In the present technology, the non-demented control (NDC) subject includes healthy humans, and means the subjects which may have any diseases but not have cognitive dysfunction diseases (non-demented control).

Also in the present technology, when referring to collectively as cognitive dysfunction diseases, it is intended that mild cognitive impairment (MCI), Alzheimer's disease (AD), and dementia-type neurological diseases are also included. In the present technology, mild cognitive impairment (MCI) and Alzheimer's disease (AD) can preferably be detected.

The peptides identified in the present technology have significance as biomarkers when detected not only in serum but also in other biological samples such as blood, serum, plasma, cerebrospinal fluid, urine, and the like. Similarly, source proteins from which the aforementioned peptides are derived (hereinafter referred to as "intact proteins") or source peptides also have a significance as biomarkers.

[0018]

Thus, in one ~~aspect~~embodiment, the present technology provides one or more biomarkers for detecting cognitive dysfunction diseases selected from the following (a), (b), and (c):

(a) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of apolipoprotein A1 comprising the amino acid sequence represented by SEQ ID NO:1 or a partial peptide thereof;

(b) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of transthyretin comprising the amino acid sequence represented by SEQ ID NO:2 or a partial peptide thereof; and,

(c) a biomarker for detecting cognitive dysfunction diseases

consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.

[0019]

In another ~~aspect~~embodiment, the present technology provides a method for detecting cognitive dysfunction diseases in which one or more biomarkers for detecting cognitive dysfunction diseases selected from the aforementioned (a) biomarker, (b) biomarker, and (c) biomarker in a biological sample are measured simultaneously or separately.

[0020]

In a further ~~aspect~~embodiment, the present technology provides a kit for detecting cognitive dysfunction diseases for measuring one or more biomarkers for detecting cognitive dysfunction diseases selected from the aforementioned (a) biomarker, (b) biomarker, and (c) biomarker.

[0021]

In yet another ~~aspect~~embodiment, the present technology provides a method for selecting a combination of multiple biomarkers for detecting cognitive dysfunction diseases which gives a high percentage of correct answers comprising measuring two or more biomarkers for cognitive dysfunction diseases in a biological sample from a subject, conducting an analysis of the measurement results of each of the aforementioned two or more biomarkers by a logistic regression analysis, and selecting a combination of the biomarkers for detecting cognitive dysfunction diseases which gives a high percentage of correct answers based on the results of the aforementioned analysis.

In one aspect, there is provided a method for detecting Alzheimer's disease or mild cognitive impairment comprising measuring biomarkers (a), (b), and (c) in a biological sample simultaneously or separately.

In another aspect, there is provided a method for detecting Alzheimer's disease comprising measuring biomarkers (b) and (c) in a biological sample simultaneously or separately.

In another aspect, there is provided a method for detecting mild cognitive impairment comprising measuring biomarkers (a) and (c) in a biological sample simultaneously or separately.

In another aspect, there is provided an Alzheimer's disease or mild cognitive impairment detection kit for measuring biomarkers (a), (b), and (c).

In a further aspect, there is provided an Alzheimer's disease detection kit for measuring biomarkers (b) and (c).

In yet another aspect, there is provided a mild cognitive impairment detection kit for measuring biomarkers (a) and (c).

## Advantageous Effects of Invention

**CLAIMS:**

~~1. One or more biomarkers for detecting cognitive dysfunction diseases selected from the following (a), (b), and (c):~~

~~(a) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of apolipoprotein A1 comprising the amino acid sequence represented by SEQ ID NO:1 or a partial peptide thereof;~~

~~(b) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of transthyretin comprising the amino acid sequence represented by SEQ ID NO:2 or a partial peptide thereof; and~~

~~(c) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.~~

12. A method for detecting Alzheimer's disease or mild cognitive impairment ~~cognitive dysfunction diseases~~ comprising measuring ~~one or more~~ biomarkers ~~for detecting cognitive dysfunction diseases selected from the following~~ (a), (b), and (c) in a biological sample simultaneously or separately:

(a) a biomarker ~~for detecting cognitive dysfunction diseases~~ consisting of an intact protein of apolipoprotein A1 comprising the amino acid sequence represented by SEQ ID NO:1 or a partial peptide thereof;

(b) a biomarker ~~for detecting cognitive dysfunction diseases~~ consisting of an intact protein of transthyretin comprising the amino acid sequence represented by SEQ ID NO:2 or a partial peptide thereof; and

(c) a biomarker ~~for detecting cognitive dysfunction diseases~~ consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.

2. A method for detecting Alzheimer's disease comprising measuring biomarkers (b) and (c) in a biological sample simultaneously or separately:

(b) a biomarker consisting of an intact protein of transthyretin comprising the amino acid sequence represented by SEQ ID NO:2 or a partial peptide thereof; and

(c) a biomarker consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.

3. A method for detecting mild cognitive impairment comprising measuring biomarkers (a) and (c) in a biological sample simultaneously or separately:

(a) a biomarker consisting of an intact protein of apolipoprotein A1 comprising the amino acid sequence represented by SEQ ID NO:1 or a partial peptide thereof; and

(c) a biomarker consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.

~~3. The method for detecting cognitive dysfunction diseases according to Claim 2 comprising measuring two biomarkers, namely, the (c) biomarker and the (a) biomarker or the (b) biomarker.~~

~~4. The method for detecting cognitive dysfunction diseases according to Claim 2 or 3 comprising measuring two biomarkers, namely, the (c) biomarker and the (a) biomarker when the detection of the cognitive dysfunction diseases is the detection of mild cognitive impairment or measuring two biomarkers, namely, the (c) biomarker and the (b) biomarker when the detection of the cognitive dysfunction diseases is Alzheimer's disease.~~

45. An Alzheimer's disease or mild cognitive impairment ~~cognitive dysfunction disease~~ detection kit for measuring ~~one or more~~ biomarkers ~~for detecting cognitive dysfunction diseases selected from the following~~ (a), (b), and (c):

(a) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of apolipoprotein A1 comprising the amino acid sequence represented by SEQ ID NO:1 or a partial peptide thereof;

(b) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of transthyretin comprising the amino acid sequence represented by SEQ ID NO:2 or a partial peptide thereof; and

(c) a biomarker for detecting cognitive dysfunction diseases consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.

~~5~~6. The Alzheimer's disease or mild cognitive impairment ~~cognitive dysfunction disease~~ detection kit according to Claim ~~4~~5 comprising an antibody ~~against the biomarker~~ or an aptamer against the biomarker.

6. An Alzheimer's disease detection kit for measuring biomarkers (b) and (c):

(b) a biomarker consisting of an intact protein of transthyretin comprising the amino acid sequence represented by SEQ ID NO:2 or a partial peptide thereof; and

(c) a biomarker consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.

7. The Alzheimer's disease detection kit according to Claim 6 comprising an antibody or an aptamer against the biomarker.

8. A mild cognitive impairment detection kit for measuring biomarkers (a) and (c):

(a) a biomarker consisting of an intact protein of apolipoprotein A1 comprising the amino acid sequence represented by SEQ ID NO:1 or a partial peptide thereof; and

(c) a biomarker consisting of an intact protein of complement C3 comprising the amino acid sequence represented by SEQ ID NO:3 or a partial peptide thereof.

9. The mild cognitive impairment detection kit according to Claim 8 comprising an antibody or an aptamer against the biomarker.

~~7. A method for selecting a combination of multiple biomarkers for detecting cognitive dysfunction diseases which gives a high percentage of correct answers comprising:~~

~~measuring two or more biomarkers for cognitive dysfunction diseases in a biological sample from a subject; conducting an analysis of the measurement results of each of the two or more biomarkers by a logistic regression analysis; and selecting a combination of the biomarkers for detecting cognitive dysfunction diseases which gives a high percentage of correct answers based on the results of the analysis.~~