

CLAIMS

1. An in-vitro method of detecting Frontotemporal Dementia (FTD) or an increased risk of FTD in a biological sample, the method comprising
 - (a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau and A β species, and quantifying a pT217/T217 value and an A β 42/A β 40 value of the processed sample; and
 - (b) detecting FTD or an increased risk of FTD when an increase in the pT217/T217 value and a normal A β 42/A β 40 value are quantified relative to a pT217/T217 value and an A β 42/A β 40 value of a healthy control population,wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject having a symptom of Alzheimer's disease, optionally wherein the subject is a *MAPT* R406W mutation carrier.
2. The method of claim 1, wherein step (a) comprises quantifying a composite pT217/T217 x A β 42/A β 40 value of the processed sample, and step (b) comprises detecting FTD or an increased risk of FTD when an increase in the composite value is quantified relative to a composite pT217/T217 x A β 42/A β 40 value of a healthy control population.
3. An in-vitro method of detecting Frontotemporal Dementia (FTD) or an increased risk of FTD in a biological sample, the method comprising
 - (a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau and A β species, and quantifying a pT217/T217 value and an A β 42/A β 40 value of the processed sample; and
 - (b) detecting FTD or an increased risk of FTD when a decrease in the pT217/T217 value and an increase in the A β 42/A β 40 value are quantified relative to a pT217/T217 value and an A β 42/A β 40 value of an Alzheimer's disease population,wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject having a symptom of Alzheimer's disease, optionally wherein the subject a *MAPT* R406W mutation carrier.
4. The method of claim 3, wherein step (a) comprises quantifying a composite pT217/T217 x A β 42/A β 40 value of the processed sample, and step (b) comprises detecting FTD or an increased risk of FTD when an increase in the composite value is quantified relative to a composite pT217/T217 x A β 42/A β 40 value of an Alzheimer's disease population.

5. An in-vitro method of detecting sporadic Frontotemporal Dementia (FTD) or an increased risk of sporadic FTD in a biological sample, the method comprising

- (a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau species quantifying a pT181/T181 value of the processed biological sample; and
- (b) detecting sporadic FTD or an increased risk of sporadic FTD when a decrease in the pT181/T181 value is quantified relative to a pT181/T181 value of a healthy control population,

wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject having a symptom of Alzheimer's disease.

6. An in-vitro method of detecting sporadic Frontotemporal Dementia (FTD) or an increased risk of sporadic FTD in a biological sample, the method comprising

- (a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau species and quantifying a pT181/T181 value of the processed sample; and
- (b) detecting sporadic FTD or an increased risk of sporadic FTD when a decrease in the pT181/T181 value is quantified relative to a pT181/T181 value of an Alzheimer's disease population,

wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject having a symptom of Alzheimer's disease.

7. An in-vitro method of discriminating a *MAPT* R406W tauopathy in a biological sample, the method comprising

- (a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau and A β species; and
- (b) quantifying a pT217/T217 value and an A β 42/A β 40 value of the processed sample, wherein an increase in the pT217/T217 value and a normal A β 42/A β 40 value discriminates a *MAPT* R406W tauopathy from a healthy state,

wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.

8. An in-vitro method of discriminating a *MAPT* R406W tauopathy in a biological sample, the method comprising

(a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau and A β species; and
(b) quantifying a pT217/T217 value and an A β 42/A β 40 value of the processed sample, wherein a decrease in the pT217/T217 value and an increase the A β 42/A β 40 value discriminates a *MAPT* R406W tauopathy from Alzheimer's disease, wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.

9. An in-vitro method of discriminating a *MAPT* R406W tauopathy in a biological sample, the method comprising

(a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau and Ab species; and
(b) quantifying a composite pT217/T217 x A β 42/A β 40 value of the processed sample, wherein the composite pT217/T217 x A β 42/A β 40 value discriminates a *MAPT* R406W tauopathy from Alzheimer's disease, 4R-tauopathy and a healthy state, wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.

10. The method of claim 9, wherein an increase in the composite pT217/T217 x A β 42/A β 40 value quantified in step (b) relative to a composite pT217/T217 x A β 42/A β 40 value of a healthy control population discriminates

- (a) a *MAPT* R406W tauopathy from a healthy state;
- (b) a *MAPT* R406W tauopathy from AD; or
- (c) a *MAPT* R406W tauopathy from a 4R-tauopathy.

11. An in-vitro method of discriminating a sporadic frontotemporal dementia (FTD) in a biological sample, the method comprising

(a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau species; and
(b) quantifying a pT181/T181 value of the processed sample, wherein the pT181/T181 value discriminates a sporadic FTD from Alzheimer's disease, non-sporadic FTD tauopathies and a healthy state, wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.

12. The method of claim 11, wherein a decrease in the pT181/T181 value quantified in step (b) relative to a pT181/T181 value in an Alzheimer's disease population discriminates

- (a) a sporadic FTD from Alzheimer's disease;
- (b) a sporadic FTD from a healthy state; or
- (c) a sporadic FTD from a non-sporadic FTD tauopathy.

13. An in-vitro method for measuring *MAPT* R406W tauopathy disease progression between a first biological sample and second biological sample, the method comprising

- (a) providing a first processed biological sample, wherein the first biological sample is enriched for one or more ptau and A β species and quantifying a pT217/T217 value and A β 42/A β 40 value of the first processed sample;
- (b) providing a second processed biological sample, wherein the second biological sample is enriched for the same ptau and A β species as in step (a) and quantifying a pT217/T217 value and A β 42/A β 40 value of the second processed sample; and
- (c) calculating the difference between the quantified pT217/T217 value and A β 42/A β 40 value of the second processed sample and the first processed sample, wherein a statistically significant difference in the quantified pT217/T217 value and A β 42/A β 40 value in the second processed sample indicates progression of tauopathy disease between the first biological sample and the second biological sample,

wherein the first and second biological sample are from a subject, and the second biological sample is obtained from the subject after the first biological sample.

14. An in-vitro method for measuring *MAPT* R406W tauopathy disease progression between a first biological sample and second biological sample, the method comprising

- (a) providing a first processed biological sample, wherein the first biological sample is enriched for one or more ptau and A β species and quantifying a composite pT217/T217 x A β 42/A β 40 value of the first processed sample;
- (b) providing a second processed biological sample, wherein the second biological sample is enriched for the same ptau and A β species as in step (a) and quantifying a composite pT217/T217 x A β 42/A β 40 value of the second processed sample; and
- (c) calculating the difference between the quantified composite pT217/T217 x A β 42/A β 40 value of the second processed sample and the first processed sample, wherein a statistically significant difference in the quantified composite pT217/T217 x

A β 42/A β 40 value in the second processed sample indicates progression of tauopathy disease between the first biological sample and the second biological sample, wherein the first and second biological sample are from a subject, and the second biological sample is obtained from the subject after the first biological sample.

15. An in-vitro method for measuring sporadic frontotemporal dementia (FTD) disease progression between a first biological sample and second biological sample the method comprising

- (a) providing a first processed biological sample, wherein the first biological sample is enriched for one or more ptau and A β species and quantifying a pT181/T181 value of the first processed sample;
- (b) providing a second processed biological sample, wherein the second biological sample is enriched for the same ptau and A β species as in step (a) and quantifying a pT181/T181 value of the second processed sample; and
- (c) calculating the difference between the quantified pT181/T181 value of the second sample and the first sample, wherein a statistically significant difference in the quantified pT181/T181 value in the second sample indicates progression of sporadic FTD between the first biological sample and the second biological sample,

wherein the first and second biological sample are from a subject, and the second biological sample is obtained from the subject after the first biological sample.

16. An in-vitro method of discriminating Alzheimer's disease (AD) in a biological sample, the method comprising

- (a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau species; and
- (b) quantifying a pT153/T153 value of the processed sample, wherein the pT153/T153 value discriminates AD from a non-AD tauopathy and a healthy state, wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.

17. An in-vitro method of discriminating Alzheimer's disease (AD) in a biological sample, the method comprising

- (a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau species; and

(b) quantifying a pT111/T111 value of the processed sample, wherein the pT111/T111 value discriminates AD from a non-AD tauopathy and a healthy state, wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.

18. An in-vitro method of discriminating a tauopathy in a biological sample, the method comprising

(a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau species; and
(b) quantifying a pT205/T205 value of the processed sample, wherein the pT205/T205 value discriminates a tauopathy and a healthy state, wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.

19. An in-vitro method of discriminating a tauopathy in a biological sample, the method comprising

(a) providing a processed biological sample, wherein the biological sample is enriched for one or more ptau species; and
(b) quantifying a pT208/T208 value of the processed sample, wherein the pT208/T208 value discriminates a tauopathy and a healthy state, wherein the biological sample is a central spinal fluid (CSF) sample or blood sample from a subject.