Gly Glu Ala Cys Lys Lys Val Phe Leu Asp
    690                 695                 700

Cys Cys Asn Tyr Ile Thr Glu Leu Arg Arg Gln His Ala Arg Ala Ser
705                 710                 715                 720

His Leu Gly Leu Ala Arg Ser Asn Leu Asp Glu Asp Ile Ile Ala Glu
                725                 730                 735

Glu Asn Ile Val Ser Arg Ser Glu Phe Pro Glu Ser Trp Leu Trp Asn
            740                 745                 750

Val Glu Asp Leu Lys Glu Pro Pro Lys Asn Gly Ile Ser Thr Lys Leu
        755                 760                 765

Met Asn Ile Phe Leu Lys Asp Ser Ile Thr Thr Trp Glu Ile Leu Ala
    770                 775                 780

Val Ser Met Ser Asp Lys Lys Gly Ile Cys Val Ala Asp Pro Phe Glu
785                 790                 795                 800

Val Thr Val Met Gln Asp Phe Phe Ile Asp Leu Arg Leu Pro Tyr Ser
                805                 810                 815

Val Val Arg Asn Glu Gln Val Glu Ile Arg Ala Val Leu Tyr Asn Tyr
            820                 825                 830

Arg Gln Asn Gln Glu Leu Lys Val Arg Val Glu Leu Leu His Asn Pro
        835                 840                 845

Ala Phe Cys Ser Leu Ala Thr Thr Lys Arg Arg His Gln Gln Thr Val
    850                 855                 860

Thr Ile Pro Pro Lys Ser Ser Leu Ser Val Pro Tyr Val Ile Val Pro
865                 870                 875                 880

Leu Lys Thr Gly Leu Gln Glu Val Glu Val Lys Ala Ala Val Tyr His
                885                 890                 895

His Phe Ile Ser Asp Gly Val Arg Lys Ser Leu Lys Val Val Pro Glu
            900                 905                 910

Gly Ile Arg Met Asn Lys Thr Val Ala Val Arg Thr Leu Asp Pro Glu
        915                 920                 925
```

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```
Arg Leu Gly Arg Glu Gly Val Gln Lys Glu Asp Ile Pro Pro Ala Asp
    930                 935                 940

Leu Ser Asp Gln Val Pro Asp Thr Glu Ser Glu Thr Arg Ile Leu Leu
945                 950                 955                 960

Gln Gly Thr Pro Val Ala Gln Met Thr Glu Asp Ala Val Asp Ala Glu
                965                 970                 975

Arg Leu Lys His Leu Ile Val Thr Pro Ser Gly Cys Gly Glu Gln Asn
            980                 985                 990

Met Ile Gly Met Thr Pro Thr Val  Ile Ala Val His Tyr  Leu Asp Glu
        995                 1000                1005

Thr Glu  Gln Trp Glu Lys Phe  Gly Leu Glu Lys Arg  Gln Gly Ala
    1010                1015                1020

Leu Glu  Leu Ile Lys Lys Gly  Tyr Thr Gln Gln Leu  Ala Phe Arg
    1025                1030                1035

Gln Pro  Ser Ser Ala Phe Ala  Ala Phe Val Lys Arg  Ala Pro Ser
    1040                1045                1050

Thr Trp  Leu Thr Ala Tyr Val  Val Lys Val Phe Ser  Leu Ala Val
    1055                1060                1065

Asn Leu  Ile Ala Ile Asp Ser  Gln Val Leu Cys Gly  Ala Val Lys
    1070                1075                1080

Trp Leu  Ile Leu Glu Lys Gln  Lys Pro Asp Gly Val  Phe Gln Glu
    1085                1090                1095

Asp Ala  Pro Val Ile His Gln  Glu Met Ile Gly Gly  Leu Arg Asn
    1100                1105                1110

Asn Asn  Glu Lys Asp Met Ala  Leu Thr Ala Phe Val  Leu Ile Ser
    1115                1120                1125

Leu Gln  Glu Ala Lys Asp Ile  Cys Glu Glu Gln Val  Asn Ser Leu
    1130                1135                1140

Pro Gly  Ser Ile Thr Lys Ala  Gly Asp Phe Leu Glu  Ala Asn Tyr
    1145                1150                1155

Met Asn  Leu Gln Arg Ser Tyr  Thr Val Ala Ile Ala  Gly Tyr Ala
    1160                1165                1170

Leu Ala  Gln Met Gly Arg Leu  Lys Gly Pro Leu Leu  Asn Lys Phe
    1175                1180                1185

Leu Thr  Thr Ala Lys Asp Lys  Asn Arg Trp Glu Asp  Pro Gly Lys
    1190                1195                1200

Gln Leu  Tyr Asn Val Glu Ala  Thr Ser Tyr Ala Leu  Leu Ala Leu
    1205                1210                1215

Leu Gln  Leu Lys Asp Phe Asp  Phe Val Pro Pro Val  Val Arg Trp
    1220                1225                1230

Leu Asn  Glu Gln Arg Tyr Tyr  Gly Gly Gly Tyr Gly  Ser Thr Gln
    1235                1240                1245

Ala Thr  Phe Met Val Phe Gln  Ala Leu Ala Gln Tyr  Gln Lys Asp
    1250                1255                1260

Ala Pro  Asp His Gln Glu Leu  Asn Leu Asp Val Ser  Leu Gln Leu
    1265                1270                1275

Pro Ser  Arg Ser Ser Lys Ile  Thr His Arg Ile His  Trp Glu Ser
    1280                1285                1290

Ala Ser  Leu Leu Arg Ser Glu  Glu Thr Lys Glu Asn  Glu Gly Phe
    1295                1300                1305
```

-continued

```
Thr Val  Thr Ala Glu Gly Lys  Gly Gln Gly Thr Leu  Ser Val Val
    1310                 1315                 1320

Thr Met  Tyr His Ala Lys Ala  Lys Asp Gln Leu Thr  Cys Asn Lys
    1325                 1330                 1335

Phe Asp  Leu Lys Val Thr Ile  Lys Pro Ala Pro Glu  Thr Glu Lys
    1340                 1345                 1350

Arg Pro  Gln Asp Ala Lys Asn  Thr Met Ile Leu Glu  Ile Cys Thr
    1355                 1360                 1365

Arg Tyr  Arg Gly Asp Gln Asp  Ala Thr Met Ser Ile  Leu Asp Ile
    1370                 1375                 1380

Ser Met  Met Thr Gly Phe Ala  Pro Asp Thr Asp Asp  Leu Lys Gln
    1385                 1390                 1395

Leu Ala  Asn Gly Val Asp Arg  Tyr Ile Ser Lys Tyr  Glu Leu Asp
    1400                 1405                 1410

Lys Ala  Phe Ser Asp Arg Asn  Thr Leu Ile Ile Tyr  Leu Asp Lys
    1415                 1420                 1425

Val Ser  His Ser Glu Asp Asp  Cys Leu Ala Phe Lys  Val His Gln
    1430                 1435                 1440

Tyr Phe  Asn Val Glu Leu Ile  Gln Pro Gly Ala Val  Lys Val Tyr
    1445                 1450                 1455

Ala Tyr  Tyr Asn Leu Glu Glu  Ser Cys Thr Arg Phe  Tyr His Pro
    1460                 1465                 1470

Glu Lys  Glu Asp Gly Lys Leu  Asn Lys Leu Cys Arg  Asp Glu Leu
    1475                 1480                 1485

Cys Arg  Cys Ala Glu Glu Asn  Cys Phe Ile Gln Lys  Ser Asp Asp
    1490                 1495                 1500

Lys Val  Thr Leu Glu Glu Arg  Leu Asp Lys Ala Cys  Glu Pro Gly
    1505                 1510                 1515

Val Asp  Tyr Val Tyr Lys Thr  Arg Leu Val Lys Val  Gln Leu Ser
    1520                 1525                 1530

Asn Asp  Phe Asp Glu Tyr Ile  Met Ala Ile Glu Gln  Thr Ile Lys
    1535                 1540                 1545

Ser Gly  Ser Asp Glu Val Gln  Val Gly Gln Gln Arg  Thr Phe Ile
    1550                 1555                 1560

Ser Pro  Ile Lys Cys Arg Glu  Ala Leu Lys Leu Glu  Glu Lys Lys
    1565                 1570                 1575

His Tyr  Leu Met Trp Gly Leu  Ser Ser Asp Phe Trp  Gly Glu Lys
    1580                 1585                 1590

Pro Asn  Leu Ser Tyr Ile Ile  Gly Lys Asp Thr Trp  Val Glu His
    1595                 1600                 1605

Trp Pro  Glu Glu Asp Glu Cys  Gln Asp Glu Glu Asn  Gln Lys Gln
    1610                 1615                 1620

Cys Gln  Asp Leu Gly Ala Phe  Thr Glu Ser Met Val  Val Phe Gly
    1625                 1630                 1635

Cys Pro  Asn
    1640


<210> SEQ ID NO 2
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2
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Ala Pro Val Ile His Gln Glu Met Ile Gly Gly Leu Arg Asn
1               5                   10


<210> SEQ ID NO 3
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Met Leu Trp Lys Ile Thr Asp Asn Val Lys Tyr Glu Glu Asp Cys Glu
1               5                   10                  15

Asp Arg His Asp Gly Ser Ser Asn Gly Asn Pro Arg Val Pro His Leu
            20                  25                  30

Ser Ser Ala Gly Gln His Leu Tyr Ser Pro Ala Pro Pro Leu Ser His
        35                  40                  45

Thr Gly Val Ala Glu Tyr Gln Pro Pro Pro Tyr Phe Pro Pro Pro Tyr
    50                  55                  60

Gln Gln Leu Ala Tyr Ser Gln Ser Ala Asp Pro Tyr Ser His Leu Gly
65                  70                  75                  80

Glu Ala Tyr Ala Ala Ala Ile Asn Pro Leu His Gln Pro Ala Pro Thr
                85                  90                  95

Gly Ser Gln Gln Gln Ala Trp Pro Gly Arg Gln Ser Gln Glu Gly Ala
            100                 105                 110

Gly Leu Pro Ser His His Gly Arg Pro Ala Gly Leu Leu Pro His Leu
        115                 120                 125

Ser Gly Leu Glu Ala Gly Ala Val Ser Ala Arg Arg Asp Ala Tyr Arg
    130                 135                 140

Arg Ser Asp Leu Leu Leu Pro His Ala His Ala Leu Asp Ala Ala Gly
145                 150                 155                 160

Leu Ala Glu Asn Leu Gly Leu His Asp Met Pro His Gln Met Asp Glu
                165                 170                 175

Val Gln Asn Val Asp Asp Gln His Leu Leu Leu His Asp Gln Thr Val
            180                 185                 190

Ile Arg Lys Gly Pro Ile Ser Met Thr Lys Asn Pro Leu Asn Leu Pro
        195                 200                 205

Cys Gln Lys Glu Leu Val Gly Ala Val Met Asn Pro Thr Glu Val Phe
    210                 215                 220

Cys Ser Val Pro Gly Arg Leu Ser Leu Leu Ser Ser Thr Ser Lys Tyr
225                 230                 235                 240

Lys Val Thr Val Ala Glu Val Gln Arg Arg Leu Ser Pro Pro Glu Cys
                245                 250                 255

Leu Asn Ala Ser Leu Leu Gly Gly Val Leu Arg Arg Ala Lys Ser Lys
            260                 265                 270

Asn Gly Gly Arg Ser Leu Arg Glu Lys Leu Asp Lys Ile Gly Leu Asn
        275                 280                 285

Leu Pro Ala Gly Arg Arg Lys Ala Ala His Val Thr Leu Leu Thr Ser
    290                 295                 300

Leu Val Glu Gly Glu Ala Val His Leu Ala Arg Asp Phe Ala Tyr Val
305                 310                 315                 320

Cys Glu Ala Glu Phe Pro Ser Lys Pro Val Ala Glu Tyr Leu Thr Arg
                325                 330                 335

Pro His Leu Gly Gly Arg Asn Glu Met Ala Ala Arg Lys Asn Met Leu
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            340                 345                 350

Leu Ala Ala Gln Gln Leu Cys Lys Glu Phe Thr Glu Leu Leu Ser Gln
        355                 360                 365

Asp Arg Thr Pro His Gly Thr Ser Arg Leu Ala Pro Val Leu Glu Thr
    370                 375                 380

Asn Ile Gln Asn Cys Leu Ser His Phe Ser Leu Ile Thr His Gly Phe
385                 390                 395                 400

Gly Ser Gln Ala Ile Cys Ala Ala Val Ser Ala Leu Gln Asn Tyr Ile
                405                 410                 415

Lys Glu Ala Leu Ile Val Ile Asp Lys Ser Tyr Met Asn Pro Gly Asp
            420                 425                 430

Gln Ser Pro Ala Asp Ser Asn Lys Thr Leu Glu Lys Met Glu Lys His
        435                 440                 445

Arg Lys
    450


<210> SEQ ID NO 4
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Pro Gly Arg Gln Ser Gln Glu Gly Ala Gly Leu Pro Ser His His Gly
1               5                   10                  15


<210> SEQ ID NO 5
<211> LENGTH: 580
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Asn Phe Leu Arg Arg Arg Leu Ser Asp Ser Ser Phe Met Ala Asn
1               5                   10                  15

Leu Pro Asn Gly Tyr Met Thr Asp Leu Gln Arg Pro Asp Ser Ser Thr
            20                  25                  30

Ser Ser Pro Ala Ser Pro Ala Met Glu Arg Arg His Pro Gln Pro Leu
        35                  40                  45

Ala Ala Ser Phe Ser Ser Pro Gly Ser Ser Leu Phe Ser Ser Leu Ser
    50                  55                  60

Ser Ala Met Lys Gln Ala Pro Gln Ala Thr Ser Gly Leu Met Glu Pro
65                  70                  75                  80

Pro Gly Pro Ser Thr Pro Ile Val Gln Arg Pro Arg Ile Leu Leu Val
                85                  90                  95

Ile Asp Asp Ala His Thr Asp Trp Ser Lys Tyr Phe His Gly Lys Lys
            100                 105                 110

Val Asn Gly Glu Ile Glu Ile Arg Val Glu Gln Ala Glu Phe Ser Glu
        115                 120                 125

Leu Asn Leu Ala Ala Tyr Val Thr Gly Gly Cys Met Val Asp Met Gln
    130                 135                 140

Val Val Arg Asn Gly Thr Lys Val Val Ser Arg Ser Phe Lys Pro Asp
145                 150                 155                 160

Phe Ile Leu Val Arg Gln His Ala Tyr Ser Met Ala Leu Gly Glu Asp
                165                 170                 175

Tyr Arg Ser Leu Val Ile Gly Leu Gln Tyr Gly Gly Leu Pro Ala Val
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            180                 185                 190

Asn Ser Leu Tyr Ser Val Tyr Asn Phe Cys Ser Lys Pro Trp Val Phe
        195                 200                 205

Ser Gln Leu Ile Lys Ile Phe His Ser Leu Gly Pro Glu Lys Phe Pro
    210                 215                 220

Leu Val Glu Gln Thr Phe Phe Pro Asn His Lys Pro Met Val Thr Ala
225                 230                 235                 240

Pro His Phe Pro Val Val Val Lys Leu Gly His Ala His Ala Gly Met
                245                 250                 255

Gly Lys Ile Lys Val Glu Asn Gln Leu Asp Phe Gln Asp Ile Thr Ser
            260                 265                 270

Val Val Ala Met Ala Lys Thr Tyr Ala Thr Thr Glu Ala Phe Ile Asp
        275                 280                 285

Ser Lys Tyr Asp Ile Arg Ile Gln Lys Ile Gly Ser Asn Tyr Lys Ala
    290                 295                 300

Tyr Met Arg Thr Ser Ile Ser Gly Asn Trp Lys Ala Asn Thr Gly Ser
305                 310                 315                 320

Ala Met Leu Glu Gln Val Ala Met Thr Glu Arg Tyr Arg Leu Trp Val
                325                 330                 335

Asp Ser Cys Ser Glu Met Phe Gly Gly Leu Asp Ile Cys Ala Val Lys
            340                 345                 350

Ala Val His Ser Lys Asp Gly Arg Asp Tyr Ile Ile Glu Val Met Asp
        355                 360                 365

Ser Ser Met Pro Leu Ile Gly Glu His Val Glu Glu Asp Arg Gln Leu
    370                 375                 380

Met Ala Asp Leu Val Val Ser Lys Met Ser Gln Leu Pro Met Pro Gly
385                 390                 395                 400

Gly Thr Ala Pro Ser Pro Leu Arg Pro Trp Ala Pro Gln Ile Lys Ser
                405                 410                 415

Ala Lys Ser Pro Gly Gln Ala Gln Leu Gly Pro Gln Leu Gly Gln Pro
            420                 425                 430

Gln Pro Arg Pro Pro Pro Gln Gly Gly Pro Arg Gln Ala Gln Ser Pro
        435                 440                 445

Gln Pro Gln Arg Ser Gly Ser Pro Ser Gln Gln Arg Leu Ser Pro Gln
    450                 455                 460

Gly Gln Gln Pro Leu Ser Pro Gln Ser Gly Ser Pro Gln Gln Gln Arg
465                 470                 475                 480

Ser Pro Gly Ser Pro Gln Leu Ser Arg Ala Ser Ser Gly Ser Ser Pro
                485                 490                 495

Asn Gln Ala Ser Lys Pro Gly Ala Thr Leu Ala Ser Gln Pro Arg Pro
            500                 505                 510

Pro Val Gln Gly Arg Ser Thr Ser Gln Gln Gly Glu Glu Ser Lys Lys
        515                 520                 525

Pro Ala Pro Pro His Pro His Leu Asn Lys Ser Gln Ser Leu Thr Asn
    530                 535                 540

Ser Leu Ser Thr Ser Asp Thr Ser Gln Arg Gly Thr Pro Ser Glu Asp
545                 550                 555                 560

Glu Ala Lys Ala Glu Thr Ile Arg Asn Leu Arg Lys Ser Phe Ala Ser
                565                 570                 575

Leu Phe Ser Asp
            580
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<210> SEQ ID NO 6
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Glu Met Phe Gly Gly Leu Asp Ile Cys Ala Val Lys Ala Val His Ser
1 5 10 15

Lys

<210> SEQ ID NO 7
<211> LENGTH: 389
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Glu Gly Ala Leu Ala Ala Asn Trp Ser Ala Glu Ala Ala Asn Ala
1 5 10 15

Ser Ala Ala Pro Pro Gly Ala Glu Gly Asn Arg Thr Ala Gly Pro Pro
20 25 30

Arg Arg Asn Glu Ala Leu Ala Arg Val Glu Val Ala Val Leu Cys Leu
35 40 45

Ile Leu Leu Leu Ala Leu Ser Gly Asn Ala Cys Val Leu Leu Ala Leu
50 55 60

Arg Thr Thr Arg Gln Lys His Ser Arg Leu Phe Phe Phe Met Lys His
65 70 75 80

Leu Ser Ile Ala Asp Leu Val Val Ala Val Phe Gln Val Leu Pro Gln
85 90 95

Leu Leu Trp Asp Ile Thr Phe Arg Phe Tyr Gly Pro Asp Leu Leu Cys
100 105 110

Arg Leu Val Lys Tyr Leu Gln Val Val Gly Met Phe Ala Ser Thr Tyr
115 120 125

Leu Leu Leu Leu Met Ser Leu Asp Arg Cys Leu Ala Ile Cys Gln Pro
130 135 140

Leu Arg Ser Leu Arg Arg Arg Thr Asp Arg Leu Ala Val Leu Ala Thr
145 150 155 160

Trp Leu Gly Cys Leu Val Ala Ser Ala Pro Gln Val His Ile Phe Ser
165 170 175

Leu Arg Glu Val Ala Asp Gly Val Phe Asp Cys Trp Ala Val Phe Ile
180 185 190

Gln Pro Trp Gly Pro Lys Ala Tyr Ile Thr Trp Ile Thr Leu Ala Val
195 200 205

Tyr Ile Val Pro Val Ile Val Leu Ala Ala Cys Tyr Gly Leu Ile Ser
210 215 220

Phe Lys Ile Trp Gln Asn Leu Arg Leu Lys Thr Ala Ala Ala Ala Ala
225 230 235 240

Ala Glu Ala Pro Glu Gly Ala Ala Ala Gly Asp Gly Gly Arg Val Ala
245 250 255

Leu Ala Arg Val Ser Ser Val Lys Leu Ile Ser Lys Ala Lys Ile Arg
260 265 270

Thr Val Lys Met Thr Phe Ile Ile Val Leu Ala Phe Ile Val Cys Trp
275 280 285

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Thr Pro Phe Phe Phe Val Gln Met Trp Ser Val Trp Asp Ala Asn Ala
    290                 295                 300

Pro Lys Glu Ala Ser Ala Phe Ile Ile Val Met Leu Leu Ala Ser Leu
305                 310                 315                 320

Asn Ser Cys Cys Asn Pro Trp Ile Tyr Met Leu Phe Thr Gly His Leu
                325                 330                 335

Phe His Glu Leu Val Gln Arg Phe Leu Cys Cys Ser Ala Ser Tyr Leu
            340                 345                 350

Lys Gly Arg Arg Leu Gly Glu Thr Ser Ala Ser Lys Lys Ser Asn Ser
        355                 360                 365

Ser Ser Phe Val Leu Ser His Arg Ser Ser Ser Gln Arg Ser Cys Ser
    370                 375                 380

Gln Pro Ser Thr Ala
385


<210> SEQ ID NO 8
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Ala Ala Pro Pro Gly Ala Glu Gly Asn Arg Thr
1               5                   10


<210> SEQ ID NO 9
<211> LENGTH: 1290
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Gly Pro Pro Val Pro Ala Ser Ser Ser Thr Lys Leu Leu Met Thr Ser
1               5                   10                  15

Tyr Ser Met Arg Ser Thr Val Val Ser Arg Tyr Ala His Thr Leu Val
            20                  25                  30

Thr Ser Val Leu Phe Asn Pro His Ala Glu Ala His Glu Ala Ile Phe
        35                  40                  45

Asp Leu Asp Leu Pro His Leu Ala Phe Ile Ser Asn Phe Thr Met Thr
    50                  55                  60

Ile Asn Asn Lys Val Tyr Ile Ala Glu Val Lys Glu Lys His Gln Ala
65                  70                  75                  80

Lys Lys Ile Tyr Glu Glu Ala His Gln Gln Gly Lys Thr Ala Ala His
                85                  90                  95

Val Gly Ile Arg Asp Arg Glu Ser Glu Lys Phe Arg Ile Ser Thr Ser
            100                 105                 110

Leu Ala Ala Gly Thr Glu Val Thr Phe Ser Leu Ala Tyr Glu Glu Leu
        115                 120                 125

Leu Gln Arg His Gln Gly Gln Tyr Gln Leu Val Val Ser Leu Arg Pro
    130                 135                 140

Gly Gln Leu Val Lys Arg Leu Ser Ile Glu Val Thr Val Ser Glu Arg
145                 150                 155                 160

Thr Gly Ile Ser Tyr Val His Ile Pro Pro Leu Arg Thr Gly Arg Leu
                165                 170                 175

Arg Thr Asn Ala His Ala Ser Glu Val Asp Ser Pro Pro Ser Thr Arg
            180                 185                 190
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Ile Glu Arg Gly Glu Thr Cys Val Arg Ile Thr Tyr Cys Pro Thr Leu
        195                 200                 205

Gln Asp Gln Ser Ser Ile Ser Gly Ser Gly Ile Met Ala Asp Phe Leu
    210                 215                 220

Val Gln Tyr Asp Val Val Met Glu Asp Ile Ile Gly Asp Val Gln Ile
225                 230                 235                 240

Tyr Asp Asp Tyr Phe Ile His Tyr Phe Ala Pro Arg Gly Leu Pro Pro
                245                 250                 255

Met Glu Lys Asn Val Val Phe Val Ile Asp Val Ser Ser Ser Met Phe
            260                 265                 270

Gly Thr Lys Met Glu Gln Thr Lys Thr Ala Met Asn Val Ile Leu Ser
        275                 280                 285

Asp Leu Gln Ala Asn Asp Tyr Phe Asn Ile Ile Ser Phe Ser Asp Thr
    290                 295                 300

Val Asn Val Trp Lys Ala Gly Gly Ser Ile Gln Ala Thr Ile Gln Asn
305                 310                 315                 320

Val His Ser Ala Lys Asp Tyr Leu His Cys Met Glu Ala Asp Gly Trp
                325                 330                 335

Thr Asp Val Asn Ser Ala Leu Leu Ala Ala Ala Ser Val Leu Asn His
            340                 345                 350

Ser Asn Gln Glu Pro Gly Arg Gly Pro Ser Val Gly Arg Ile Pro Leu
        355                 360                 365

Ile Ile Phe Leu Thr Asp Gly Glu Pro Thr Ala Gly Val Thr Thr Pro
    370                 375                 380

Ser Val Ile Leu Ser Asn Val Arg Gln Ala Leu Gly His Arg Val Ser
385                 390                 395                 400

Leu Phe Ser Leu Ala Phe Gly Asp Asp Ala Asp Phe Thr Leu Leu Arg
                405                 410                 415

Arg Leu Ser Leu Glu Asn Arg Gly Ile Ala Arg Arg Ile Tyr Glu Asp
            420                 425                 430

Thr Asp Ala Ala Leu Gln Leu Lys Gly Leu Tyr Glu Glu Ile Ser Met
        435                 440                 445

Pro Leu Leu Ala Asp Val Arg Leu Asn Tyr Leu Gly Gly Leu Val Gly
    450                 455                 460

Ala Ser Pro Trp Ala Val Phe Pro Asn Tyr Phe Gly Gly Ser Glu Leu
465                 470                 475                 480

Val Val Ala Gly Gln Val Gln Pro Gly Lys Gln Glu Leu Gly Ile His
                485                 490                 495

Leu Ala Ala Arg Gly Pro Lys Asp Gln Leu Leu Val Ala His His Ser
            500                 505                 510

Glu Gly Ala Thr Asn Asn Ser Gln Lys Ala Phe Gly Cys Pro Gly Glu
        515                 520                 525

Pro Ala Pro Asn Val Ala His Phe Ile Arg Arg Leu Trp Ala Tyr Val
    530                 535                 540

Thr Ile Gly Glu Leu Leu Asp Ala His Phe Gln Ala Arg Asp Thr Thr
545                 550                 555                 560

Thr Arg His Leu Leu Ala Ala Lys Val Leu Asn Leu Ser Leu Glu Tyr
                565                 570                 575

Asn Phe Val Thr Pro Leu Thr Ser Leu Val Met Val Gln Pro Lys Gln
            580                 585                 590

Ala Ser Glu Glu Thr Arg Arg Gln Thr Ser Thr Ser Ala Gly Pro Asp
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        595                 600                 605

Thr Ile Met Pro Ser Ser Ser Ser Arg His Gly Leu Gly Val Ser Thr
    610                 615                 620

Ala Gln Pro Ala Leu Val Pro Lys Val Ile Ser Pro Lys Ser Arg Pro
625                 630                 635                 640

Val Lys Pro Lys Phe Tyr Leu Ser Ser Thr Thr Thr Ala Ser Thr Lys
                645                 650                 655

Lys Met Leu Ser Ser Lys Glu Leu Glu Pro Leu Gly Glu Ser Pro His
            660                 665                 670

Thr Leu Ser Met Pro Thr Tyr Pro Lys Ala Lys Ile Pro Ala Gln Gln
        675                 680                 685

Asp Ser Gly Thr Leu Ala Gln Pro Thr Leu Arg Thr Lys Pro Thr Ile
    690                 695                 700

Leu Val Pro Ser Asn Ser Gly Thr Leu Leu Pro Leu Lys Pro Gly Ser
705                 710                 715                 720

Leu Ser His Gln Asn Pro Asp Ile Leu Pro Thr Asn Ser Arg Thr Gln
                725                 730                 735

Val Pro Pro Val Lys Pro Gly Ile Pro Ala Ser Pro Lys Ala Asp Thr
            740                 745                 750

Val Lys Cys Val Thr Pro Leu His Ser Lys Pro Gly Ala Pro Ser His
        755                 760                 765

Pro Gln Leu Gly Ala Leu Thr Ser Gln Ala Pro Lys Gly Leu Pro Gln
    770                 775                 780

Ser Arg Pro Gly Val Ser Thr Leu Gln Val Pro Lys Tyr Pro Leu His
785                 790                 795                 800

Thr Arg Pro Arg Val Pro Ala Pro Lys Thr Arg Asn Asn Met Pro His
                805                 810                 815

Leu Gly Pro Gly Ile Leu Leu Ser Lys Thr Pro Lys Ile Leu Leu Ser
            820                 825                 830

Leu Lys Pro Ser Ala Pro Pro His Gln Ile Ser Thr Ser Ile Ser Leu
        835                 840                 845

Ser Lys Pro Glu Thr Pro Asn Pro His Met Pro Gln Thr Pro Leu Pro
    850                 855                 860

Pro Arg Pro Asp Arg Pro Arg Pro Pro Leu Pro Glu Ser Leu Ser Thr
865                 870                 875                 880

Phe Pro Asn Thr Ile Ser Ser Ser Thr Gly Pro Ser Ser Thr Thr Thr
                885                 890                 895

Thr Ser Val Leu Gly Glu Pro Leu Pro Met Pro Phe Thr Pro Thr Leu
            900                 905                 910

Pro Pro Gly Arg Phe Trp His Gln Tyr Asp Leu Leu Pro Gly Pro Gln
        915                 920                 925

Arg Thr Arg Gln Val Leu Gly Pro Ser Arg Pro Gly Val Pro Thr Met
    930                 935                 940

Ser Leu Leu Asn Ser Ser Arg Pro Thr Pro Glu Gly Ser Pro Pro Asn
945                 950                 955                 960

Leu Pro Ile Leu Leu Pro Ser Ser Ile Leu Pro Glu Ala Ile Ser Leu
                965                 970                 975

Leu Leu Leu Pro Glu Glu Leu Glu Leu Leu Ser Glu Ser Met Val Glu
            980                 985                 990

Ser Lys Phe Val Glu Ser Leu Asn  Pro Pro Ala Phe Tyr  Thr Phe Leu
        995                 1000                1005
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Thr Pro  Asp Glu Asp Gly Ser  Pro Asn Trp Asp Gly  Asn Ser Glu
    1010                1015                1020

Glu Ile  Leu Gly Gly Ala Gly  Gly Ser Met Glu Ser  Gln Gly Ser
    1025                1030                1035

Ser Val  Gly Leu Ala Lys Gly  Thr Leu Pro Ser Ile  Phe Thr Phe
    1040                1045                1050

Ser Ser  Ser Val Asp Gly Asp  Pro His Phe Val Ile  Gln Ile Pro
    1055                1060                1065

His Ser  Glu Glu Lys Ile Cys  Phe Thr Leu Asn Gly  His Pro Gly
    1070                1075                1080

Asp Leu  Leu Gln Leu Ile Glu  Asp Pro Lys Ala Gly  Leu His Val
    1085                1090                1095

Ser Gly  Lys Leu Leu Gly Ala  Pro Pro Arg Pro Gly  His Lys Asp
    1100                1105                1110

Gln Thr  Arg Thr Tyr Phe Gln  Ile Ile Thr Val Thr  Thr Asp Lys
    1115                1120                1125

Pro Arg  Ala Tyr Thr Ile Thr  Ile Ser Arg Ser Ser  Ile Ser Leu
    1130                1135                1140

Arg Gly  Glu Gly Thr Leu Arg  Leu Ser Trp Asp Gln  Pro Ala Leu
    1145                1150                1155

Leu Lys  Arg Pro Gln Leu Glu  Leu Tyr Val Ala Ala  Ala Ala Arg
    1160                1165                1170

Leu Thr  Leu Arg Leu Gly Pro  Tyr Leu Glu Phe Leu  Val Leu Arg
    1175                1180                1185

His Arg  Tyr Arg His Pro Ser  Thr Leu Gln Leu Pro  His Leu Gly
    1190                1195                1200

Phe Tyr  Val Ala Asn Gly Ser  Gly Leu Ser Pro Ser  Ala Arg Gly
    1205                1210                1215

Leu Ile  Gly Gln Phe Gln His  Ala Asp Ile Arg Leu  Val Thr Gly
    1220                1225                1230

Pro Met  Gly Pro Cys Leu Arg  Arg His His Gly Pro  Asp Val Pro
    1235                1240                1245

Val Ile  Leu Gly Lys Arg Leu  Leu Lys Asp Ser Pro  Arg Leu Leu
    1250                1255                1260

Pro Arg  Trp Ala Ser Cys Trp  Leu Val Lys Arg Ser  His Val Glu
    1265                1270                1275

Leu Leu  Leu Gly His Pro Tyr  Leu Ser Tyr Val Leu
    1280                1285                1290


<210> SEQ ID NO 10
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Arg Val Ser Leu Phe Ser Leu Ala Phe Gly Asp Asp Ala Asp
1               5                   10


<210> SEQ ID NO 11
<211> LENGTH: 4834
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11
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Met Pro Ser Glu Ser Phe Cys Leu Ala Ala Gln Ala Arg Leu Asp Ser
1               5                  10                  15

Lys Trp Leu Lys Thr Asp Ile Gln Leu Ala Phe Thr Arg Asp Gly Leu
            20                  25                  30

Cys Gly Leu Trp Asn Glu Met Val Lys Asp Gly Glu Ile Val Tyr Thr
        35                  40                  45

Gly Thr Glu Ser Thr Gln Asn Gly Glu Leu Pro Pro Arg Lys Asp Asp
    50                  55                  60

Ser Val Glu Pro Ser Gly Thr Lys Lys Glu Asp Leu Asn Asp Lys Glu
65                  70                  75                  80

Lys Lys Asp Glu Glu Glu Thr Pro Ala Pro Ile Tyr Arg Ala Lys Ser
                85                  90                  95

Ile Leu Asp Ser Trp Val Trp Gly Lys Gln Pro Asp Val Asn Glu Leu
            100                 105                 110

Lys Glu Cys Leu Ser Val Leu Val Lys Glu Gln Gln Ala Leu Ala Val
        115                 120                 125

Gln Ser Ala Thr Thr Thr Leu Ser Ala Leu Arg Leu Lys Gln Arg Leu
    130                 135                 140

Val Ile Leu Glu Arg Tyr Phe Ile Ala Leu Asn Arg Thr Val Phe Gln
145                 150                 155                 160

Glu Asn Val Lys Val Lys Trp Lys Ser Ser Gly Ile Ser Leu Pro Pro
                165                 170                 175

Val Asp Lys Lys Ser Ser Arg Pro Ala Gly Lys Gly Val Glu Gly Leu
            180                 185                 190

Ala Arg Val Gly Ser Arg Ala Ala Leu Ser Phe Ala Phe Ala Phe Leu
        195                 200                 205

Arg Arg Ala Trp Arg Ser Gly Glu Asp Ala Asp Leu Cys Ser Glu Leu
    210                 215                 220

Leu Gln Glu Ser Leu Asp Ala Leu Arg Ala Leu Pro Glu Ala Ser Leu
225                 230                 235                 240

Phe Asp Glu Ser Thr Val Ser Ser Val Trp Leu Glu Val Val Glu Arg
                245                 250                 255

Ala Thr Arg Phe Leu Arg Ser Val Val Thr Gly Asp Val His Gly Thr
            260                 265                 270

Pro Ala Thr Lys Gly Pro Gly Ser Ile Pro Leu Gln Asp Gln His Leu
        275                 280                 285

Ala Leu Ala Ile Leu Leu Glu Leu Ala Val Gln Arg Gly Thr Leu Ser
    290                 295                 300

Gln Met Leu Ser Ala Ile Leu Leu Leu Leu Gln Leu Trp Asp Ser Gly
305                 310                 315                 320

Ala Gln Glu Thr Asp Asn Glu Arg Ser Ala Gln Gly Thr Ser Ala Pro
                325                 330                 335

Leu Leu Pro Leu Leu Gln Arg Phe Gln Ser Ile Ile Cys Arg Lys Asp
            340                 345                 350

Ala Pro His Ser Glu Gly Asp Met His Leu Leu Ser Gly Pro Leu Ser
        355                 360                 365

Pro Asn Glu Ser Phe Leu Arg Tyr Leu Thr Leu Pro Gln Asp Asn Glu
    370                 375                 380

Leu Ala Ile Asp Leu Arg Gln Thr Ala Val Val Val Met Ala His Leu
385                 390                 395                 400
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Asp Arg Leu Ala Thr Pro Cys Met Pro Pro Leu Cys Ser Ser Pro Thr
                405                 410                 415

Ser His Lys Gly Ser Leu Gln Glu Val Ile Gly Trp Gly Leu Ile Gly
            420                 425                 430

Trp Lys Tyr Tyr Ala Asn Val Ile Gly Pro Ile Gln Cys Glu Gly Leu
        435                 440                 445

Ala Asn Leu Gly Val Thr Gln Ile Ala Cys Ala Glu Lys Arg Phe Leu
    450                 455                 460

Ile Leu Ser Arg Asn Gly Arg Val Tyr Thr Gln Ala Tyr Asn Ser Asp
465                 470                 475                 480

Thr Leu Ala Pro Gln Leu Val Gln Gly Leu Ala Ser Arg Asn Ile Val
                485                 490                 495

Lys Ile Ala Ala His Ser Asp Gly His His Tyr Leu Ala Leu Ala Ala
            500                 505                 510

Thr Gly Glu Val Tyr Ser Trp Gly Cys Gly Asp Gly Gly Arg Leu Gly
        515                 520                 525

His Gly Asp Thr Val Pro Leu Glu Glu Pro Lys Val Ile Ser Ala Phe
    530                 535                 540

Ser Gly Lys Gln Ala Gly Lys His Val Val His Ile Ala Cys Gly Ser
545                 550                 555                 560

Thr Tyr Ser Ala Ala Ile Thr Ala Glu Gly Glu Leu Tyr Thr Trp Gly
                565                 570                 575

Arg Gly Asn Tyr Gly Arg Leu Gly His Gly Ser Ser Glu Asp Glu Ala
            580                 585                 590

Ile Pro Met Leu Val Ala Gly Leu Lys Gly Leu Lys Val Ile Asp Val
        595                 600                 605

Ala Cys Gly Ser Gly Asp Ala Gln Thr Leu Ala Val Thr Glu Asn Gly
    610                 615                 620

Gln Val Trp Ser Trp Gly Asp Gly Asp Tyr Gly Lys Leu Gly Arg Gly
625                 630                 635                 640

Gly Ser Asp Gly Cys Lys Thr Pro Lys Leu Ile Glu Lys Leu Gln Asp
                645                 650                 655

Leu Asp Val Val Lys Val Arg Cys Gly Ser Gln Phe Ser Ile Ala Leu
            660                 665                 670

Thr Lys Asp Gly Gln Val Tyr Ser Trp Gly Lys Gly Asp Asn Gln Arg
        675                 680                 685

Leu Gly His Gly Thr Glu Glu His Val Arg Tyr Pro Lys Leu Leu Glu
    690                 695                 700

Gly Leu Gln Gly Lys Lys Val Ile Asp Val Ala Ala Gly Ser Thr His
705                 710                 715                 720

Cys Leu Ala Leu Thr Glu Asp Ser Glu Val His Ser Trp Gly Ser Asn
                725                 730                 735

Asp Gln Cys Gln His Phe Asp Thr Leu Arg Val Thr Lys Pro Glu Pro
            740                 745                 750

Ala Ala Leu Pro Gly Leu Asp Thr Lys His Ile Val Gly Ile Ala Cys
        755                 760                 765

Gly Pro Ala Gln Ser Phe Ala Trp Ser Ser Cys Ser Glu Trp Ser Ile
    770                 775                 780

Gly Leu Arg Val Pro Phe Val Val Asp Ile Cys Ser Met Thr Phe Glu
785                 790                 795                 800

Gln Leu Asp Leu Leu Leu Arg Gln Val Ser Glu Gly Met Asp Gly Ser
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               805                 810                 815

Ala Asp Trp Pro Pro Pro Gln Glu Lys Glu Cys Val Ala Val Ala Thr
            820                 825                 830

Leu Asn Leu Leu Arg Leu Gln Leu His Ala Ala Ile Ser His Gln Val
        835                 840                 845

Asp Pro Glu Phe Leu Gly Leu Gly Leu Gly Ser Ile Leu Leu Asn Ser
    850                 855                 860

Leu Lys Gln Thr Val Val Thr Leu Ala Ser Ser Ala Gly Val Leu Ser
865                 870                 875                 880

Thr Val Gln Ser Ala Ala Gln Ala Val Leu Gln Ser Gly Trp Ser Val
               885                 890                 895

Leu Leu Pro Thr Ala Glu Glu Arg Ala Arg Ala Leu Ser Ala Leu Leu
            900                 905                 910

Pro Cys Ala Val Ser Gly Asn Glu Val Asn Ile Ser Pro Gly Arg Arg
        915                 920                 925

Phe Met Ile Asp Leu Leu Val Gly Ser Leu Met Ala Asp Gly Gly Leu
    930                 935                 940

Glu Ser Ala Leu His Ala Ala Ile Thr Ala Glu Ile Gln Asp Ile Glu
945                 950                 955                 960

Ala Lys Lys Glu Ala Gln Lys Glu Lys Glu Ile Asp Glu Gln Glu Ala
               965                 970                 975

Asn Ala Ser Thr Phe His Arg Ser Arg Thr Pro Leu Asp Lys Asp Leu
            980                 985                 990

Ile Asn Thr Gly Ile Cys Glu Ser  Ser Gly Lys Gln Cys  Leu Pro Leu
        995                 1000                1005

Val Gln  Leu Ile Gln Gln Leu  Leu Arg Asn Ile Ala  Ser Gln Thr
    1010                1015                1020

Val Ala  Arg Leu Lys Asp Val  Ala Arg Arg Ile Ser  Ser Cys Leu
    1025                1030                1035

Asp Phe  Glu Gln His Ser Arg  Glu Arg Ser Ala Ser  Leu Asp Leu
    1040                1045                1050

Leu Leu  Arg Phe Gln Arg Leu  Leu Ile Ser Lys Leu  Tyr Pro Gly
    1055                1060                1065

Glu Ser  Ile Gly Gln Thr Ser  Asp Ile Ser Ser Pro  Glu Leu Met
    1070                1075                1080

Gly Val  Gly Ser Leu Leu Lys  Lys Tyr Thr Ala Leu  Leu Cys Thr
    1085                1090                1095

His Ile  Gly Asp Ile Leu Pro  Val Ala Ala Ser Ile  Ala Ser Thr
    1100                1105                1110

Ser Trp  Arg His Phe Ala Glu  Val Ala Tyr Ile Val  Glu Gly Asp
    1115                1120                1125

Phe Thr  Gly Val Leu Leu Pro  Glu Leu Val Val Ser  Ile Val Leu
    1130                1135                1140

Leu Leu  Ser Lys Asn Ala Gly  Leu Met Gln Glu Ala  Gly Ala Val
    1145                1150                1155

Pro Leu  Leu Gly Gly Leu Leu  Glu His Leu Asp Arg  Phe Asn His
    1160                1165                1170

Leu Ala  Pro Gly Lys Glu Arg  Asp Asp His Glu Glu  Leu Ala Trp
    1175                1180                1185

Pro Gly  Ile Met Glu Ser Phe  Phe Thr Gly Gln Asn  Cys Arg Asn
    1190                1195                1200
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Asn Glu  Glu Val Thr Leu Ile  Arg Lys Ala Asp Leu  Glu Asn His
    1205                 1210                 1215

Asn Lys  Asp Gly Gly Phe Trp  Thr Val Ile Asp Gly  Lys Val Tyr
    1220                 1225                 1230

Asp Ile  Lys Asp Phe Gln Thr  Gln Ser Leu Thr Gly  Asn Ser Ile
    1235                 1240                 1245

Leu Ala  Gln Phe Ala Gly Glu  Asp Pro Val Val Ala  Leu Glu Ala
    1250                 1255                 1260

Ala Leu  Gln Phe Glu Asp Thr  Arg Glu Ser Met His  Ala Phe Cys
    1265                 1270                 1275

Val Gly  Gln Tyr Leu Glu Pro  Asp Gln Glu Ile Val  Thr Ile Pro
    1280                 1285                 1290

Asp Leu  Gly Ser Leu Ser Ser  Pro Leu Ile Asp Thr  Glu Arg Asn
    1295                 1300                 1305

Leu Gly  Leu Leu Leu Gly Leu  His Ala Ser Tyr Leu  Ala Met Ser
    1310                 1315                 1320

Thr Pro  Leu Ser Pro Val Glu  Ile Glu Cys Ala Lys  Trp Leu Gln
    1325                 1330                 1335

Ser Ser  Ile Phe Ser Gly Gly  Leu Gln Thr Ser Gln  Ile His Tyr
    1340                 1345                 1350

Ser Tyr  Asn Glu Glu Lys Asp  Glu Asp His Cys Ser  Ser Pro Gly
    1355                 1360                 1365

Gly Thr  Pro Ala Ser Lys Ser  Arg Leu Cys Ser His  Arg Arg Ala
    1370                 1375                 1380

Leu Gly  Asp His Ser Gln Ala  Phe Leu Gln Ala Ile  Ala Asp Asn
    1385                 1390                 1395

Asn Ile  Gln Asp His Asn Val  Lys Asp Phe Leu Cys  Gln Ile Glu
    1400                 1405                 1410

Arg Tyr  Cys Arg Gln Cys His  Leu Thr Thr Pro Ile  Met Phe Pro
    1415                 1420                 1425

Pro Glu  His Pro Val Glu Glu  Val Gly Arg Leu Leu  Leu Cys Cys
    1430                 1435                 1440

Leu Leu  Lys His Glu Asp Leu  Gly His Val Ala Leu  Ser Leu Val
    1445                 1450                 1455

His Ala  Gly Ala Leu Gly Ile  Glu Gln Val Lys His  Arg Thr Leu
    1460                 1465                 1470

Pro Lys  Ser Val Val Asp Val  Cys Arg Val Val Tyr  Gln Ala Lys
    1475                 1480                 1485

Cys Ser  Leu Ile Lys Thr His  Gln Glu Gln Gly Arg  Ser Tyr Lys
    1490                 1495                 1500

Glu Val  Cys Ala Pro Val Ile  Glu Arg Leu Arg Phe  Leu Phe Asn
    1505                 1510                 1515

Glu Leu  Arg Pro Ala Val Cys  Asn Asp Leu Ser Ile  Met Ser Lys
    1520                 1525                 1530

Phe Lys  Leu Leu Ser Ser Leu  Pro Arg Trp Arg Arg  Ile Ala Gln
    1535                 1540                 1545

Lys Ile  Ile Arg Glu Arg Arg  Lys Lys Arg Val Pro  Lys Lys Pro
    1550                 1555                 1560

Glu Ser  Thr Asp Asp Glu Glu  Lys Ile Gly Asn Glu  Glu Ser Asp
    1565                 1570                 1575
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Leu Glu  Glu Ala Cys Ile Leu  Pro His Ser Pro Ile  Asn Val Asp
    1580                 1585                 1590

Lys Arg  Pro Ile Ala Ile Lys  Ser Pro Lys Asp Lys  Trp Gln Pro
    1595                 1600                 1605

Leu Leu  Ser Thr Val Thr Gly  Val His Lys Tyr Lys  Trp Leu Lys
    1610                 1615                 1620

Gln Asn  Val Gln Gly Leu Tyr  Pro Gln Ser Pro Leu  Leu Ser Thr
    1625                 1630                 1635

Ile Ala  Glu Phe Ala Leu Lys  Glu Glu Pro Val Asp  Val Glu Lys
    1640                 1645                 1650

Met Arg  Lys Cys Leu Leu Lys  Gln Leu Glu Arg Ala  Glu Val Arg
    1655                 1660                 1665

Leu Glu  Gly Ile Asp Thr Ile  Leu Lys Leu Ala Ser  Lys Asn Phe
    1670                 1675                 1680

Leu Leu  Pro Ser Val Gln Tyr  Ala Met Phe Cys Gly  Trp Gln Arg
    1685                 1690                 1695

Leu Ile  Pro Glu Gly Ile Asp  Ile Gly Glu Pro Leu  Thr Asp Cys
    1700                 1705                 1710

Leu Lys  Asp Val Asp Leu Ile  Pro Pro Phe Asn Arg  Met Leu Leu
    1715                 1720                 1725

Glu Val  Thr Phe Gly Lys Leu  Tyr Ala Trp Ala Val  Gln Asn Ile
    1730                 1735                 1740

Arg Asn  Val Leu Met Asp Ala  Ser Ala Lys Phe Lys  Glu Leu Gly
    1745                 1750                 1755

Ile Gln  Pro Val Pro Leu Gln  Thr Ile Thr Asn Glu  Asn Pro Ser
    1760                 1765                 1770

Gly Pro  Ser Leu Gly Thr Ile  Pro Gln Ala Arg Phe  Leu Leu Val
    1775                 1780                 1785

Met Leu  Ser Met Leu Thr Leu  Gln His Gly Ala Asn  Asn Leu Asp
    1790                 1795                 1800

Leu Leu  Leu Asn Ser Gly Met  Leu Ala Leu Thr Gln  Thr Ala Leu
    1805                 1810                 1815

Arg Leu  Ile Gly Pro Ser Cys  Asp Asn Val Glu Glu  Asp Met Asn
    1820                 1825                 1830

Ala Ser  Ala Gln Gly Ala Ser  Ala Thr Val Leu Glu  Glu Thr Arg
    1835                 1840                 1845

Lys Glu  Thr Ala Pro Val Gln  Leu Pro Val Ser Gly  Pro Glu Leu
    1850                 1855                 1860

Ala Ala  Met Met Lys Ile Gly  Thr Arg Val Met Arg  Gly Val Asp
    1865                 1870                 1875

Trp Lys  Trp Gly Asp Gln Asp  Gly Pro Pro Pro Gly  Leu Gly Arg
    1880                 1885                 1890

Val Ile  Gly Glu Leu Gly Glu  Asp Gly Trp Ile Arg  Val Gln Trp
    1895                 1900                 1905

Asp Thr  Gly Ser Thr Asn Ser  Tyr Arg Met Gly Lys  Glu Gly Lys
    1910                 1915                 1920

Tyr Asp  Leu Lys Leu Ala Glu  Leu Pro Ala Ala Ala  Gln Pro Ser
    1925                 1930                 1935

Ala Glu  Asp Ser Asp Thr Glu  Asp Asp Ser Glu Ala  Glu Gln Thr
    1940                 1945                 1950

Glu Arg  Asn Ile His Pro Thr  Ala Met Met Phe Thr  Ser Thr Ile
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    1955                1960                1965

Asn Leu  Leu Gln Thr Leu Cys  Leu Ser Ala Gly Val  His Ala Glu
    1970                1975                1980

Ile Met  Gln Ser Glu Ala Thr  Lys Thr Leu Cys Gly  Leu Leu Arg
    1985                1990                1995

Met Leu  Val Glu Ser Gly Thr  Thr Asp Lys Thr Ser  Ser Pro Asn
    2000                2005                2010

Arg Leu  Val Tyr Arg Glu Gln  His Arg Ser Trp Cys  Thr Leu Gly
    2015                2020                2025

Phe Val  Arg Ser Ile Ala Leu  Thr Pro Gln Val Cys  Gly Ala Leu
    2030                2035                2040

Ser Ser  Pro Gln Trp Ile Thr  Leu Leu Met Lys Val  Val Glu Gly
    2045                2050                2055

His Ala  Pro Phe Thr Ala Thr  Ser Leu Gln Arg Gln  Ile Leu Ala
    2060                2065                2070

Val His  Leu Leu Gln Ala Val  Leu Pro Ser Trp Asp  Lys Thr Glu
    2075                2080                2085

Arg Ala  Arg Asp Met Lys Cys  Leu Val Glu Lys Leu  Phe Asp Phe
    2090                2095                2100

Leu Gly  Ser Leu Leu Thr Thr  Cys Ser Ser Asp Val  Pro Leu Leu
    2105                2110                2115

Arg Glu  Ser Thr Leu Arg Arg  Arg Arg Val Arg Pro  Gln Ala Ser
    2120                2125                2130

Leu Thr  Ala Thr His Ser Ser  Thr Leu Ala Glu Glu  Val Val Ala
    2135                2140                2145

Leu Leu  Arg Thr Leu His Ser  Leu Thr Gln Trp Asn  Gly Leu Ile
    2150                2155                2160

Asn Lys  Tyr Ile Asn Ser Gln  Leu Arg Ser Ile Thr  His Ser Phe
    2165                2170                2175

Val Gly  Arg Pro Ser Glu Gly  Ala Gln Leu Glu Asp  Tyr Phe Pro
    2180                2185                2190

Asp Ser  Glu Asn Pro Glu Val  Gly Gly Leu Met Ala  Val Leu Ala
    2195                2200                2205

Val Ile  Gly Gly Ile Asp Gly  Arg Leu Arg Leu Gly  Gly Gln Val
    2210                2215                2220

Met His  Asp Glu Phe Gly Glu  Gly Thr Val Thr Arg  Ile Thr Pro
    2225                2230                2235

Lys Gly  Lys Ile Thr Val Gln  Phe Ser Asp Met Arg  Thr Cys Arg
    2240                2245                2250

Val Cys  Pro Leu Asn Gln Leu  Lys Pro Leu Pro Ala  Val Ala Phe
    2255                2260                2265

Asn Val  Asn Asn Leu Pro Phe  Thr Glu Pro Met Leu  Ser Val Trp
    2270                2275                2280

Ala Gln  Leu Val Asn Leu Ala  Gly Ser Lys Leu Glu  Lys His Lys
    2285                2290                2295

Ile Lys  Lys Ser Thr Lys Gln  Ala Phe Ala Gly Gln  Val Asp Leu
    2300                2305                2310

Asp Leu  Leu Arg Cys Gln Gln  Leu Lys Leu Tyr Ile  Leu Lys Ala
    2315                2320                2325

Gly Arg  Ala Leu Leu Ser His  Gln Asp Lys Leu Arg  Gln Ile Leu
    2330                2335                2340
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Ser Gln  Pro Ala Val Gln Glu  Thr Gly Thr Val His  Thr Asp Asp
    2345                2350                2355

Gly Ala  Val Val Ser Pro Asp  Leu Gly Asp Met Ser  Pro Glu Gly
    2360                2365                2370

Pro Gln  Pro Pro Met Ile Leu  Leu Gln Gln Leu Leu  Ala Ser Ala
    2375                2380                2385

Thr Gln  Pro Ser Pro Val Lys  Ala Ile Phe Asp Lys  Gln Glu Leu
    2390                2395                2400

Glu Ala  Ala Ala Leu Ala Val  Cys Gln Cys Leu Ala  Val Glu Ser
    2405                2410                2415

Thr His  Pro Ser Ser Pro Gly  Phe Glu Asp Cys Ser  Ser Ser Glu
    2420                2425                2430

Ala Thr  Thr Pro Val Ala Val  Gln His Ile Arg Pro  Ala Arg Val
    2435                2440                2445

Lys Arg  Arg Lys Gln Ser Pro  Val Pro Ala Leu Pro  Ile Val Val
    2450                2455                2460

Gln Leu  Met Glu Met Gly Phe  Ser Arg Arg Asn Ile  Glu Phe Ala
    2465                2470                2475

Leu Lys  Ser Leu Thr Gly Ala  Ser Gly Asn Ala Ser  Ser Leu Pro
    2480                2485                2490

Gly Val  Glu Ala Leu Val Gly  Trp Leu Leu Asp His  Ser Asp Ile
    2495                2500                2505

Gln Val  Thr Glu Leu Ser Asp  Ala Asp Thr Val Ser  Asp Glu Tyr
    2510                2515                2520

Ser Asp  Glu Glu Val Val Glu  Asp Val Asp Asp Ala  Ala Tyr Ser
    2525                2530                2535

Met Ser  Thr Gly Ala Val Val  Thr Glu Ser Gln Thr  Tyr Lys Lys
    2540                2545                2550

Arg Ala  Asp Phe Leu Ser Asn  Asp Asp Tyr Ala Val  Tyr Val Arg
    2555                2560                2565

Glu Asn  Ile Gln Val Gly Met  Met Val Arg Cys Cys  Arg Ala Tyr
    2570                2575                2580

Glu Glu  Val Cys Glu Gly Asp  Val Gly Lys Val Ile  Lys Leu Asp
    2585                2590                2595

Arg Asp  Gly Leu His Asp Leu  Asn Val Gln Cys Asp  Trp Gln Gln
    2600                2605                2610

Lys Gly  Gly Thr Tyr Trp Val  Arg Tyr Ile His Val  Glu Leu Ile
    2615                2620                2625

Gly Tyr  Pro Pro Pro Ser Ser  Ser Ser His Ile Lys  Ile Gly Asp
    2630                2635                2640

Lys Val  Arg Val Lys Ala Ser  Val Thr Thr Pro Lys  Tyr Lys Trp
    2645                2650                2655

Gly Ser  Val Thr His Gln Ser  Val Gly Val Val Lys  Ala Phe Ser
    2660                2665                2670

Ala Asn  Gly Lys Asp Ile Ile  Val Asp Phe Pro Gln  Gln Ser His
    2675                2680                2685

Trp Thr  Gly Leu Leu Ser Glu  Met Glu Leu Val Pro  Ser Ile His
    2690                2695                2700

Pro Gly  Val Thr Cys Asp Gly  Cys Gln Met Phe Pro  Ile Asn Gly
    2705                2710                2715
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Ser Arg  Phe Lys Cys Arg Asn  Cys Asp Asp Phe Asp  Phe Cys Glu
    2720                 2725                 2730

Thr Cys  Phe Lys Thr Lys Lys  His Asn Thr Arg His  Thr Phe Gly
    2735                 2740                 2745

Arg Ile  Asn Glu Pro Gly Gln  Ser Ala Val Phe Cys  Gly Arg Ser
    2750                 2755                 2760

Gly Lys  Gln Leu Lys Arg Cys  His Ser Ser Gln Pro  Gly Met Leu
    2765                 2770                 2775

Leu Asp  Ser Trp Ser Arg Met  Val Lys Ser Leu Asn  Val Ser Ser
    2780                 2785                 2790

Ser Val  Asn Gln Ala Ser Arg  Leu Ile Asp Gly Ser  Glu Pro Cys
    2795                 2800                 2805

Trp Gln  Ser Ser Gly Ser Gln  Gly Lys His Trp Ile  Arg Leu Glu
    2810                 2815                 2820

Ile Phe  Pro Asp Val Leu Val  His Arg Leu Lys Met  Ile Val Asp
    2825                 2830                 2835

Pro Ala  Asp Ser Ser Tyr Met  Pro Ser Leu Val Val  Val Ser Gly
    2840                 2845                 2850

Gly Asn  Ser Leu Asn Asn Leu  Ile Glu Leu Lys Thr  Ile Asn Ile
    2855                 2860                 2865

Asn Pro  Ser Asp Thr Thr Val  Pro Leu Leu Asn Asp  Cys Thr Glu
    2870                 2875                 2880

Tyr His  Arg Tyr Ile Glu Ile  Ala Ile Lys Gln Cys  Arg Ser Ser
    2885                 2890                 2895

Gly Ile  Asp Cys Lys Ile His  Gly Leu Ile Leu Leu  Gly Arg Ile
    2900                 2905                 2910

Arg Ala  Glu Glu Glu Asp Leu  Ala Ala Val Pro Phe  Leu Ala Ser
    2915                 2920                 2925

Asp Asn  Glu Glu Glu Glu Asp  Glu Lys Gly Asn Ser  Gly Ser Leu
    2930                 2935                 2940

Ile Arg  Lys Lys Ala Ala Gly  Leu Glu Ser Ala Ala  Thr Ile Arg
    2945                 2950                 2955

Thr Lys  Val Phe Val Trp Gly  Leu Asn Asp Lys Asp  Gln Leu Gly
    2960                 2965                 2970

Gly Leu  Lys Gly Ser Lys Ile  Lys Val Pro Ser Phe  Ser Glu Thr
    2975                 2980                 2985

Leu Ser  Ala Leu Asn Val Val  Gln Val Ala Gly Gly  Ser Lys Ser
    2990                 2995                 3000

Leu Phe  Ala Val Thr Val Glu  Gly Lys Val Tyr Ala  Cys Gly Glu
    3005                 3010                 3015

Ala Thr  Asn Gly Arg Leu Gly  Leu Gly Ile Ser Ser  Gly Thr Val
    3020                 3025                 3030

Pro Ile  Pro Arg Gln Ile Thr  Ala Leu Ser Ser Tyr  Val Val Lys
    3035                 3040                 3045

Lys Val  Ala Val His Ser Gly  Gly Arg His Ala Thr  Ala Leu Thr
    3050                 3055                 3060

Val Asp  Gly Lys Val Phe Ser  Trp Gly Glu Gly Asp  Asp Gly Lys
    3065                 3070                 3075

Leu Gly  His Phe Ser Arg Met  Asn Cys Asp Lys Pro  Arg Leu Ile
    3080                 3085                 3090

Glu Ala  Leu Lys Thr Lys Arg  Ile Arg Asp Ile Ala  Cys Gly Ser
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    3095                3100                3105

Ser His  Ser Ala Ala Leu Thr  Ser Ser Gly Glu Leu  Tyr Thr Trp
    3110                3115                3120

Gly Leu  Gly Glu Tyr Gly Arg  Leu Gly His Gly Asp  Asn Thr Thr
    3125                3130                3135

Gln Leu  Lys Pro Lys Met Val  Lys Val Leu Leu Gly  His Arg Val
    3140                3145                3150

Ile Gln  Val Ala Cys Gly Ser  Arg Asp Ala Gln Thr  Leu Ala Leu
    3155                3160                3165

Thr Asp  Glu Gly Leu Val Phe  Ser Trp Gly Asp Gly  Asp Phe Gly
    3170                3175                3180

Lys Leu  Gly Arg Gly Gly Ser  Glu Gly Cys Asn Ile  Pro Gln Asn
    3185                3190                3195

Ile Glu  Arg Leu Asn Gly Gln  Gly Val Cys Gln Ile  Glu Cys Gly
    3200                3205                3210

Ala Gln  Phe Ser Leu Ala Leu  Thr Lys Ser Gly Val  Val Trp Thr
    3215                3220                3225

Trp Gly  Lys Gly Asp Tyr Phe  Arg Leu Gly His Gly  Ser Asp Val
    3230                3235                3240

His Val  Arg Lys Pro Gln Val  Val Glu Gly Leu Arg  Gly Lys Lys
    3245                3250                3255

Ile Val  His Val Ala Val Gly  Ala Leu His Cys Leu  Ala Val Thr
    3260                3265                3270

Asp Ser  Gly Gln Val Tyr Ala  Trp Gly Asp Asn Asp  His Gly Gln
    3275                3280                3285

Gln Gly  Asn Gly Thr Thr Thr  Val Asn Arg Lys Pro  Thr Leu Val
    3290                3295                3300

Gln Gly  Leu Glu Gly Gln Lys  Ile Thr Arg Val Ala  Cys Gly Ser
    3305                3310                3315

Ser His  Ser Val Ala Trp Thr  Thr Val Asp Val Ala  Thr Pro Ser
    3320                3325                3330

Val His  Glu Pro Val Leu Phe  Gln Thr Ala Arg Asp  Pro Leu Gly
    3335                3340                3345

Ala Ser  Tyr Leu Gly Val Pro  Ser Asp Ala Asp Ser  Ser Ala Ala
    3350                3355                3360

Ser Asn  Lys Ile Ser Gly Ala  Ser Asn Ser Lys Pro  Asn Arg Pro
    3365                3370                3375

Ser Leu  Ala Lys Ile Leu Leu  Ser Leu Asp Gly Asn  Leu Ala Lys
    3380                3385                3390

Gln Gln  Ala Leu Ser His Ile  Leu Thr Ala Leu Gln  Ile Met Tyr
    3395                3400                3405

Ala Arg  Asp Ala Val Val Gly  Ala Leu Met Pro Ala  Ala Met Ile
    3410                3415                3420

Ala Pro  Val Glu Cys Pro Ser  Phe Ser Ser Ala Ala  Pro Ser Asp
    3425                3430                3435

Ala Ser  Ala Met Ala Ser Pro  Met Asn Gly Glu Glu  Cys Met Leu
    3440                3445                3450

Ala Val  Asp Ile Glu Asp Arg  Leu Ser Pro Asn Pro  Trp Gln Glu
    3455                3460                3465

Lys Arg  Glu Ile Val Ser Ser  Glu Asp Ala Val Thr  Pro Ser Ala
    3470                3475                3480
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Val Thr  Pro Ser Ala Pro Ser  Ala Ser Ala Arg Pro  Phe Ile Pro
    3485                 3490                 3495

Val Thr  Asp Asp Leu Gly Ala  Ala Ser Ile Ile Ala  Glu Thr Met
    3500                 3505                 3510

Thr Lys  Thr Lys Glu Asp Val  Glu Ser Gln Asn Lys  Ala Ala Gly
    3515                 3520                 3525

Pro Glu  Pro Gln Ala Leu Asp  Glu Phe Thr Ser Leu  Leu Ile Ala
    3530                 3535                 3540

Asp Asp  Thr Arg Val Val Val  Asp Leu Leu Lys Leu  Ser Val Cys
    3545                 3550                 3555

Ser Arg  Ala Gly Asp Arg Gly  Arg Asp Val Leu Ser  Ala Val Leu
    3560                 3565                 3570

Ser Gly  Met Gly Thr Ala Tyr  Pro Gln Val Ala Asp  Met Leu Leu
    3575                 3580                 3585

Glu Leu  Cys Val Thr Glu Leu  Glu Asp Val Ala Thr  Asp Ser Gln
    3590                 3595                 3600

Ser Gly  Arg Leu Ser Ser Gln  Pro Val Val Val Glu  Ser Ser His
    3605                 3610                 3615

Pro Tyr  Thr Asp Asp Thr Ser  Thr Ser Gly Thr Val  Lys Ile Pro
    3620                 3625                 3630

Gly Ala  Glu Gly Leu Arg Val  Glu Phe Asp Arg Gln  Cys Ser Thr
    3635                 3640                 3645

Glu Arg  Arg His Asp Pro Leu  Thr Val Met Asp Gly  Val Asn Arg
    3650                 3655                 3660

Ile Val  Ser Val Arg Ser Gly  Arg Glu Trp Ser Asp  Trp Ser Ser
    3665                 3670                 3675

Glu Leu  Arg Ile Pro Gly Asp  Glu Leu Lys Trp Lys  Phe Ile Ser
    3680                 3685                 3690

Asp Gly  Ser Val Asn Gly Trp  Gly Trp Arg Phe Thr  Val Tyr Pro
    3695                 3700                 3705

Ile Met  Pro Ala Ala Gly Pro  Lys Glu Leu Leu Ser  Asp Arg Cys
    3710                 3715                 3720

Val Leu  Ser Cys Pro Ser Met  Asp Leu Val Thr Cys  Leu Leu Asp
    3725                 3730                 3735

Phe Arg  Leu Asn Leu Ala Ser  Asn Arg Ser Ile Val  Pro Arg Leu
    3740                 3745                 3750

Ala Ala  Ser Leu Ala Ala Cys  Ala Gln Leu Ser Ala  Leu Ala Ala
    3755                 3760                 3765

Ser His  Arg Met Trp Ala Leu  Gln Arg Leu Arg Lys  Leu Leu Thr
    3770                 3775                 3780

Thr Glu  Phe Gly Gln Ser Ile  Asn Ile Asn Arg Leu  Leu Gly Glu
    3785                 3790                 3795

Asn Asp  Gly Glu Thr Arg Ala  Leu Ser Phe Thr Gly  Ser Ala Leu
    3800                 3805                 3810

Ala Ala  Leu Val Lys Gly Leu  Pro Glu Ala Leu Gln  Arg Gln Phe
    3815                 3820                 3825

Glu Tyr  Glu Asp Pro Ile Val  Arg Gly Gly Lys Gln  Leu Leu His
    3830                 3835                 3840

Ser Pro  Phe Phe Lys Val Leu  Val Ala Leu Ala Cys  Asp Leu Glu
    3845                 3850                 3855
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Leu Asp  Thr Leu Pro Cys Cys  Ala Glu Thr His Lys  Trp Ala Trp
    3860                 3865                 3870

Phe Arg  Arg Tyr Cys Met Ala  Ser Arg Val Ala Val  Ala Leu Asp
    3875                 3880                 3885

Lys Arg  Thr Pro Leu Pro Arg  Leu Phe Leu Asp Glu  Val Ala Lys
    3890                 3895                 3900

Lys Ile  Arg Glu Leu Met Ala  Asp Ser Glu Asn Met  Asp Val Leu
    3905                 3910                 3915

His Glu  Ser His Asp Ile Phe  Lys Arg Glu Gln Asp  Glu Gln Leu
    3920                 3925                 3930

Val Gln  Trp Met Asn Arg Arg  Pro Asp Asp Trp Thr  Leu Ser Ala
    3935                 3940                 3945

Gly Gly  Ser Gly Thr Ile Tyr  Gly Trp Gly His Asn  His Arg Gly
    3950                 3955                 3960

Gln Leu  Gly Gly Ile Glu Gly  Ala Lys Val Lys Val  Pro Thr Pro
    3965                 3970                 3975

Cys Glu  Ala Leu Ala Thr Leu  Arg Pro Val Gln Leu  Ile Gly Gly
    3980                 3985                 3990

Glu Gln  Thr Leu Phe Ala Val  Thr Ala Asp Gly Lys  Leu Tyr Ala
    3995                 4000                 4005

Thr Gly  Tyr Gly Ala Gly Gly  Arg Leu Gly Ile Gly  Gly Thr Glu
    4010                 4015                 4020

Ser Val  Ser Thr Pro Thr Leu  Leu Glu Ser Ile Gln  His Val Phe
    4025                 4030                 4035

Ile Lys  Lys Val Ala Val Asn  Ser Gly Gly Lys His  Cys Leu Ala
    4040                 4045                 4050

Leu Ser  Ser Glu Gly Glu Val  Tyr Ser Trp Gly Glu  Ala Glu Asp
    4055                 4060                 4065

Gly Lys  Leu Gly His Gly Asn  Arg Ser Pro Cys Asp  Arg Pro Arg
    4070                 4075                 4080

Val Ile  Glu Ser Leu Arg Gly  Ile Glu Val Val Asp  Val Ala Ala
    4085                 4090                 4095

Gly Gly  Ala His Ser Ala Cys  Val Thr Ala Ala Gly  Asp Leu Tyr
    4100                 4105                 4110

Thr Trp  Gly Lys Gly Arg Tyr  Gly Arg Leu Gly His  Ser Asp Ser
    4115                 4120                 4125

Glu Asp  Gln Leu Lys Pro Lys  Leu Val Glu Ala Leu  Gln Gly His
    4130                 4135                 4140

Arg Val  Val Asp Ile Ala Cys  Gly Ser Gly Asp Ala  Gln Thr Leu
    4145                 4150                 4155

Cys Leu  Thr Asp Asp Asp Thr  Val Trp Ser Trp Gly  Asp Gly Asp
    4160                 4165                 4170

Tyr Gly  Lys Leu Gly Arg Gly  Gly Ser Asp Gly Cys  Lys Val Pro
    4175                 4180                 4185

Met Lys  Ile Asp Ser Leu Thr  Gly Leu Gly Val Val  Lys Val Glu
    4190                 4195                 4200

Cys Gly  Ser Gln Phe Ser Val  Ala Leu Thr Lys Ser  Gly Ala Val
    4205                 4210                 4215

Tyr Thr  Trp Gly Lys Gly Asp  Tyr His Arg Leu Gly  His Gly Ser
    4220                 4225                 4230

Asp Asp  His Val Arg Arg Pro  Arg Gln Val Gln Gly  Leu Gln Gly
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    4235                4240                4245

Lys Lys  Val Ile Ala Ile Ala  Thr Gly Ser Leu His  Cys Val Cys
    4250                4255                4260

Cys Thr  Glu Asp Gly Glu Val  Tyr Thr Trp Gly Asp  Asn Asp Glu
    4265                4270                4275

Gly Gln  Leu Gly Asp Gly Thr  Thr Asn Ala Ile Gln  Arg Pro Arg
    4280                4285                4290

Leu Val  Ala Ala Leu Gln Gly  Lys Lys Val Asn Arg  Val Ala Cys
    4295                4300                4305

Gly Ser  Ala His Thr Leu Ala  Trp Ser Thr Ser Lys  Pro Ala Ser
    4310                4315                4320

Ala Gly  Lys Leu Pro Ala Gln  Val Pro Met Glu Tyr  Asn His Leu
    4325                4330                4335

Gln Glu  Ile Pro Ile Ile Ala  Leu Arg Asn Arg Leu  Leu Leu Leu
    4340                4345                4350

His His  Leu Ser Glu Leu Phe  Cys Pro Cys Ile Pro  Met Phe Asp
    4355                4360                4365

Leu Glu  Gly Ser Leu Asp Glu  Thr Gly Leu Gly Pro  Ser Val Gly
    4370                4375                4380

Phe Asp  Thr Leu Arg Gly Ile  Leu Ile Ser Gln Gly  Lys Glu Ala
    4385                4390                4395

Ala Phe  Arg Lys Val Val Gln  Ala Thr Met Val Arg  Asp Arg Gln
    4400                4405                4410

His Gly  Pro Val Val Glu Leu  Asn Arg Ile Gln Val  Lys Arg Ser
    4415                4420                4425

Arg Ser  Lys Gly Gly Leu Ala  Gly Pro Asp Gly Thr  Lys Ser Val
    4430                4435                4440

Phe Gly  Gln Met Cys Ala Lys  Met Ser Ser Phe Gly  Pro Asp Ser
    4445                4450                4455

Leu Leu  Leu Pro His Arg Val  Trp Lys Val Lys Phe  Val Gly Glu
    4460                4465                4470

Ser Val  Asp Asp Cys Gly Gly  Gly Tyr Ser Glu Ser  Ile Ala Glu
    4475                4480                4485

Ile Cys  Glu Glu Leu Gln Asn  Gly Leu Thr Pro Leu  Leu Ile Val
    4490                4495                4500

Thr Pro  Asn Gly Arg Asp Glu  Ser Gly Ala Asn Arg  Asp Cys Tyr
    4505                4510                4515

Leu Leu  Ser Pro Ala Ala Arg  Ala Pro Val His Ser  Ser Met Phe
    4520                4525                4530

Arg Phe  Leu Gly Val Leu Leu  Gly Ile Ala Ile Arg  Thr Gly Ser
    4535                4540                4545

Pro Leu  Ser Leu Asn Leu Ala  Glu Pro Val Trp Lys  Gln Leu Ala
    4550                4555                4560

Gly Met  Ser Leu Thr Ile Ala  Asp Leu Ser Glu Val  Asp Lys Asp
    4565                4570                4575

Phe Ile  Pro Gly Leu Met Tyr  Ile Arg Asp Asn Glu  Ala Thr Ser
    4580                4585                4590

Glu Glu  Phe Glu Ala Met Ser  Leu Pro Phe Thr Val  Pro Ser Ala
    4595                4600                4605

Ser Gly  Gln Asp Ile Gln Leu  Ser Ser Lys His Thr  His Ile Thr
    4610                4615                4620
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```
Leu Asp  Asn Arg Ala Glu Tyr  Val Arg Leu Ala Ile  Asn Tyr Arg
    4625                4630                4635

Leu His  Glu Phe Asp Glu Gln  Val Ala Ala Val Arg  Glu Gly Met
    4640                4645                4650

Ala Arg  Val Val Pro Val Pro  Leu Leu Ser Leu Phe  Thr Gly Tyr
    4655                4660                4665

Glu Leu  Glu Thr Met Val Cys  Gly Ser Pro Asp Ile  Pro Leu His
    4670                4675                4680

Leu Leu  Lys Ser Val Ala Thr  Tyr Lys Gly Ile Glu  Pro Ser Ala
    4685                4690                4695

Ser Leu  Ile Gln Trp Phe Trp  Glu Val Met Glu Ser  Phe Ser Asn
    4700                4705                4710

Thr Glu  Arg Ser Leu Phe Leu  Arg Phe Val Trp Gly  Arg Thr Arg
    4715                4720                4725

Leu Pro  Arg Thr Ile Ala Asp  Phe Arg Gly Arg Asp  Phe Val Ile
    4730                4735                4740

Gln Val  Leu Asp Lys Tyr Asn  Pro Pro Asp His Phe  Leu Pro Glu
    4745                4750                4755

Ser Tyr  Thr Cys Phe Phe Leu  Leu Lys Leu Pro Arg  Tyr Ser Cys
    4760                4765                4770

Lys Gln  Val Leu Glu Glu Lys  Leu Lys Tyr Ala Ile  His Phe Cys
    4775                4780                4785

Lys Ser  Ile Asp Thr Asp Asp  Tyr Ala Arg Ile Ala  Leu Thr Gly
    4790                4795                4800

Glu Pro  Ala Ala Asp Asp Ser  Ser Asp Asp Ser Asp  Asn Glu Asp
    4805                4810                4815

Val Asp  Ser Phe Ala Ser Asp  Ser Thr Gln Asp Tyr  Leu Thr Gly
    4820                4825                4830

His
```

<210> SEQ ID NO 12
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

```
Lys Leu Ala Glu Leu Pro Ala Ala Ala Gln Pro Ser Ala Glu Asp Ser
1               5                   10                  15

Asp
```

<210> SEQ ID NO 13
<211> LENGTH: 579
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

```
Ala Asn Thr Phe Leu Glu Glu Val Arg Lys Gly Asn Leu Glu Arg Glu
1               5                   10                  15

Cys Val Glu Glu Thr Cys Ser Tyr Glu Glu Ala Phe Glu Ala Leu Glu
            20                  25                  30

Ser Ser Thr Ala Thr Asp Val Phe Trp Ala Lys Tyr Thr Ala Cys Glu
        35                  40                  45

Thr Ala Arg Thr Pro Arg Asp Lys Leu Ala Ala Cys Leu Glu Gly Asn
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    50                  55                  60

Cys Ala Glu Gly Leu Gly Thr Asn Tyr Arg Gly His Val Asn Ile Thr
65                  70                  75                  80

Arg Ser Gly Ile Glu Cys Gln Leu Trp Arg Ser Arg Tyr Pro His Lys
                85                  90                  95

Pro Glu Ile Asn Ser Thr Thr His Pro Gly Ala Asp Leu Gln Glu Asn
            100                 105                 110

Phe Cys Arg Asn Pro Asp Ser Ser Thr Thr Gly Pro Trp Cys Tyr Thr
        115                 120                 125

Thr Asp Pro Thr Val Arg Arg Gln Glu Cys Ser Ile Pro Val Cys Gly
    130                 135                 140

Gln Asp Gln Val Thr Val Ala Met Thr Pro Arg Ser Glu Gly Ser Ser
145                 150                 155                 160

Val Asn Leu Ser Pro Pro Leu Glu Gln Cys Val Pro Asp Arg Gly Gln
                165                 170                 175

Gln Tyr Gln Gly Arg Leu Ala Val Thr Thr His Gly Leu Pro Cys Leu
            180                 185                 190

Ala Trp Ala Ser Ala Gln Ala Lys Ala Leu Ser Lys His Gln Asp Phe
        195                 200                 205

Asn Ser Ala Val Gln Leu Val Glu Asn Phe Cys Arg Asn Pro Asp Gly
    210                 215                 220

Asp Glu Glu Gly Val Trp Cys Tyr Val Ala Gly Lys Pro Gly Asp Phe
225                 230                 235                 240

Gly Tyr Cys Asp Leu Asn Tyr Cys Glu Glu Ala Val Glu Glu Glu Thr
                245                 250                 255

Gly Asp Gly Leu Asp Glu Asp Ser Asp Arg Ala Ile Glu Gly Arg Thr
            260                 265                 270

Ala Thr Ser Glu Tyr Gln Thr Phe Phe Asn Pro Arg Thr Phe Gly Ser
        275                 280                 285

Gly Glu Ala Asp Cys Gly Leu Arg Pro Leu Phe Glu Lys Lys Ser Leu
    290                 295                 300

Glu Asp Lys Thr Glu Arg Glu Leu Leu Glu Ser Tyr Ile Asp Gly Arg
305                 310                 315                 320

Ile Val Glu Gly Ser Asp Ala Glu Ile Gly Met Ser Pro Trp Gln Val
                325                 330                 335

Met Leu Phe Arg Lys Ser Pro Gln Glu Leu Leu Cys Gly Ala Ser Leu
            340                 345                 350

Ile Ser Asp Arg Trp Val Leu Thr Ala Ala His Cys Leu Leu Tyr Pro
        355                 360                 365

Pro Trp Asp Lys Asn Phe Thr Glu Asn Asp Leu Leu Val Arg Ile Gly
    370                 375                 380

Lys His Ser Arg Thr Arg Tyr Glu Arg Asn Ile Glu Lys Ile Ser Met
385                 390                 395                 400

Leu Glu Lys Ile Tyr Ile His Pro Arg Tyr Asn Trp Arg Glu Asn Leu
                405                 410                 415

Asp Arg Asp Ile Ala Leu Met Lys Leu Lys Lys Pro Val Ala Phe Ser
            420                 425                 430

Asp Tyr Ile His Pro Val Cys Leu Pro Asp Arg Glu Thr Ala Ala Ser
        435                 440                 445

Leu Leu Gln Ala Gly Tyr Lys Gly Arg Val Thr Gly Trp Gly Asn Leu
    450                 455                 460
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```
Lys Glu Thr Trp Thr Ala Asn Val Gly Lys Gly Gln Pro Ser Val Leu
465                 470                 475                 480

Gln Val Val Asn Leu Pro Ile Val Glu Arg Pro Val Cys Lys Asp Ser
                485                 490                 495

Thr Arg Ile Arg Ile Thr Asp Asn Met Phe Cys Ala Gly Tyr Lys Pro
            500                 505                 510

Asp Glu Gly Lys Arg Gly Asp Ala Cys Glu Gly Asp Ser Gly Gly Pro
        515                 520                 525

Phe Val Met Lys Ser Pro Phe Asn Asn Arg Trp Tyr Gln Met Gly Ile
    530                 535                 540

Val Ser Trp Gly Glu Gly Cys Asp Arg Asp Gly Lys Tyr Gly Phe Tyr
545                 550                 555                 560

Thr His Val Phe Arg Leu Lys Lys Trp Ile Gln Lys Val Ile Asp Gln
                565                 570                 575

Phe Gly Glu


<210> SEQ ID NO 14
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Thr Ala Thr Ser Glu Tyr Gln Thr Phe Phe Asn Pro Arg Thr Phe Gly
1               5                   10                  15

Ser Gly Glu Ala Asp
            20


<210> SEQ ID NO 15
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Gly Pro Thr Gly Thr Gly Glu Ser Lys Cys Pro Leu Met Val Lys Val
1               5                   10                  15

Leu Asp Ala Val Arg Gly Ser Pro Ala Ile Asn Val Ala Val His Val
            20                  25                  30

Phe Arg Lys Ala Ala Asp Asp Thr Trp Glu Pro Phe Ala Ser Gly Lys
        35                  40                  45

Thr Ser Glu Ser Gly Glu Leu His Gly Leu Thr Thr Glu Glu Glu Phe
    50                  55                  60

Val Glu Gly Ile Tyr Lys Val Glu Ile Asp Thr Lys Ser Tyr Trp Lys
65                  70                  75                  80

Ala Leu Gly Ile Ser Pro Phe His Glu His Ala Glu Val Val Phe Thr
                85                  90                  95

Ala Asn Asp Ser Gly Pro Arg Arg Tyr Thr Ile Ala Ala Leu Leu Ser
            100                 105                 110

Pro Tyr Ser Tyr Ser Thr Thr Ala Val Val Thr Asn Pro Lys Glu
        115                 120                 125


<210> SEQ ID NO 16
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 16

Ala Val Arg Gly Ser Pro Ala Ile Asn Val Ala Val His Val Phe Arg
1 5 10 15

Lys Ala Ala Asp
20

<210> SEQ ID NO 17
<211> LENGTH: 399
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Lys Glu Ala Cys Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys
1 5 10 15

Lys Ala Cys Asn Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn
20 25 30

Gln Thr Val Cys Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val
35 40 45

Val Ser Ala Thr Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu
50 55 60

Gln Ser Met Ser Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg
65 70 75 80

Cys Ala Tyr Gly Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala
85 90 95

Cys Arg Val Cys Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp
100 105 110

Lys Gln Asn Thr Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp
115 120 125

Glu Ala Asn His Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp
130 135 140

Thr Glu Arg Gln Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys
145 150 155 160

Glu Glu Ile Pro Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly
165 170 175

Ser Asp Ser Thr Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu
180 185 190

Gln Asp Leu Ile Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met
195 200 205

Gly Ser Ser Gln Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile
210 215 220

Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu Val Ala
225 230 235 240

Tyr Ile Ala Phe Lys Arg Trp Asn Ser Cys Lys Gln Asn Lys Gln Gly
245 250 255

Ala Asn Ser Arg Pro Val Asn Gln Thr Pro Pro Pro Glu Gly Glu Lys
260 265 270

Leu His Ser Asp Ser Gly Ile Ser Val Asp Ser Gln Ser Leu His Asp
275 280 285

Gln Gln Pro His Thr Gln Thr Ala Ser Gly Gln Ala Leu Lys Gly Asp
290 295 300

Gly Gly Leu Tyr Ser Ser Leu Pro Pro Ala Lys Arg Glu Glu Val Glu
305 310 315 320

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Lys Leu Leu Asn Gly Ser Ala Gly Asp Thr Trp Arg His Leu Ala Gly
                325                 330                 335

Glu Leu Gly Tyr Gln Pro Glu His Ile Asp Ser Phe Thr His Glu Ala
            340                 345                 350

Cys Pro Val Arg Ala Leu Leu Ala Ser Trp Ala Thr Gln Asp Ser Ala
        355                 360                 365

Thr Leu Asp Ala Leu Leu Ala Ala Leu Arg Arg Ile Gln Arg Ala Asp
    370                 375                 380

Leu Val Glu Ser Leu Cys Ser Glu Ser Thr Ala Thr Ser Pro Val
385                 390                 395


<210> SEQ ID NO 18
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Gln Thr Ala Ser Gly Gln Ala Leu Lys Gly Asp Gly Gly Leu Tyr Ser
1               5                   10                  15


<210> SEQ ID NO 19
<211> LENGTH: 1725
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Lys Pro Arg Leu Leu Leu Phe Ser Pro Ser Val Val His Leu Gly Val
1               5                   10                  15

Pro Leu Ser Val Gly Val Gln Leu Gln Asp Val Pro Arg Gly Gln Val
            20                  25                  30

Val Lys Gly Ser Val Phe Leu Arg Asn Pro Ser Arg Asn Asn Val Pro
        35                  40                  45

Cys Ser Pro Lys Val Asp Phe Thr Leu Ser Ser Glu Arg Asp Phe Ala
    50                  55                  60

Leu Leu Ser Leu Gln Val Pro Leu Lys Asp Ala Lys Ser Cys Gly Leu
65                  70                  75                  80

His Gln Leu Leu Arg Gly Pro Glu Val Gln Leu Val Ala His Ser Pro
                85                  90                  95

Trp Leu Lys Asp Ser Leu Ser Arg Thr Thr Asn Ile Gln Gly Ile Asn
            100                 105                 110

Leu Leu Phe Ser Ser Arg Arg Gly His Leu Phe Leu Gln Thr Asp Gln
        115                 120                 125

Pro Ile Tyr Asn Pro Gly Gln Arg Val Arg Tyr Arg Val Phe Ala Leu
    130                 135                 140

Asp Gln Lys Met Arg Pro Ser Thr Asp Thr Ile Thr Val Met Val Glu
145                 150                 155                 160

Asn Ser His Gly Leu Arg Val Arg Lys Lys Glu Val Tyr Met Pro Ser
                165                 170                 175

Ser Ile Phe Gln Asp Asp Phe Val Ile Pro Asp Ile Ser Glu Pro Gly
            180                 185                 190

Thr Trp Lys Ile Ser Ala Arg Phe Ser Asp Gly Leu Glu Ser Asn Ser
        195                 200                 205

Ser Thr Gln Phe Glu Val Lys Lys Tyr Val Leu Pro Asn Phe Glu Val
    210                 215                 220
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```
Lys Ile Thr Pro Gly Lys Pro Tyr Ile Leu Thr Val Pro Gly His Leu
225                 230                 235                 240

Asp Glu Met Gln Leu Asp Ile Gln Ala Arg Tyr Ile Tyr Gly Lys Pro
                245                 250                 255

Val Gln Gly Val Ala Tyr Val Arg Phe Gly Leu Leu Asp Glu Asp Gly
            260                 265                 270

Lys Lys Thr Phe Phe Arg Gly Leu Glu Ser Gln Thr Lys Leu Val Asn
        275                 280                 285

Gly Gln Ser His Ile Ser Leu Ser Lys Ala Glu Phe Gln Asp Ala Leu
    290                 295                 300

Glu Lys Leu Asn Met Gly Ile Thr Asp Leu Gln Gly Leu Arg Leu Tyr
305                 310                 315                 320

Val Ala Ala Ala Ile Ile Glu Ser Pro Gly Gly Glu Met Glu Glu Ala
                325                 330                 335

Glu Leu Thr Ser Trp Tyr Phe Val Ser Ser Pro Phe Ser Leu Asp Leu
            340                 345                 350

Ser Lys Thr Lys Arg His Leu Val Pro Gly Ala Pro Phe Leu Leu Gln
        355                 360                 365

Ala Leu Val Arg Glu Met Ser Gly Ser Pro Ala Ser Gly Ile Pro Val
    370                 375                 380

Lys Val Ser Ala Thr Val Ser Ser Pro Gly Ser Val Pro Glu Val Gln
385                 390                 395                 400

Asp Ile Gln Gln Asn Thr Asp Gly Ser Gly Gln Val Ser Ile Pro Ile
                405                 410                 415

Ile Ile Pro Gln Thr Ile Ser Glu Leu Gln Leu Ser Val Ser Ala Gly
            420                 425                 430

Ser Pro His Pro Ala Ile Ala Arg Leu Thr Val Ala Ala Pro Pro Ser
        435                 440                 445

Gly Gly Pro Gly Phe Leu Ser Ile Glu Arg Pro Asp Ser Arg Pro Pro
    450                 455                 460

Arg Val Gly Asp Thr Leu Asn Leu Asn Leu Arg Ala Val Gly Ser Gly
465                 470                 475                 480

Ala Thr Phe Ser His Tyr Tyr Tyr Met Ile Leu Ser Arg Gly Gln Ile
                485                 490                 495

Val Phe Met Asn Arg Glu Pro Lys Arg Thr Leu Thr Ser Val Ser Val
            500                 505                 510

Phe Val Asp His His Leu Ala Pro Ser Phe Tyr Phe Val Ala Phe Tyr
        515                 520                 525

Tyr His Gly Asp His Pro Val Ala Asn Ser Leu Arg Val Asp Val Gln
    530                 535                 540

Ala Gly Ala Cys Glu Gly Lys Leu Glu Leu Ser Val Asp Gly Ala Lys
545                 550                 555                 560

Gln Tyr Arg Asn Gly Glu Ser Val Lys Leu His Leu Glu Thr Asp Ser
                565                 570                 575

Leu Ala Leu Val Ala Leu Gly Ala Leu Asp Thr Ala Leu Tyr Ala Ala
            580                 585                 590

Gly Ser Lys Ser His Lys Pro Leu Asn Met Gly Lys Val Phe Glu Ala
        595                 600                 605

Met Asn Ser Tyr Asp Leu Gly Cys Gly Pro Gly Gly Gly Asp Ser Ala
    610                 615                 620

Leu Gln Val Phe Gln Ala Ala Gly Leu Ala Phe Ser Asp Gly Asp Gln
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625                 630                 635                 640

Trp Thr Leu Ser Arg Lys Arg Leu Ser Cys Pro Lys Glu Lys Thr Thr
                645                 650                 655

Arg Lys Lys Arg Asn Val Asn Phe Gln Lys Ala Ile Asn Glu Lys Leu
            660                 665                 670

Gly Gln Tyr Ala Ser Pro Thr Ala Lys Arg Cys Cys Gln Asp Gly Val
        675                 680                 685

Thr Arg Leu Pro Met Met Arg Ser Cys Glu Gln Arg Ala Ala Arg Val
    690                 695                 700

Gln Gln Pro Asp Cys Arg Glu Pro Phe Leu Ser Cys Cys Gln Phe Ala
705                 710                 715                 720

Glu Ser Leu Arg Lys Lys Ser Arg Asp Lys Gly Gln Ala Gly Leu Gln
                725                 730                 735

Arg Ala Leu Glu Ile Leu Gln Glu Glu Asp Leu Ile Asp Glu Asp Asp
            740                 745                 750

Ile Pro Val Arg Ser Phe Phe Pro Glu Asn Trp Leu Trp Arg Val Glu
        755                 760                 765

Thr Val Asp Arg Phe Gln Ile Leu Thr Leu Trp Leu Pro Asp Ser Leu
    770                 775                 780

Thr Thr Trp Glu Ile His Gly Leu Ser Leu Ser Lys Thr Lys Gly Leu
785                 790                 795                 800

Cys Val Ala Thr Pro Val Gln Leu Arg Val Phe Arg Glu Phe His Leu
                805                 810                 815

His Leu Arg Leu Pro Met Ser Val Arg Arg Phe Glu Gln Leu Glu Leu
            820                 825                 830

Arg Pro Val Leu Tyr Asn Tyr Leu Asp Lys Asn Leu Thr Val Ser Val
        835                 840                 845

His Val Ser Pro Val Glu Gly Leu Cys Leu Ala Gly Gly Gly Gly Leu
    850                 855                 860

Ala Gln Gln Val Leu Val Pro Ala Gly Ser Ala Arg Pro Val Ala Phe
865                 870                 875                 880

Ser Val Val Pro Thr Ala Ala Ala Ala Val Ser Leu Lys Val Val Ala
                885                 890                 895

Arg Gly Ser Phe Glu Phe Pro Val Gly Asp Ala Val Ser Lys Val Leu
            900                 905                 910

Gln Ile Glu Lys Glu Gly Ala Ile His Arg Glu Glu Leu Val Tyr Glu
        915                 920                 925

Leu Asn Pro Leu Asp His Arg Gly Arg Thr Leu Glu Ile Pro Gly Asn
    930                 935                 940

Ser Asp Pro Asn Met Ile Pro Asp Gly Asp Phe Asn Ser Tyr Val Arg
945                 950                 955                 960

Val Thr Ala Ser Asp Pro Leu Asp Thr Leu Gly Ser Glu Gly Ala Leu
                965                 970                 975

Ser Pro Gly Gly Val Ala Ser Leu Leu Arg Leu Pro Arg Gly Cys Gly
            980                 985                 990

Glu Gln Thr Met Ile Tyr Leu Ala  Pro Thr Leu Ala Ala  Ser Arg Tyr
        995                 1000                1005

Leu Asp  Lys Thr Glu Gln Trp  Ser Thr Leu Pro Pro  Glu Thr Lys
    1010                1015                1020

Asp His  Ala Val Asp Leu Ile  Gln Lys Gly Tyr Met  Arg Ile Gln
    1025                1030                1035
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Gln Phe  Arg Lys Ala Asp Gly  Ser Tyr Ala Ala Trp  Leu Ser Arg
    1040                1045                1050

Asp Ser  Ser Thr Trp Leu Thr  Ala Phe Val Leu Lys  Val Leu Ser
    1055                1060                1065

Leu Ala  Gln Glu Gln Val Gly  Gly Ser Pro Glu Lys  Leu Gln Glu
    1070                1075                1080

Thr Ser  Asn Trp Leu Leu Ser  Gln Gln Gln Ala Asp  Gly Ser Phe
    1085                1090                1095

Gln Asp  Pro Cys Pro Val Leu  Asp Arg Ser Met Gln  Gly Gly Leu
    1100                1105                1110

Val Gly  Asn Asp Glu Thr Val  Ala Leu Thr Ala Phe  Val Thr Ile
    1115                1120                1125

Ala Leu  His His Gly Leu Ala  Val Phe Gln Asp Glu  Gly Ala Glu
    1130                1135                1140

Pro Leu  Lys Gln Arg Val Glu  Ala Ser Ile Ser Lys  Ala Asn Ser
    1145                1150                1155

Phe Leu  Gly Glu Lys Ala Ser  Ala Gly Leu Leu Gly  Ala His Ala
    1160                1165                1170

Ala Ala  Ile Thr Ala Tyr Ala  Leu Ser Leu Thr Lys  Ala Pro Val
    1175                1180                1185

Asp Leu  Leu Gly Val Ala His  Asn Asn Leu Met Ala  Met Ala Gln
    1190                1195                1200

Glu Thr  Gly Asp Asn Leu Tyr  Trp Gly Ser Val Thr  Gly Ser Gln
    1205                1210                1215

Ser Asn  Ala Val Ser Pro Thr  Pro Ala Pro Arg Asn  Pro Ser Asp
    1220                1225                1230

Pro Met  Pro Gln Ala Pro Ala  Leu Trp Ile Glu Thr  Thr Ala Tyr
    1235                1240                1245

Ala Leu  Leu His Leu Leu Leu  His Glu Gly Lys Ala  Glu Met Ala
    1250                1255                1260

Asp Gln  Ala Ser Ala Trp Leu  Thr Arg Gln Gly Ser  Phe Gln Gly
    1265                1270                1275

Gly Phe  Arg Ser Thr Gln Asp  Thr Val Ile Ala Leu  Asp Ala Leu
    1280                1285                1290

Ser Ala  Tyr Trp Ile Ala Ser  His Thr Thr Glu Glu  Arg Gly Leu
    1295                1300                1305

Asn Val  Thr Leu Ser Ser Thr  Gly Arg Asn Gly Phe  Lys Ser His
    1310                1315                1320

Ala Leu  Gln Leu Asn Asn Arg  Gln Ile Arg Gly Leu  Glu Glu Glu
    1325                1330                1335

Leu Gln  Phe Ser Leu Gly Ser  Lys Ile Asn Val Lys  Val Gly Gly
    1340                1345                1350

Asn Ser  Lys Gly Thr Leu Lys  Val Leu Arg Thr Tyr  Asn Val Leu
    1355                1360                1365

Asp Met  Lys Asn Thr Thr Cys  Gln Asp Leu Gln Ile  Glu Val Thr
    1370                1375                1380

Val Lys  Gly His Val Glu Tyr  Thr Met Glu Ala Asn  Glu Asp Tyr
    1385                1390                1395

Glu Asp  Tyr Glu Tyr Asp Glu  Leu Pro Ala Lys Asp  Asp Pro Asp
    1400                1405                1410
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Ala Pro  Leu Gln Pro Val Thr  Pro Leu Gln Leu Phe  Glu Gly Arg
    1415                 1420                 1425

Arg Asn  Arg Arg Arg Arg Glu  Ala Pro Lys Val Val  Glu Glu Gln
    1430                 1435                 1440

Glu Ser  Arg Val His Tyr Thr  Val Cys Ile Trp Arg  Asn Gly Lys
    1445                 1450                 1455

Val Gly  Leu Ser Gly Met Ala  Ile Ala Asp Val Thr  Leu Leu Ser
    1460                 1465                 1470

Gly Phe  His Ala Leu Arg Ala  Asp Leu Glu Lys Leu  Thr Ser Leu
    1475                 1480                 1485

Ser Asp  Arg Tyr Val Ser His  Phe Glu Thr Glu Gly  Pro His Val
    1490                 1495                 1500

Leu Leu  Tyr Phe Asp Ser Val  Pro Thr Ser Arg Glu  Cys Val Gly
    1505                 1510                 1515

Phe Glu  Ala Val Gln Glu Val  Pro Val Gly Leu Val  Gln Pro Ala
    1520                 1525                 1530

Ser Ala  Thr Leu Tyr Asp Tyr  Tyr Asn Pro Glu Arg  Arg Cys Ser
    1535                 1540                 1545

Val Phe  Tyr Gly Ala Pro Ser  Lys Ser Arg Leu Leu  Ala Thr Leu
    1550                 1555                 1560

Cys Ser  Ala Glu Val Cys Gln  Cys Ala Glu Gly Lys  Cys Pro Arg
    1565                 1570                 1575

Gln Arg  Arg Ala Leu Glu Arg  Gly Leu Gln Asp Glu  Asp Gly Tyr
    1580                 1585                 1590

Arg Met  Lys Phe Ala Cys Tyr  Tyr Pro Arg Val Glu  Tyr Gly Phe
    1595                 1600                 1605

Gln Val  Lys Val Leu Arg Glu  Asp Ser Arg Ala Ala  Phe Arg Leu
    1610                 1615                 1620

Phe Glu  Thr Lys Ile Thr Gln  Val Leu His Phe Thr  Lys Asp Val
    1625                 1630                 1635

Lys Ala  Ala Ala Asn Gln Met  Arg Asn Phe Leu Val  Arg Ala Ser
    1640                 1645                 1650

Cys Arg  Leu Arg Leu Glu Pro  Gly Lys Glu Tyr Leu  Ile Met Gly
    1655                 1660                 1665

Leu Asp  Gly Ala Thr Tyr Asp  Leu Glu Gly His Pro  Gln Tyr Leu
    1670                 1675                 1680

Leu Asp  Ser Asn Ser Trp Ile  Glu Glu Met Pro Ser  Glu Arg Leu
    1685                 1690                 1695

Cys Arg  Ser Thr Arg Gln Arg  Ala Ala Cys Ala Gln  Leu Asn Asp
    1700                 1705                 1710

Phe Leu  Gln Glu Tyr Gly Thr  Gln Gly Cys Gln Val
    1715                 1720                 1725


<210> SEQ ID NO 20
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Asn Gly Phe Lys Ser His Ala Leu Gln Leu Asn Asn Arg Gln Ile Arg
1               5                  10                  15


<210> SEQ ID NO 21
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<211> LENGTH: 1725
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

```
Lys Pro Arg Leu Leu Leu Phe Ser Pro Ser Val Val His Leu Gly Val
1               5                   10                  15

Pro Leu Ser Val Gly Val Gln Leu Gln Asp Val Pro Arg Gly Gln Val
            20                  25                  30

Val Lys Gly Ser Val Phe Leu Arg Asn Pro Ser Arg Asn Asn Val Pro
        35                  40                  45

Cys Ser Pro Lys Val Asp Phe Thr Leu Ser Ser Glu Arg Asp Phe Ala
    50                  55                  60

Leu Leu Ser Leu Gln Val Pro Leu Lys Asp Ala Lys Ser Cys Gly Leu
65                  70                  75                  80

His Gln Leu Leu Arg Gly Pro Glu Val Gln Leu Val Ala His Ser Pro
                85                  90                  95

Trp Leu Lys Asp Ser Leu Ser Arg Thr Thr Asn Ile Gln Gly Ile Asn
            100                 105                 110

Leu Leu Phe Ser Ser Arg Arg Gly His Leu Phe Leu Gln Thr Asp Gln
        115                 120                 125

Pro Ile Tyr Asn Pro Gly Gln Arg Val Arg Tyr Arg Val Phe Ala Leu
    130                 135                 140

Asp Gln Lys Met Arg Pro Ser Thr Asp Thr Ile Thr Val Met Val Glu
145                 150                 155                 160

Asn Ser His Gly Leu Arg Val Arg Lys Lys Glu Val Tyr Met Pro Ser
                165                 170                 175

Ser Ile Phe Gln Asp Asp Phe Val Ile Pro Asp Ile Ser Glu Pro Gly
            180                 185                 190

Thr Trp Lys Ile Ser Ala Arg Phe Ser Asp Gly Leu Glu Ser Asn Ser
        195                 200                 205

Ser Thr Gln Phe Glu Val Lys Lys Tyr Val Leu Pro Asn Phe Glu Val
    210                 215                 220

Lys Ile Thr Pro Gly Lys Pro Tyr Ile Leu Thr Val Pro Gly His Leu
225                 230                 235                 240

Asp Glu Met Gln Leu Asp Ile Gln Ala Arg Tyr Ile Tyr Gly Lys Pro
                245                 250                 255

Val Gln Gly Val Ala Tyr Val Arg Phe Gly Leu Leu Asp Glu Asp Gly
            260                 265                 270

Lys Lys Thr Phe Phe Arg Gly Leu Glu Ser Gln Thr Lys Leu Val Asn
        275                 280                 285

Gly Gln Ser His Ile Ser Leu Ser Lys Ala Glu Phe Gln Asp Ala Leu
    290                 295                 300

Glu Lys Leu Asn Met Gly Ile Thr Asp Leu Gln Gly Leu Arg Leu Tyr
305                 310                 315                 320

Val Ala Ala Ala Ile Ile Glu Ser Pro Gly Gly Glu Met Glu Glu Ala
                325                 330                 335

Glu Leu Thr Ser Trp Tyr Phe Val Ser Ser Pro Phe Ser Leu Asp Leu
            340                 345                 350

Ser Lys Thr Lys Arg His Leu Val Pro Gly Ala Pro Phe Leu Leu Gln
        355                 360                 365

Ala Leu Val Arg Glu Met Ser Gly Ser Pro Ala Ser Gly Ile Pro Val
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    370                 375                 380

Lys Val Ser Ala Thr Val Ser Ser Pro Gly Ser Val Pro Glu Val Gln
385                 390                 395                 400

Asp Ile Gln Gln Asn Thr Asp Gly Ser Gly Gln Val Ser Ile Pro Ile
                405                 410                 415

Ile Ile Pro Gln Thr Ile Ser Glu Leu Gln Leu Ser Val Ser Ala Gly
            420                 425                 430

Ser Pro His Pro Ala Ile Ala Arg Leu Thr Val Ala Ala Pro Pro Ser
        435                 440                 445

Gly Gly Pro Gly Phe Leu Ser Ile Glu Arg Pro Asp Ser Arg Pro Pro
    450                 455                 460

Arg Val Gly Asp Thr Leu Asn Leu Asn Leu Arg Ala Val Gly Ser Gly
465                 470                 475                 480

Ala Thr Phe Ser His Tyr Tyr Tyr Met Ile Leu Ser Arg Gly Gln Ile
                485                 490                 495

Val Phe Met Asn Arg Glu Pro Lys Arg Thr Leu Thr Ser Val Ser Val
            500                 505                 510

Phe Val Asp His His Leu Ala Pro Ser Phe Tyr Phe Val Ala Phe Tyr
        515                 520                 525

Tyr His Gly Asp His Pro Val Ala Asn Ser Leu Arg Val Asp Val Gln
    530                 535                 540

Ala Gly Ala Cys Glu Gly Lys Leu Glu Leu Ser Val Asp Gly Ala Lys
545                 550                 555                 560

Gln Tyr Arg Asn Gly Glu Ser Val Lys Leu His Leu Glu Thr Asp Ser
                565                 570                 575

Leu Ala Leu Val Ala Leu Gly Ala Leu Asp Thr Ala Leu Tyr Ala Ala
            580                 585                 590

Gly Ser Lys Ser His Lys Pro Leu Asn Met Gly Lys Val Phe Glu Ala
        595                 600                 605

Met Asn Ser Tyr Asp Leu Gly Cys Gly Pro Gly Gly Gly Asp Ser Ala
    610                 615                 620

Leu Gln Val Phe Gln Ala Ala Gly Leu Ala Phe Ser Asp Gly Asp Gln
625                 630                 635                 640

Trp Thr Leu Ser Arg Lys Arg Leu Ser Cys Pro Lys Glu Lys Thr Thr
                645                 650                 655

Arg Lys Lys Arg Asn Val Asn Phe Gln Lys Ala Ile Asn Glu Lys Leu
            660                 665                 670

Gly Gln Tyr Ala Ser Pro Thr Ala Lys Arg Cys Cys Gln Asp Gly Val
        675                 680                 685

Thr Arg Leu Pro Met Met Arg Ser Cys Glu Gln Arg Ala Ala Arg Val
    690                 695                 700

Gln Gln Pro Asp Cys Arg Glu Pro Phe Leu Ser Cys Cys Gln Phe Ala
705                 710                 715                 720

Glu Ser Leu Arg Lys Lys Ser Arg Asp Lys Gly Gln Ala Gly Leu Gln
                725                 730                 735

Arg Ala Leu Glu Ile Leu Gln Glu Glu Asp Leu Ile Asp Glu Asp Asp
            740                 745                 750

Ile Pro Val Arg Ser Phe Phe Pro Glu Asn Trp Leu Trp Arg Val Glu
        755                 760                 765

Thr Val Asp Arg Phe Gln Ile Leu Thr Leu Trp Leu Pro Asp Ser Leu
    770                 775                 780
```

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```
Thr Thr Trp Glu Ile His Gly Leu Ser Leu Ser Lys Thr Lys Gly Leu
785                 790                 795                 800

Cys Val Ala Thr Pro Val Gln Leu Arg Val Phe Arg Glu Phe His Leu
                805                 810                 815

His Leu Arg Leu Pro Met Ser Val Arg Arg Phe Glu Gln Leu Glu Leu
            820                 825                 830

Arg Pro Val Leu Tyr Asn Tyr Leu Asp Lys Asn Leu Thr Val Ser Val
        835                 840                 845

His Val Ser Pro Val Glu Gly Leu Cys Leu Ala Gly Gly Gly Gly Leu
    850                 855                 860

Ala Gln Gln Val Leu Val Pro Ala Gly Ser Ala Arg Pro Val Ala Phe
865                 870                 875                 880

Ser Val Val Pro Thr Ala Ala Ala Ala Val Ser Leu Lys Val Val Ala
                885                 890                 895

Arg Gly Ser Phe Glu Phe Pro Val Gly Asp Ala Val Ser Lys Val Leu
            900                 905                 910

Gln Ile Glu Lys Glu Gly Ala Ile His Arg Glu Glu Leu Val Tyr Glu
        915                 920                 925

Leu Asn Pro Leu Asp His Arg Gly Arg Thr Leu Glu Ile Pro Gly Asn
    930                 935                 940

Ser Asp Pro Asn Met Ile Pro Asp Gly Asp Phe Asn Ser Tyr Val Arg
945                 950                 955                 960

Val Thr Ala Ser Asp Pro Leu Asp Thr Leu Gly Ser Glu Gly Ala Leu
                965                 970                 975

Ser Pro Gly Gly Val Ala Ser Leu Leu Arg Leu Pro Arg Gly Cys Gly
            980                 985                 990

Glu Gln Thr Met Ile Tyr Leu Ala  Pro Thr Leu Ala Ala  Ser Arg Tyr
        995                 1000                1005

Leu Asp  Lys Thr Glu Gln Trp  Ser Thr Leu Pro Pro  Glu Thr Lys
    1010                1015                1020

Asp His  Ala Val Asp Leu Ile  Gln Lys Gly Tyr Met  Arg Ile Gln
    1025                1030                1035

Gln Phe  Arg Lys Ala Asp Gly  Ser Tyr Ala Ala Trp  Leu Ser Arg
    1040                1045                1050

Asp Ser  Ser Thr Trp Leu Thr  Ala Phe Val Leu Lys  Val Leu Ser
    1055                1060                1065

Leu Ala  Gln Glu Gln Val Gly  Gly Ser Pro Glu Lys  Leu Gln Glu
    1070                1075                1080

Thr Ser  Asn Trp Leu Leu Ser  Gln Gln Gln Ala Asp  Gly Ser Phe
    1085                1090                1095

Gln Asp  Leu Ser Pro Val Ile  His Arg Ser Met Gln  Gly Gly Leu
    1100                1105                1110

Val Gly  Asn Asp Glu Thr Val  Ala Leu Thr Ala Phe  Val Thr Ile
    1115                1120                1125

Ala Leu  His His Gly Leu Ala  Val Phe Gln Asp Glu  Gly Ala Glu
    1130                1135                1140

Pro Leu  Lys Gln Arg Val Glu  Ala Ser Ile Ser Lys  Ala Asn Ser
    1145                1150                1155

Phe Leu  Gly Glu Lys Ala Ser  Ala Gly Leu Leu Gly  Ala His Ala
    1160                1165                1170
```

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```
Ala Ala  Ile Thr Ala Tyr Ala  Leu Ser Leu Thr Lys  Ala Pro Val
    1175                1180                1185

Asp Leu  Leu Gly Val Ala His  Asn Asn Leu Met Ala  Met Ala Gln
    1190                1195                1200

Glu Thr  Gly Asp Asn Leu Tyr  Trp Gly Ser Val Thr  Gly Ser Gln
    1205                1210                1215

Ser Asn  Ala Val Ser Pro Thr  Pro Ala Pro Arg Asn  Pro Ser Asp
    1220                1225                1230

Pro Met  Pro Gln Ala Pro Ala  Leu Trp Ile Glu Thr  Thr Ala Tyr
    1235                1240                1245

Ala Leu  Leu His Leu Leu Leu  His Glu Gly Lys Ala  Glu Met Ala
    1250                1255                1260

Asp Gln  Ala Ser Ala Trp Leu  Thr Arg Gln Gly Ser  Phe Gln Gly
    1265                1270                1275

Gly Phe  Arg Ser Thr Gln Asp  Thr Val Ile Ala Leu  Asp Ala Leu
    1280                1285                1290

Ser Ala  Tyr Trp Ile Ala Ser  His Thr Thr Glu Glu  Arg Gly Leu
    1295                1300                1305

Asn Val  Thr Leu Ser Ser Thr  Gly Arg Asn Gly Phe  Lys Ser His
    1310                1315                1320

Ala Leu  Gln Leu Asn Asn Arg  Gln Ile Arg Gly Leu  Glu Glu Glu
    1325                1330                1335

Leu Gln  Phe Ser Leu Gly Ser  Lys Ile Asn Val Lys  Val Gly Gly
    1340                1345                1350

Asn Ser  Lys Gly Thr Leu Lys  Val Leu Arg Thr Tyr  Asn Val Leu
    1355                1360                1365

Asp Met  Lys Asn Thr Thr Cys  Gln Asp Leu Gln Ile  Glu Val Thr
    1370                1375                1380

Val Lys  Gly His Val Glu Tyr  Thr Met Glu Ala Asn  Glu Asp Tyr
    1385                1390                1395

Glu Asp  Tyr Glu Tyr Asp Glu  Leu Pro Ala Lys Asp  Asp Pro Asp
    1400                1405                1410

Ala Pro  Leu Gln Pro Val Thr  Pro Leu Gln Leu Phe  Glu Gly Arg
    1415                1420                1425

Arg Asn  Arg Arg Arg Arg Glu  Ala Pro Lys Val Val  Glu Glu Gln
    1430                1435                1440

Glu Ser  Arg Val His Tyr Thr  Val Cys Ile Trp Arg  Asn Gly Lys
    1445                1450                1455

Val Gly  Leu Ser Gly Met Ala  Ile Ala Asp Val Thr  Leu Leu Ser
    1460                1465                1470

Gly Phe  His Ala Leu Arg Ala  Asp Leu Glu Lys Leu  Thr Ser Leu
    1475                1480                1485

Ser Asp  Arg Tyr Val Ser His  Phe Glu Thr Glu Gly  Pro His Val
    1490                1495                1500

Leu Leu  Tyr Phe Asp Ser Val  Pro Thr Ser Arg Glu  Cys Val Gly
    1505                1510                1515

Phe Glu  Ala Val Gln Glu Val  Pro Val Gly Leu Val  Gln Pro Ala
    1520                1525                1530

Ser Ala  Thr Leu Tyr Asp Tyr  Tyr Asn Pro Glu Arg  Arg Cys Ser
    1535                1540                1545

Val Phe  Tyr Gly Ala Pro Ser  Lys Ser Arg Leu Leu  Ala Thr Leu
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    1550                1555                1560

Cys Ser  Ala Glu Val Cys Gln  Cys Ala Glu Gly Lys  Cys Pro Arg
    1565                1570                1575

Gln Arg  Arg Ala Leu Glu Arg  Gly Leu Gln Asp Glu  Asp Gly Tyr
    1580                1585                1590

Arg Met  Lys Phe Ala Cys Tyr  Tyr Pro Arg Val Glu  Tyr Gly Phe
    1595                1600                1605

Gln Val  Lys Val Leu Arg Glu  Asp Ser Arg Ala Ala  Phe Arg Leu
    1610                1615                1620

Phe Glu  Thr Lys Ile Thr Gln  Val Leu His Phe Thr  Lys Asp Val
    1625                1630                1635

Lys Ala  Ala Ala Asn Gln Met  Arg Asn Phe Leu Val  Arg Ala Ser
    1640                1645                1650

Cys Arg  Leu Arg Leu Glu Pro  Gly Lys Glu Tyr Leu  Ile Met Gly
    1655                1660                1665

Leu Asp  Gly Ala Thr Tyr Asp  Leu Glu Gly His Pro  Gln Tyr Leu
    1670                1675                1680

Leu Asp  Ser Asn Ser Trp Ile  Glu Glu Met Pro Ser  Glu Arg Leu
    1685                1690                1695

Cys Arg  Ser Thr Arg Gln Arg  Ala Ala Cys Ala Gln  Leu Asn Asp
    1700                1705                1710

Phe Leu  Gln Glu Tyr Gly Thr  Gln Gly Cys Gln Val
    1715                1720                1725


<210> SEQ ID NO 22
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Ala Pro Leu Gln Pro Val Thr Pro Leu Gln Leu Phe Glu Gly Arg Arg
1               5                   10                  15

Asn


<210> SEQ ID NO 23
<211> LENGTH: 831
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Gly Pro Arg Val Val Glu Arg His Gln Ser Ala Cys Lys Asp Ser Asp
1               5                   10                  15

Trp Pro Phe Cys Ser Asp Glu Asp Trp Asn Tyr Lys Cys Pro Ser Gly
            20                  25                  30

Cys Arg Met Lys Gly Leu Ile Asp Glu Val Asn Gln Asp Phe Thr Asn
        35                  40                  45

Arg Ile Asn Lys Leu Lys Asn Ser Leu Phe Glu Tyr Gln Lys Asn Asn
    50                  55                  60

Lys Asp Ser His Ser Leu Thr Thr Asn Ile Met Glu Ile Leu Arg Gly
65                  70                  75                  80

Asp Phe Ser Ser Ala Asn Asn Arg Asp Asn Thr Tyr Asn Arg Val Ser
                85                  90                  95

Glu Asp Leu Arg Ser Arg Ile Glu Val Leu Lys Arg Lys Val Ile Glu
            100                 105                 110
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```
Lys Val Gln His Ile Gln Leu Leu Gln Lys Asn Val Arg Ala Gln Leu
        115                 120                 125

Val Asp Met Lys Arg Leu Glu Val Asp Ile Asp Ile Lys Ile Arg Ser
    130                 135                 140

Cys Arg Gly Ser Cys Ser Arg Ala Leu Ala Arg Glu Val Asp Leu Lys
145                 150                 155                 160

Asp Tyr Glu Asp Gln Gln Lys Gln Leu Glu Gln Val Ile Ala Lys Asp
                165                 170                 175

Leu Leu Pro Ser Arg Asp Arg Gln His Leu Pro Leu Ile Lys Met Lys
            180                 185                 190

Pro Val Pro Asp Leu Val Pro Gly Asn Phe Lys Ser Gln Leu Gln Lys
        195                 200                 205

Val Pro Pro Glu Trp Lys Ala Leu Thr Asp Met Pro Gln Met Arg Met
    210                 215                 220

Glu Leu Glu Arg Pro Gly Gly Asn Glu Ile Thr Arg Gly Gly Ser Thr
225                 230                 235                 240

Ser Tyr Gly Thr Gly Ser Glu Thr Glu Ser Pro Arg Asn Pro Ser Ser
                245                 250                 255

Ala Gly Ser Trp Asn Ser Gly Ser Ser Gly Pro Gly Ser Thr Gly Asn
            260                 265                 270

Arg Asn Pro Gly Ser Ser Gly Thr Gly Gly Thr Ala Thr Trp Lys Pro
        275                 280                 285

Gly Ser Ser Gly Pro Gly Ser Thr Gly Ser Trp Asn Ser Gly Ser Ser
    290                 295                 300

Gly Thr Gly Ser Thr Gly Asn Gln Asn Pro Gly Ser Pro Arg Pro Gly
305                 310                 315                 320

Ser Thr Gly Thr Trp Asn Pro Gly Ser Ser Glu Arg Gly Ser Ala Gly
                325                 330                 335

His Trp Thr Ser Glu Ser Ser Val Ser Gly Ser Thr Gly Gln Trp His
            340                 345                 350

Ser Glu Ser Gly Ser Phe Arg Pro Asp Ser Pro Gly Ser Gly Asn Ala
        355                 360                 365

Arg Pro Asn Asn Pro Asp Trp Gly Thr Phe Glu Glu Val Ser Gly Asn
    370                 375                 380

Val Ser Pro Gly Thr Arg Arg Glu Tyr His Thr Glu Lys Leu Val Thr
385                 390                 395                 400

Ser Lys Gly Asp Lys Glu Leu Arg Thr Gly Lys Glu Lys Val Thr Ser
                405                 410                 415

Gly Ser Thr Thr Thr Thr Arg Arg Ser Cys Ser Lys Thr Val Thr Lys
            420                 425                 430

Thr Val Ile Gly Pro Asp Gly His Lys Glu Val Thr Lys Glu Val Val
        435                 440                 445

Thr Ser Glu Asp Gly Ser Asp Cys Pro Glu Ala Met Asp Leu Gly Thr
    450                 455                 460

Leu Ser Gly Ile Gly Thr Leu Asp Gly Phe Arg His Arg His Pro Asp
465                 470                 475                 480

Glu Ala Ala Phe Phe Asp Thr Ala Ser Thr Gly Lys Thr Phe Pro Gly
                485                 490                 495

Phe Phe Ser Pro Met Leu Gly Glu Phe Val Ser Glu Thr Glu Ser Arg
            500                 505                 510
```

-continued

```
Gly Ser Glu Ser Gly Ile Phe Thr Asn Thr Lys Glu Ser Ser Ser His
        515                 520                 525

His Pro Gly Ile Ala Glu Phe Pro Ser Arg Gly Lys Ser Ser Ser Tyr
    530                 535                 540

Ser Lys Gln Phe Thr Ser Ser Thr Ser Tyr Asn Arg Gly Asp Ser Thr
545                 550                 555                 560

Phe Glu Ser Lys Ser Tyr Lys Met Ala Asp Glu Ala Gly Ser Glu Ala
                565                 570                 575

Asp His Glu Gly Thr His Ser Thr Lys Arg Gly His Ala Lys Ser Arg
            580                 585                 590

Pro Val Arg Asp Cys Asp Asp Val Leu Gln Thr His Pro Ser Gly Thr
        595                 600                 605

Gln Ser Gly Ile Phe Asn Ile Lys Leu Pro Gly Ser Ser Lys Ile Phe
    610                 615                 620

Ser Val Tyr Cys Asp Gln Glu Thr Ser Leu Gly Gly Trp Leu Leu Ile
625                 630                 635                 640

Gln Gln Arg Met Asp Gly Ser Leu Asn Phe Asn Arg Thr Trp Gln Asp
                645                 650                 655

Tyr Lys Arg Gly Phe Gly Ser Leu Asn Asp Glu Gly Glu Gly Glu Phe
            660                 665                 670

Trp Leu Gly Asn Asp Tyr Leu His Leu Leu Thr Gln Arg Gly Ser Val
        675                 680                 685

Leu Arg Val Glu Leu Glu Asp Trp Ala Gly Asn Glu Ala Tyr Ala Glu
    690                 695                 700

Tyr His Phe Arg Val Gly Ser Glu Ala Glu Gly Tyr Ala Leu Gln Val
705                 710                 715                 720

Ser Ser Tyr Glu Gly Thr Ala Gly Asp Ala Leu Ile Glu Gly Ser Val
                725                 730                 735

Glu Glu Gly Ala Glu Tyr Thr Ser His Asn Asn Met Gln Phe Ser Thr
            740                 745                 750

Phe Asp Arg Asp Ala Asp Gln Trp Glu Glu Asn Cys Ala Glu Val Tyr
        755                 760                 765

Gly Gly Gly Trp Trp Tyr Asn Asn Cys Gln Ala Ala Asn Leu Asn Gly
    770                 775                 780

Ile Tyr Tyr Pro Gly Gly Ser Tyr Asp Pro Arg Asn Asn Ser Pro Tyr
785                 790                 795                 800

Glu Ile Glu Asn Gly Val Val Trp Val Ser Phe Arg Gly Ala Asp Tyr
                805                 810                 815

Ser Leu Arg Ala Val Arg Met Lys Ile Arg Pro Leu Val Thr Gln
            820                 825                 830


<210> SEQ ID NO 24
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Ser Ser Ser Tyr Ser Lys Gln Phe Thr Ser Ser Thr Ser Tyr Asn Arg
1               5                   10                  15

Gly Asp Ser Thr Phe Glu Ser
            20


<210> SEQ ID NO 25
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-continued

<211> LENGTH: 609
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

```
Gly Pro Arg Val Val Glu Arg His Gln Ser Ala Cys Lys Asp Ser Asp
1               5                   10                  15

Trp Pro Phe Cys Ser Asp Glu Asp Trp Asn Tyr Lys Cys Pro Ser Gly
            20                  25                  30

Cys Arg Met Lys Gly Leu Ile Asp Glu Val Asn Gln Asp Phe Thr Asn
        35                  40                  45

Arg Ile Asn Lys Leu Lys Asn Ser Leu Phe Glu Tyr Gln Lys Asn Asn
    50                  55                  60

Lys Asp Ser His Ser Leu Thr Thr Asn Ile Met Glu Ile Leu Arg Gly
65                  70                  75                  80

Asp Phe Ser Ser Ala Asn Asn Arg Asp Asn Thr Tyr Asn Arg Val Ser
                85                  90                  95

Glu Asp Leu Arg Ser Arg Ile Glu Val Leu Lys Arg Lys Val Ile Glu
            100                 105                 110

Lys Val Gln His Ile Gln Leu Leu Gln Lys Asn Val Arg Ala Gln Leu
        115                 120                 125

Val Asp Met Lys Arg Leu Glu Val Asp Ile Asp Ile Lys Ile Arg Ser
    130                 135                 140

Cys Arg Gly Ser Cys Ser Arg Ala Leu Ala Arg Glu Val Asp Leu Lys
145                 150                 155                 160

Asp Tyr Glu Asp Gln Gln Lys Gln Leu Glu Gln Val Ile Ala Lys Asp
                165                 170                 175

Leu Leu Pro Ser Arg Asp Arg Gln His Leu Pro Leu Ile Lys Met Lys
            180                 185                 190

Pro Val Pro Asp Leu Val Pro Gly Asn Phe Lys Ser Gln Leu Gln Lys
        195                 200                 205

Val Pro Pro Glu Trp Lys Ala Leu Thr Asp Met Pro Gln Met Arg Met
    210                 215                 220

Glu Leu Glu Arg Pro Gly Gly Asn Glu Ile Thr Arg Gly Gly Ser Thr
225                 230                 235                 240

Ser Tyr Gly Thr Gly Ser Glu Thr Glu Ser Pro Arg Asn Pro Ser Ser
                245                 250                 255

Ala Gly Ser Trp Asn Ser Gly Ser Ser Gly Pro Gly Ser Thr Gly Asn
            260                 265                 270

Arg Asn Pro Gly Ser Ser Gly Thr Gly Gly Thr Ala Thr Trp Lys Pro
        275                 280                 285

Gly Ser Ser Gly Pro Gly Ser Thr Gly Ser Trp Asn Ser Gly Ser Ser
    290                 295                 300

Gly Thr Gly Ser Thr Gly Asn Gln Asn Pro Gly Ser Pro Arg Pro Gly
305                 310                 315                 320

Ser Thr Gly Thr Trp Asn Pro Gly Ser Ser Glu Arg Gly Ser Ala Gly
                325                 330                 335

His Trp Thr Ser Glu Ser Ser Val Ser Gly Ser Thr Gly Gln Trp His
            340                 345                 350

Ser Glu Ser Gly Ser Phe Arg Pro Asp Ser Pro Gly Ser Gly Asn Ala
        355                 360                 365

Arg Pro Asn Asn Pro Asp Trp Gly Thr Phe Glu Glu Val Ser Gly Asn
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```
    370                 375                 380

Val Ser Pro Gly Thr Arg Arg Glu Tyr His Thr Glu Lys Leu Val Thr
385                 390                 395                 400

Ser Lys Gly Asp Lys Glu Leu Arg Thr Gly Lys Glu Lys Val Thr Ser
                405                 410                 415

Gly Ser Thr Thr Thr Thr Arg Arg Ser Cys Ser Lys Thr Val Thr Lys
            420                 425                 430

Thr Val Ile Gly Pro Asp Gly His Lys Glu Val Thr Lys Glu Val Val
        435                 440                 445

Thr Ser Glu Asp Gly Ser Asp Cys Pro Glu Ala Met Asp Leu Gly Thr
    450                 455                 460

Leu Ser Gly Ile Gly Thr Leu Asp Gly Phe Arg His Arg His Pro Asp
465                 470                 475                 480

Glu Ala Ala Phe Phe Asp Thr Ala Ser Thr Gly Lys Thr Phe Pro Gly
                485                 490                 495

Phe Phe Ser Pro Met Leu Gly Glu Phe Val Ser Glu Thr Glu Ser Arg
            500                 505                 510

Gly Ser Glu Ser Gly Ile Phe Thr Asn Thr Lys Glu Ser Ser Ser His
        515                 520                 525

His Pro Gly Ile Ala Glu Phe Pro Ser Arg Gly Lys Ser Ser Ser Tyr
    530                 535                 540

Ser Lys Gln Phe Thr Ser Ser Thr Ser Tyr Asn Arg Gly Asp Ser Thr
545                 550                 555                 560

Phe Glu Ser Lys Ser Tyr Lys Met Ala Asp Glu Ala Gly Ser Glu Ala
                565                 570                 575

Asp His Glu Gly Thr His Ser Thr Lys Arg Gly His Ala Lys Ser Arg
            580                 585                 590

Pro Val Arg Gly Ile His Thr Ser Pro Leu Gly Lys Pro Ser Leu Ser
        595                 600                 605

Pro
```

<210> SEQ ID NO 26
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

```
Ser Ser Ser Tyr Ser Lys Gln Phe Thr Ser Ser Thr Ser Tyr Asn Arg
1               5                   10                  15

Gly Asp Ser Thr Phe Glu Ser Lys Ser
            20                  25
```

<210> SEQ ID NO 27
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

```
Ser Ser Ser Tyr Ser Lys Gln Phe Thr Ser Ser Thr Ser Tyr Asn Arg
1               5                   10                  15

Gly Asp Ser Thr Phe Glu Ser Lys Ser Tyr
            20                  25
```

1. A method of detecting Complement C4-derived peptide CO4-2 in a patient, said method comprising:

a. obtaining a biological material from a human patient; and

b. detecting presence or an amount of the Complement C4-derived peptide CO4-2 consisting of amino acid sequence of SEQ ID NO: 22 in the biological material by contacting the biological material with an antibody or aptamer that specifically binds to the peptide CO4-2 and detecting binding between the Complement C4-derived peptide CO4-2 and the antibody or aptamer.

2. The method of claim **1**, wherein the biological material is serum, blood, plasma, cerebrospinal fluid, or urine.

3. A method of diagnosing and treating cognitive impairment in a patient, said method comprising:

a. obtaining a biological material from a human patient;

b. detecting an amount of Complement C4-derived peptide CO4-2 consisting of amino acid sequence of SEQ ID NO: 22 in the biological material by contacting the biological material with an antibody or aptamer that specifically binds to the peptide CO4-2 and detecting binding between the peptide CO4-2 and the antibody or aptamer;

c. diagnosing the patient with cognitive impairment when a higher amount of the Complement C4-derived peptide CO4-2 in the biological material is detected by comparing the amount of the Complement C4-derived peptide CO4-2 in the patient with an amount of the Complement C4-derived peptide CO4-2 in a biological material obtained from a non-psychiatry disease subject; and

d. administering an effective amount of an anti-acetylcholine esterase inhibitor to the diagnosed patient.

4. The method of claim **3**, wherein the biological material is serum, blood, plasma, cerebrospinal fluid, or urine.

5. The method of claim **3**, wherein the cognitive impairment includes Alzheimer's dementia, mild cognitive impairment, Dementia with Lewy bodies, and frontotemporal dementia.

6. The method of claim **3**, wherein the anti-acetylcholine esterase inhibitor is Donepezil-hydrochloride.

* * * * *