

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.
2. The method of claim 1, wherein the subject is a *MAPT* R406W mutation carrier.
3. 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.
4. 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.
5. The method of claim 4, wherein the subject is a *MAPT* R406W mutation carrier
6. The method of claim 4, 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.

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. The method of claim 7, wherein the composite pT217/T217 $\times$ A β 42/A β 40 value is greater than or equal to 0.4989.
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 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 in 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.
10. 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 composite pT217/T217 $\times$ A β 42/A β 40 value of the processed sample, wherein the composite pT217/T217 $\times$ 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.

11. The method of claim 10, wherein an increase in the composite $pT217/T217 \times A\beta42/A\beta40$ value quantified in step (b) relative to a composite $pT217/T217 \times A\beta42/A\beta40$ value of a healthy control population discriminates a *MAPT* R406W tauopathy from a healthy state.
12. The method of claim 10, wherein an increase in the composite $pT217/T217 \times A\beta42/A\beta40$ value quantified in step (b) relative to a composite $pT217/T217 \times A\beta42/A\beta40$ value of a healthy control population discriminates a *MAPT* R406W tauopathy from Alzheimer's disease.
13. The method of claim 10, wherein an increase in the composite $pT217/T217 \times A\beta42/A\beta40$ value quantified in step (b) relative to a composite $pT217/T217 \times A\beta42/A\beta40$ value of a healthy control population discriminates a *MAPT* R406W tauopathy from a 4R-tauopathy.
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 $A\beta$ species and quantifying a $pT217/T217$ value and $A\beta42/A\beta40$ 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 $A\beta$ species as in step (a) and quantifying a $pT217/T217$ value and $A\beta42/A\beta40$ value of the second processed sample; and
 - (c) calculating the difference between the quantified $pT217/T217$ value and $A\beta42/A\beta40$ value of the second processed sample and the first processed sample, wherein a statistically significant difference in the quantified $pT217/T217$ value and $A\beta42/40$ 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 *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 $A\beta$ species and quantifying a composite $pT217/T217 \times A\beta42/A\beta40$ 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.
16. The method of claim 1, wherein the processed biological sample is prepared by:
- (a) immunoprecipitating amyloid beta species using an epitope-binding agent that binds an epitope within the mid-domain of amyloid beta; and
 - (b) sequentially immunoprecipitating tau species using:
 - (i) a first epitope-binding agent that binds an epitope within the mid-domain of tau; and
 - (ii) a second epitope-binding agent that binds an epitope within the N-terminus of tau.
17. The method of claim 16, wherein:
- (a) the amyloid beta species are immunoprecipitated using an HJ5.1 antibody;
 - (b) the first epitope-binding agent comprises a Tau1 antibody; and/or
 - (c) the second epitope-binding agent comprises an HJ8.5 antibody.
18. The method of claim 1, wherein:
- (a) the A β 42/A β 40 value is less than or equal to 0.086; or
 - (b) the pT217/T217 value is greater than or equal to 4.76.
19. The method of claim 1, wherein:
- (a) the A β 42/A β 40 value is less than or equal to 0.086; and
 - (b) the pT217/T217 value is greater than or equal to 4.76.
20. A kit for detecting Frontotemporal Dementia (FTD), discriminating a MAPT R406W tauopathy, or measuring progression of a tauopathy in a subject, the kit comprising:

- (a) one or more epitope-binding agents configured to immunoprecipitate tau species from a biological sample;
 - (b) one or more reagents configured to detect phosphorylation at residue T217 of tau and total T217; and/or
 - (c) one or more reagents configured to detect A β 42 and A β 40; and
- instructions for use that instruct a user to:
- (i) quantify a pT217/T217 value and an A β 42/A β 40 value from the biological sample; and
 - (ii) detect FTD, discriminate a MAPT R406W tauopathy, or determine disease progression according to the method of any one of claims 1–19.