Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAI2809(M00Y10)	**Protocol Status:**	Approved
		Expiration Date:	07/22/2021
Originating Department Code:		TBI Taub Institute (758100X)	
Principal Investigator:		Huey, Edward (edh2126)	
From what Columbia campus does this research originate:		Medical Center	
Title:	Examination of the earliest symptoms and biomarkers of FTLD MAPT carriers		
Protocol Version #:		**Abbreviated Title:**	Early symptoms of FTLD
Was this protocol previously assigned a number by an IRB:		Yes	
Previous Columbia IRB#:		**Previous External IRB#:**	NYSPI5550

Attributes

Special review type: Check all that apply or check "None of the Above" box.

[ ]Review for 45 CFR 46.118 Determination (involvement of human subjects is anticipated but is not yet defined)

[ ]Funding review for Administrative IRB approval (such as for Center or Training Grants)

[x]None of the above

IRB of record information: Will a Columbia IRB be the IRB that is responsible for providing review, approval, and oversight for this study?

Yes

Select the most appropriate response:

Columbia will be the IRB of record for the study procedures conducted by Columbia researchers (Note: this response will apply to most submissions).

Is this research part of a multicenter study?

Yes

Indicate Columbia's involvement by checking all applicable roles below

[x] Columbia is a study site

Does this submission describe and seek approval for the study procedures at Columbia?

Yes

[x] Columbia is the Lead Institution

Is the purpose of this submission to obtain approval for the Lead Institution responsibilities?

Yes

[x] Columbia is serving as the Clinical Coordinating Center

Is the purpose of this submission to obtain approval for Clinical Coordinating Center responsibilities?

Yes

[x] Columbia is serving as the Data Coordinating Center

Is the purpose of this submission to obtain approval for Data Coordinating Center responsibilities?

Yes

[x] Columbia is serving as the site for a repository of biological specimens related to this study

Make sure that "Future use of data and/or specimens" is marked "Yes" on the Procedures page and that the corresponding "Future use of data and/or specimens" page is completed.

Please indicate if any of the following University resources are utilized:

[ ] Cancer Center Clinical Protocol Data Management Compliance Core (CPDM)

[x] CTSA-Irving Institute Clinical Research Resource (CRR)

[ ] CTSA- Irving Institute Columbia Community Partnership for Health (CCPH)

[ ] None of the above

Lead Institution/Coordinating Center

It was indicated on the Attributes Page that this submission includes details related to Columbia serving as a Coordinating Center or Lead Institution. If this is incorrect, please make the necessary revisions on the Attributes Page. Otherwise, provide the following information or indicate that it is included in an attached stand-alone protocol. If a particular section does not apply to your protocol, it is appropriate to enter 'N/A' in the text field.

Provide an outline of the organizational structure of the multicenter protocol, including all sites where enrollment is expected and any committees responsible for administrative duties, subject/data/site monitoring, facilitation of communications, data analysis, etc.:

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Explanation of funding and organizational relationship: Our NINDS grant includes funds awarded for consortium activity with the Dublin Neurological Institute at the Mater Misericordiae University Hospital. Under consortium agreements, the PIs at each site are accountable for the performance of the project at that site and the appropriate expenditure of grant funds at the site. For the Irish consortium site, Dr. Lynch, M.B., MRCP is the designated lead investigator responsible for ensuring proper conduct of the project. Dr. Lynch is an expert on the genetics of FLTD, has worked with the family we propose to study for over 15 years, and is the first author of the original 1994 study on this family.

The University of Michigan in Ann Arbor is being added as an additional site to our study, which was not originally included in the grant. The NIH has approved the reallocation of the budget to include this site. Dr. Judith Heidebrink, M.D. will be the Principal Investigator at this site. This site was added to accommodate evaluation of multiple family members who were unwilling to travel to NY for participation in the study. The University of Michigan has a dementia research program for similar disorders and Dr. Heidebrink is familiar with this particular disease.

Description of procedures: Investigators at the Dublin Neurological Institute are in communication with members of the family living in Ireland. They will contact them to detail the study and offer them the opportunity to participate in the proposed research. A full history and physical and neurological examination will be conducted by a nurse and/or physician on the research team at the Dublin Neurological Institute. Dr. Lynch will be available to provide genetic counseling to participants.

For members of the family seen in Michigan, investigators at CUMC will be the primary liaison. CUMC personnel will assist in establishing a connection between the family and the Michigan personnel. Genetic counseling will be provided by a trained genetic counselor in Michigan or our site's genetic counselor, Jill Goldman.

Procedures at the Ireland site will be identical to those at CUMC. De-identified biological samples will be sent to CUMC every three months. De-identified clinical data will be sent to CUMC following the research visit. Samples collected from the Irish site will be processed at Columbia and samples collected from the University of Michigan site will be processed at their site. Whole blood, and CSF samples from both sites will be sent to the NINDS repository as outlined in Section 2 above.

Provide a description of the responsibilities of the coordinating center / lead institution with regard to communication and training of research personnel across sites:

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Plans for data and safety monitoring: Several steps will be taken to ensure standardization of data collection methods across sites. First, a five-day training meeting will be held at the start of the study by Drs. Cosentino, Huey, and Asllani to train and certify all research staff in the collection and coding of all genetic, imaging, clinical, and lifestyle data. Staff certification in the administration of all instruments will be required prior to data collection, and will be achieved through in-person observation by Drs. Huey, Cosentino, and Asllani. Certification procedures will consist of the PIs observing staff members administer full research batteries to one another. Following this initial meeting, investigators at CUMC and Ireland will have monthly conference calls to review data collection procedures and ensure that consent procedures at the Dublin site are conducted in accord with the approved IRB, and that informed consent is being documented properly. Formal quality control checks will be conducted at both sites, three times a year in each data collection year (1, 3, and 5) to evaluate the integrity of the data collected and any systematic differences across sites. A second in-person meeting will be conducted in Year 3 to identify and correct any drift in methods between sites over time and to re-certify all staff in data collection procedures. A final in-person meeting will be conducted in Year 5 to identify and correct any drift in methods between sites over time and to re-certify all staff in data collection procedures. Standardization of imaging procedures across NY, Ireland, and Michigan is a critical component of this study and will be conducted in person by Dr. Asllani. Dr. Asllani has demonstrated the capability to standardize scanning procedures across multiple centers, and will assess and reconcile differences between the 2 scanners using methods previously used in an ASL reproducibility study that examined the SNR properties of the ASL signal across 28 laboratories located in Asia, Europe and North America.

Provide a plan to ensure that collaborating sites do not begin any research-related activity until IRB approval has been granted for the conduct of research at that site:

(If Columbia is not the lead institution, enter "N/A" in the text box)

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Plans for authorization and/or IRB approval at each site: The Mater Misericordiae University Hospital Research Ethics Committee will review and approve the study protocol and consent form. The University of Michigan Institutional Review Board will review and approve the study protocol and consent form. Sites will not begin research related activity until they have received the applicable approvals from their respective institutions.

Provide a description of the transmission of data to the data coordinating center:
(If there is not a designated data coordinating center, enter "N/A" in the text box)

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

De-identified biological samples will be sent to CUMC every three months. De-identified clinical data will be sent to CUMC following the research visit. Samples collected from the Irish site will be processed at Columbia and samples collected from the University of Michigan site will be processed at their site. Whole blood, and CSF samples from both sites will be sent to the NINDS repository as outlined in Section 2 above.

Each participant's identity and participation in this study will be kept confidential in our database, including data collected from participants in Ireland. All records will be stored in a computer file and access will be restricted to research staff. All questionnaires and other forms generated from the data collection will be kept in locked file cabinets, and only the investigators will have access to this information. Participant names will not be used. Rather, we will assign a code number that will be associated with all information collected. Data that has been stripped of all identifying information from genetic analysis will be kept separate from the clinical and demographic data stored at the Taub Institute Human Genetics Resources Core and can only be accessed by authorized individuals. The Irish site will be responsible for ensuring subject and data confidentiality and protection and subject safety as reviewed by the Mater Misericordiae University Hospital Research Ethics Committee. The Michigan site will be responsible for ensuring subject and data confidentiality and protection and subject safety as reviewed by the Institutional Review Board at the University of Michigan. Data transmitted electronically between these sites will be limited to contain the minimum necessary subject identifying information, and will be conducted by research study personnel using encrypted and protected information-storage devices and endpoint devices. Clinical data, neuroimaging data, and biological samples from all sites will be sent to and stored at CUMC, the designated coordinating center and data coordinating center for this multi-site study. However, a subset of the clinical data will also be entered into Redcap, an electronic data capture managed and hosted by the Michigan site.

Specify how and where the data will be analyzed and who is responsible for the analysis(es):

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Data collected from all sites will be analyzed by personnel at Columbia.

Background

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH

cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives.
If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Study Purpose and Rationale:
Provide pertinent background description with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

FTD is a debilitating neurodegenerative disease. The proposed study seeks to identify its earliest clinical features, in an effort to improve early detection of the disease and ultimately facilitate timely intervention and treatment. Mutations in the microtubule-associated protein tau (MAPT) and progranulin (PGRN) genes are two of the most common established genetic causes of frontotemporal lobar degeneration (FTLD). MAPT mutations on chromosome 17 account for 10-20% of familial cases, and are associated with disruption of the normal function of the tau protein. Abnormal deposits of tau are associated with approximately 40% of FTLD cases, familial or sporadic. This study seeks to identify the earliest indicators of disease in MAPT mutation carriers and to characterize lifestyle factors and their potential effects on symptom onset and course. At the Taub Institute, we have unique access to the offspring generation of a large family with an exon 10 +14 C>T MAPT mutation in whom the FTLD syndrome was first linked to chromosome 17. This project provides us with the unique opportunity to recruit all branches of the offspring cohort (n =75). Additional families with similar genetic mutations will be recruited to achieve the desired sample size if necessary. In this project, we will determine carrier status, and conduct longitudinal assessments including neuroimaging, cognitive testing, behavioral characterization, plasma and cerebrospinal fluid collection, and psychiatric evaluation to examine the earliest features of FTLD. Moreover, examination of early and current lifestyle features will inform the extent to which specific behaviors may modify symptom onset and course. The specific aims of the grant are as follows:

Specific Aim #1: Characterize the earliest effects of the exon 10 +14 C>T MAPT mutation on clinical presentation and
rate of decline.

Our hypotheses are that:

A. Mutation carriers will evidence lower cognitive scores (primarily in social cognition and executive function), and more behavioral features, psychiatric symptoms, dietary abnormalities, and addictive behaviors as compared to noncarriers at baseline.
B. Mutation carriers will show more rapid changes in cognition, behavior, and diet over the 5-year course of the study as compared with non-carriers.

Specific Aim #2: Evaluate the utility of structural and functional neuroimaging measures as

biomarkers of the exon 10 +14 C>T MAPT mutation.

Our hypotheses are that:
A. Univariate analyses will reveal structural and functional regional abnormalities (in the cingulate gyrus, frontal insular, ventromedial prefrontal and polar cortices, and anterior temporal lobes) and the associated white matter tracts in mutation carriers as compared to non-carriers.
B. Mutation carriers will demonstrate more rapid brain changes than non-carriers over 5 years of follow-up.
C. Multivariate analyses of structural and functional data, examining covariance patterns across distributed regions, will distinguish mutation carriers and non-carriers with greater sensitivity and specificity than univariate analyses.

Specific Aim #3: Characterize lifestyle variables in carriers and non-carriers of the exon 10 +14 C>T MAPT mutation, and examine such variables as potential symptoms or modifiers of disease.

Our hypotheses are that:
A. There will be a higher frequency of substance use in carriers than in non-carriers.
B. Higher levels of life-long physical activity will delay symptom onset in mutation carriers.

Study Design:

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Eligible participants live throughout the USA, primarily in NY and Michigan, as well as in Ireland. Subjects from New York and Michigan will be seen at Columbia University Medical Center in New York City or the University of Michigan in Ann Arbor. Approval for the study will be obtained by the University of Michigan Institutional Review Board. The Irish branch of the family will be studied in Dublin, Ireland under the supervision of Dr. Lynch. Approval for the study has been obtained by the Mater Misericordiae University Hospital Research Ethics Committee in Dublin, Ireland. All procedures will be consistent across the U.S. and Ireland sites.

Participants who are able to come to the medical center will arrive for a one to three day visit. During that time, they will receive a battery of cognitive tests designed to measure memory, visuospatial, attentional, language, executive, and social cognitive abilities. They will also complete questionnaires that ask about mood, behavior, diet, exercise and substance use. In addition, they will undergo a full neurological examination, psychiatric evaluation, and will undergo structural and functional neuroimaging. Participants will also undergo a blood draw to assess carrier status and to collect plasma. This will be performed by a certified phlebotomist, and sterile techniques will be used. Subjects who agree will undergo a lumbar puncture for the collection of cerebrospinal fluid (CSF). Subjects who agree will also undergo a skin biopsy for the collection of skin and underlying tissue. With the participants' permission, study informants will complete a set of questionnaires

pertaining to the participant. Participants can choose not to participate in any of these procedures and still participate in the other procedures of the study.

Participants who are unable to come to the medical center may be seen in their home for clinical assessments. In the event that we cannot make direct person-to-person contact with an individual, we will mail the participant a blood kit to be used by a certified phlebotomist and returned to CUMC. Finally, in the event that we are unable to obtain a blood sample to ascertain DNA on any participant, we will mail a saliva kit to be returned by mail. Participants will be asked to participate in the cognitive and behavioral components of the study approximately once every two years, such that they will be seen approximately three times over the course of a five year study (year 1, year 3 and year 5). They will also be asked to provide blood at each visit. The lumbar puncture and neuroimaging will occur at the baseline visit and year 5 of the study. The skin biopsy will only occur once, preferably at the baseline visit, unless another biopsy is required because of any problems with the initial biopsy (e.g., unable to derive pluripotent cells). If after the initial visit, participants later reconsider and elect to undergo any procedures not completed during the baseline visit (e.g. lumbar puncture or neuroimaging procedures), they will be accommodated.

Cognitive data collected as part of the study will be shared with the NIH. A portion of the biological samples collected from participants enrolled in this study at US sites will be submitted to the NINDS Repository, a research resource supported by the NIH/NINDS. Volumes submitted to the NINDS repository for each biospecimen collected will include the following: up to 30 ml of CSF, up to 12 tablespoons of whole blood and a skin and underlying tissue sample obtained from a punch biopsy. A limited de-identified data set will be sent to the NINDS repository for cataloging with the biospecimen samples. Biospecimens collected by the clinical site in Ireland and the University of Michigan will submit samples to CUMC every 3 months. The samples will be submitted under standard collection operating procedures developed with the Principal Investigators of this study and the NINDS repository. The samples will be stored indefinitely. No personal identifiers will be sent to the Repository as the sample will be identified by a number assigned by the Principal Investigators or study coordinator. The specimens will be used for preparation of DNA and may be used for cell culture from which DNA will be prepared. The DNA and cell culture will be distributed to scientists for use for cell culture from which DNA will be prepared. The DNA and cell culture will be distributed to scientists for use in research and teaching only, and as such the Repository does not return results to donors. The sample could be used for research in any type of disease and other genetic factors, not just FTD. The skin biopsy sample may also be used to create a cell line. The cells from the samples may be isolated and modified so that they divide forever. These modified cells may be maintained in culture indefinitely. In addition, various techniques may be used to return the cells to a stem cell-like state, from which they can be turned into other cell types. These cells would also be maintained indefinitely for use in experiments researching the development of FTD. These cell lines will be deidentified from the subjects from whom the biopsies were taken. The sample and unidentified data will be available to researchers at hospitals, universities, and commercial organizations.

Biospecimens collected in the study may also be directly shared with collaborators/researchers (within and outside of Columbia), as evaluated on a case-by-case basis by the principal

investigator. As with biospecimens available to researchers through the NINDS Repository, biospecimens shared directly by the research team will be identified only by a study ID number and a limited de-identified data set.

Statistical Procedures:

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations to justify the number of participants to be enrolled into the study. Definitions of subject terms such as enrolled and accrued as used for Rascal submissions can be found in the Subjects section.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

All analyses will be adjusted for age, sex, and education.

Specific Aim 1: Adjusted Generalized Estimating Equations (GEEs) will be used to determine if carrier status: A) is associated with baseline clinical features; and B) predicts rate of change in clinical features over the 5 year follow up period. A single GEE model compares baseline values and change over time by carrier status, taking into account the fact that characteristics of an individual over time are likely correlated, as are characteristics of sibship members. Specifically, GEE treats repeated measures and sibship for each subject as clusters. Individual GEEs will be applied to individual outcomes.

Specific Aim 2: Adjusted GEEs will be used to determine if carrier status: A) is associated with regional differences in brain integrity at baseline, and B) predicts rate of change in regional brain variables over the 5-year follow-up period. Spatial covariance analyses will then be used to determine whether quantitative and qualitative differences exist between carriers and non-carriers across a network of distributed brain regions, and C) whether such networks have greater sensitivity and specificity than regional variables. Dr. Christian Habeck, an expert in covariance analysis, will serve as a co-investigator on this grant and conduct these analyses. The following steps will be completed separately for volumetric, ASL, and DTI data. In a first step, we will perform a Principal Components (PC) analysis on all regions of interest (or voxels) and use the subject score of the first PC as the dependent variable in a GEE model as described in Aim 1 to determine if network scores differ by carrier status at baseline or over time. This approach has the potential advantage of avoiding type-I error inflation by multiple tests of the same null-hypothesis, instead ascertaining the relationship between carrier status and brain integrity in a single spatial pattern. Specifically, the Subscale Profile Model will be used to derive a spatial covariance pattern that distinguishes between carriers and non-carriers. The key outcomes of this kind of analysis are: (1) a spatial covariance pattern that assigns different loadings to all regions included in the analysis and can be visualized as a brain image, (2) an overall network score that is a scalar number quantifying the extent to which a study participant expresses the particular covariance pattern. In a second step, using a permutation test and the area under the ROC-curve (AUC) as a test statistic, we can directly compare univariate brain markers (e.g., regional volume) with multivariate brain markers (e.g., overall volumetric network score) by computing an ROC-curve for each marker with area statistics AUC1 and AUC2, and forming the difference (AUC = AUC1-AUC2). For the permutation tests, we then break the subject group assignment and randomly swap participants between the carrier and non-carrier group, each time re-computing our markers, recording the area statistic and computing the AUC (10,000 iterations). This will generate a null-

histogram for AUC, and we can perform a twotailed test to see whether AUC in the unperturbed sample lies in the tail of this null-distribution. The fraction of iterations with a AUC value more extreme than our point estimate can be taken as the p-level that one marker has a statistically significant advantage over the other marker, with the sign of the difference determining the marker preference.

Specific Aim 3: This aim will characterize lifestyle features (LFs) including substance use and physical activity, and preliminarily examine whether they may modify symptom onset or course. We are aware that these analyses are complicated by temporal sequence, and will attempt to deal with this issue by evaluating early versus current lifestyle features across carriers and non-carriers. We anticipate two general data scenarios that will determine the manner in which we treat the data. If it is determined that lifestyle features differ by carrier status either in early adulthood or at the current time, such features will be treated as potential symptoms of disease and analyzed in Specific Aim 1. However, if both early adulthood and current LFs are comparable across carriers and non-carriers over time, overall lifetime levels of physical activity and substance use will be examined as potential modifiers of symptom onset in mutation carriers. Specifically, LFs will be entered as covariates (along with sex, education, and sibship) in a linear regression model to determine if they modify the association between baseline age and various clinical and imaging variables. Second, to examine the effect of LFs on symptom course in carriers over the five year follow up period, lifetime values of physical activity and substance use will be entered as predictors in GEE models with age, education, and sex as covariates, and rate of symptom change as the outcome. Based on the expected number of carriers, we do not anticipate having sufficient power to detect statistically significant effects on symptom onset or course. However, this initial work is important to determine basic trends and to generate hypotheses for future work.

With regard to power for Specific Aim 1 (Characterize the earliest effects of the exon 10 +14 C>T MAPT mutation on clinical presentation and rate of decline), preliminary data collected in our center in 2009 examining non-demented children of an affected versus unaffected parent demonstrated a large effect size of d = 1.8 on executive function tasks. Based on this anticipated effect size, we estimated power for the current proposal based on a 4-year follow up period (three visits including baseline) and 10% loss to follow-up. For comparing the rate of decline using GEE, we calculated the minimal detectable difference levels for power for a total sample size of 75 (25 families, average 3 per family) and 25% carrier rate (about 19 carriers), determining that we will have 80% power to detect an effect size of 0.17 sd per year. This is likely an underestimate of the rate of change that can be expected based on a previous study examining rate of change in FTD that documented a 1.13 sd per year change on a measure of global cognition. With regard to power for Specific Aim 2 (Evaluate the utility of structural and functional neuroimaging measures as biomarkers of the exon 10 +14 C>T MAPT mutation), a previous study examining change in frontal cortical thickness in presymptomatic carriers versus non-carriers demonstrated a large effect size of d = 1.44. Specifically, mutation carriers demonstrated a 4.18% (+ 3.73) decline of baseline thickness in the left frontal lobe as opposed to a mean change of 0.50% (+ 3.51) in non-carriers over an average of 1.3 years. For comparing the rate of decline in this same brain region (for example) using GEE, we calculated the minimal detectable difference levels for power for a total sample size of 75 (25 families, average 3 per family) and 25% carrier rate (about 19 carriers),

determining that we will have 80% power to detect 1.58% change in baseline frontal cortical thickness per year.

Exempt and Expedited

Is the purpose of this submission to obtain an exemption determination, in accordance with 45CFR46.101(b):
No

Is the purpose of this submission to seek expedited review , as per the federal categories referenced in 45CFR46.110?
No

Funding

Is there any external funding or support that is applied for or awarded, or are you the recipient of a gift, for this project?
Yes

Award Type	Funding Source Name	Name of awarding agency	Status	Award # or Application Date	Federal/State/Local Government Direct or Subcontract	What is the award covering?	Rascal PT Number
Federal/State/Local Government	NIH NINDS	National Institute of Neurological Disorders and Stroke/NIH/DHHS	Awarded/Received	R01 NS076837	Direct Recipient: With Subcontract Sites	Entire Protocol	
	Subcontract site(s), procedures taking place at each site and FWA# for federally funded studies: 1. Site at Michigan(procedures identical to Columbia procedures) 2. Site at Ireland (procedures identical to Columbia procedures) Please see documents for an attachment listing Federal-wide Assurance Number.						

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Offsite	Participant's home (for those who request home visit as an alternative to on-site participation)	Domestic	Varies by participant	Yes	Yes
Offsite	Dublin Neurological Institute at Mater Misericordiae University Hospital	International	Dublin, Ireland	Yes	Yes

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Offsite	Michigan Alzheimer's Disease Center	Domestic	Ann Arbor, Michigan	Yes	Yes
NewYork-Presbyterian Hospital @ Columbia	Irving Institute at Presbyterian Hospital Floor 10				
Columbia/CUMC	Neurologic Institute				

Personnel

UNI/Phone	Name	Role	Department	Edit/View	Obtaining Informed Consent
edh2126 212-305-1134	Huey, Edward	Principal Investigator	TBI Research (758130X)	Edit	Y
amb2139	Brickman, Adam	Other Engaged Personnel	TBI Research (758130X)	View	N
	Roles and Experience: Neuroimaging Analysis				
ch629	Habeck, Christian	Other Engaged Personnel	TBI Research (758130X)	View	N
	Roles and Experience: Neuroimaging Analysis				
fap2005	Provenzano, Frank	Other Engaged Personnel	TBI Research (758130X)	View	N
	Roles and Experience: Neuroimaging Analysis				
gc2646	Cheran, Gayathri	Other Engaged Personnel	TBI Research (758130X)	Edit	Y
	Roles and Experience: Ms. Cheran will assist with data analysis and reconsent procedures.				
hs2971	Silverman, Hannah	Other Engaged Personnel	TBI Research (758130X)	View	N
	Roles and Experience: Hannah will assist with procedures such as accompanying subjects to the MRI and phlebotomist, and assisting with data analysis.				
jg2673 212-305-7382	Goldman, Jill	Investigator	PRV Provost Office (200210X)	Edit	Y
kc2963	Chan, Kathleen	Other Engaged Personnel	TBI Taub Institute (758100X)	View	Y
	Roles and Experience: Research Assistant				
ked2115	Duff, Karen	Investigator	GEU FBE Retirement Plan (2554302)	View	N
lh456	Honig, Lawrence	Other Engaged Personnel	TBI Research (758130X)	View	N
	Roles and Experience: Study Physician (Lumbar puncture procedure)				
mm2626	Manoochehri, Masood	Coordinator	TBI Research (758130X)	Edit	Y
msb2228	Barker, Megan	Investigator	TBI Research (758130X)	Edit	Y
	Roles and Experience: Dr. Barker is a post-doctoral fellow who will be involved in data analyses and preparation of manuscripts.				
rap2204	Patel, Ruhee	Other Engaged Personnel	TBI Taub Institute (758100X)	View	Y

UNI/Phone	Name	Role	Department	Edit/View	Obtaining Informed Consent
	Roles and Experience: Research Assistant				
rea2154	Abraham, Rebecca	Other Engaged Personnel	TBI Research (758130X)	View	Y
	Roles and Experience: Research Assistant				
rpm2	Mayeux, Richard Paul	Non-Engaged Personnel	NEU Neurology (752400X)	View	N
	Roles and Experience: Consultant				
sc2460 212-342-0289	Cosentino, Stephanie	Investigator	SGV Research (758230X)	Edit	Y
wwp2105	Post, William	Other Engaged Personnel	TBI Research (758130X)	View	Y
	Roles and Experience: Research Assistant				
zz2509	Zheng, Zhiwei	Other Engaged Personnel	TBI Taub Institute (758100X)	View	Y
	Roles and Experience: Research Assistant				

Training and COI

The PI must ensure that each individual that is added as personnel has met the training requirements for this study (http://www.cumc.columbia.edu/dept/irb/education/index.html). For help identifying which research compliance trainings you may be required to take, visit the Research Compliance Training Finder.

UNI	Name	COI	HIPAA	HSP (CITI)	Research with Minors (CITI)	FDA-Regulated Research (CITI)	S-I	CRC	Good Clinical Practice (GCP)	GCP - Third-party tracking	GCP Refresher	Genetic Research Consent
edh2126	Huey, Edward	09/03/2019	10/25/2010	09/11/2018	10/09/2015	10/09/2015	10/07/2014		03/17/2020			09/11/2017
amb2139	Brickman, Adam	08/31/2019	12/02/2004	12/28/2019	12/28/2019	12/21/2012	12/21/2012		12/28/2019			
ch629	Habeck, Christian	04/22/2020	05/19/2004	08/21/2019		10/18/2016					01/03/2020	
fap2005	Provenzano, Frank	01/14/2020	10/19/2006	02/13/2018	02/13/2018	02/13/2018			02/13/2018			
gc2646	Cheran, Gayathri	07/21/2020	03/30/2015	09/14/2017	12/02/2014	12/02/2014		12/31/2014				10/10/2017
hs2971	Silverman, Hannah	07/02/2020	09/26/2016	10/23/2019		09/26/2016		09/27/2016	03/06/2020			10/10/2017
jg2673	Goldman, Jill	03/02/2020	07/18/2006	06/04/2019	03/29/2011	01/09/2017		06/08/2011	12/04/2019			
kc2963	Chan, Kathleen	07/13/2020	08/27/2019	08/28/2019		02/22/2015						
ked2115	Duff, Karen	03/16/2020	05/03/2019	05/03/2019								
lh456	Honig, Lawrence	09/30/2019	09/30/2017	11/17/2019	12/17/2016	12/17/2016	05/23/2010	12/19/2015	11/17/2019			10/26/2019
mm2626	Manoochehri, Masood	07/10/2020	12/16/2010	02/20/2020	02/01/2017	11/04/2019		12/30/2010	02/21/2020			11/17/2019
msb2228	Barker, Megan	01/02/2020	12/28/2018	12/28/2018					12/28/2018			

rap2204	Patel, Ruhee	08/21/2019	08/23/2019	08/23/2019		08/21/2019			08/23/2019			
rea2154	Abraham, Rebecca	07/24/2019	07/30/2019	07/30/2019					07/30/2019			
rpm2	Mayeux, Richard Paul	03/01/2020	01/02/2017	12/27/2019	12/27/2019	09/27/2013			01/03/2018			
sc2460	Cosentino, Stephanie	08/08/2019	05/11/2005	10/03/2018		07/23/2015			03/16/2020			
wwp2105	Post, William	07/24/2019	07/30/2019	08/01/2019		07/30/2019			07/30/2019			
zz2509	Zheng, Zhiwei	12/30/2019	01/23/2019	01/23/2019					01/23/2019			

Privacy & Data Security

Indicate the methods by which data/research records will be maintained or stored (select all that apply):

[x]Hardcopy (i.e., paper)

Describe where and how the data will be stored:

Research data and clinical documents will be stored in a locked file cabinet in the Principal Investigator's office. Only staff directly involved with the study subjects will have access to these clinical documents. Research data and clinical documents that are being examined by the study staff may temporarily be stored in locked file cabinets in the study coordinator's office, and will be returned afterward to the locked file cabinet of the Principal Investigator's office.

[x]Electronic

Where will the data be stored?

Y

[x]On a System

[x]On an Endpoint

Identify what type of endpoint will be used (select all that apply):

[x]Desktop Computer

[ ]Laptop Computer

[ ]Mobile Device

[ ]Other

Does this study involve the receipt or collection of Sensitive Data?

Yes

If any Sensitive Data is lost or stolen as part of your research protocol, you must inform both the IRB and the appropriate IT Security Office (CUMC IT Security if at CUMC; CUIT if at any other University campus).

What type of Sensitive Data will be obtained or collected? Select all that apply:

[x]Personally Identifiable Information (PII), including Social Security Numbers (SSN)

Will Social Security Numbers (SSNs) be collected for any purpose?

No

[x]Protected Health Information (PHI), including a Limited Data Set (LDS)

If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

Indicate plans for secure storage of electronic sensitive data: check all that apply

[ ]Sensitive data will not be stored in electronic format

[x]Sensitive data will be stored on a multi-user system

Provide the System ID numbers for the certified environment in which the Sensitive Data will be stored

3879

[x]Sensitive data will be stored on an encrypted endpoint

By Selecting an Endpoint Device and approving this protocol for submission to the IRB, the PI is attesting that the device and any removable media that may be used have been or will be registered and/or will be maintained in compliance with the University's Information Security Charter and all related policies. It is important that this information is updated, during the course of the study, as new devices are added.

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):

Each subject will be assigned a research number for research purposes. The subject names will be revealed to personnel who need to know the subjects' names to perform their duties. This includes clinical and research staff that interacts directly with the patients (for example, nursing and physician staff, testers, research coordinators, and imaging technicians). Subject names and limited demographic information will also be included in the Columbia University Alzheimer's Disease Research Center (ADRC) database (stored on the Department of Neurology Babylon server, a CUMC IT certified environment, System ID 3879), to prevent duplicate enrollment of subjects in Taub Institute studies submitting data to NACC. Other staff involved in data management / analysis who do not interact with the patients will be given coded lists of research numbers without names.

Research data will be maintained in a database on a password and firewall-protected server. The PI will maintain the lists and know the subjects' research numbers and names. The data will also be entered into Redcap, an electronic data capture (EDC) managed by our study team at the University of Michigan.

Only members of the study team will have access to these data. The research and clinical staff will take all necessary steps to ensure subject confidentiality. These measures will include: (1) all subjects will be assigned an identification number at study entry; (2) all data will be coded using this subject identification number rather than subject names; (3) only members of the research team will have access to the coded data; (4) only staff directly involved with the study subjects will have access to clinical documents or identifying information; and (5) all information-storage devices in use by the research team (i.e., servers) will be protected by passwords and firewalls. In addition to their study identification number, subjects will also be assigned a Global Unique Identifier (GUID) which will be used to identify their biological

samples.

Electronic transmittal of data containing subject identifying information will be minimized wherever possible, except in cases of unavoidable necessity wherein the data transmitted electronically will be limited to the minimum amount necessary and conducted using encrypted and protected information-storage devices and/or endpoint devices.

With the subject's consent, clinical data will be shared with the National Alzheimer's Coordinating Center (NACC) for inclusion in the NACC Database, a comprehensive database consisting of standardized data collected across Alzheimer's Disease Centers nationwide. This data will be transmitted electronically with a subject ID code through encrypted and password-protected endpoint devices.

Biological samples without subject identifying information, as well as clinical research data, will be submitted to the NINDS Repository, with the subject's consent. The NINDS Repository will be responsible for ensuring data confidentiality and protection through external auditing and strict standards for safety measures and confidentiality. The NINDS Repository will also be sent the Global Unique Identifier (GUID) assigned to each subject.

Research data, including audio files compiled during cognitive testing, will be shared with outside academic collaborators, including at the University of Pennsylvania. All data will be transmitted electronically through encrypted files, labeled with a subject ID code and no personal identifiers.

If your project is not NIH funded, has a Certificate of Confidentiality (CoC) been requested for this research?
No

Provide a description of the protections in place to safeguard participants' privacy while information is being collected:
Medical records: The information gathered in the protocol will be kept in a separate, research record, unless the patient requests information from the research record to be placed in their clinical chart.

Research data: All information collected from study participants for research purposes will be kept in the Taub Institute. Strict standards of confidentiality will be upheld at all times.

Procedures

Is this project a clinical trial?
No
Is this project associated with, or an extension of, an existing Rascal protocol?
No
Do study procedures involve any of the following?
Analysis of existing data and/or prospective record review
No
Audio and/or video recording of research subjects
Yes
Behavioral Intervention?
No
Biological specimens (collection or use of)
Yes

Cancer-related research

No

Drugs or Biologics

No

Future use of data and/or specimens

Yes

Genetic research

Yes

Indicate which, if any, of the following apply:

Genetic Testing as defined by NYS 79-l

No

Gene Transfer

No

Generation of large scale genomic data (e.g. GWAS studies)

No

Human embryos or human embryonic stem cells

No

Imaging procedures or radiation

Yes

Medical Devices

No

Surgical procedures that would not otherwise be conducted or are beyond standard of care

No

Will any of the following qualitative research methods be used?

Survey/interview/questionnaire

Yes

NOTE: You must attach a PDF version of the survey(s)/interview(s)/questionnaire(s) to this protocol prior to submission.

Systematic observation of public or group behavior

No

Program evaluation

No

Will any of the following tests or evaluations be used?

Cognitive testing

Yes

Educational testing

No

Non-invasive physical measurements

Yes

Taste testing

No

Is there an external protocol that describes ALL procedures in this study?

No

Please describe ALL study procedures in detail.

NOTE: Be sure to detail all of the procedures above to which a "yes" response was selected. Also detail any additional procedures that may or may not fall into the categories listed above.

Procedure summary: Individuals who consent to participate in the proposed study will be seen for clinical assessment,

and neuroimaging will be completed. Carrier status will be determined using DNA obtained from blood draws. A blood draw will also be performed at each visit to collect plasma. CSF will be obtained via a lumbar puncture. A small piece of skin and underlying tissue will be obtained via a skin biopsy.

Blood draw: Plasma will be collected and stored at each visit. Consenting individuals will undergo blood draw by a certified phlebotomist, and sterile techniques will be used. During the first year, blood will also be collected for DNA to determine MAPT carrier status. DNA is already available for individuals who participated in the pilot phase of this study. A study nurse or physician trained in phlebotomy will perform standard phlebotomy procedures. Up to 12 tablespoons of blood will be collected including citrate tubes for DNA isolation (Year 1), and heparin tubes for plasma isolation (year 1, year 3 and year 5). DNA and plasma will be prepared by the Columbia Human Genome Center by standard protocols. Blood samples will be submitted to the NINDS Repository at Indiana University. Plasma samples will be stored frozen at -80C in 0.5 ml aliquots.

Genotyping: Polymerase chain reaction (PCR) and amplification of ~300bp that contain the intron 10 mutation, IVS10 +14C>T, will be performed. The PCR and sequencing primers used for amplification and sequencing will be designed using Primer 3 (http://frodo.wi.mit.edu/primer3/). Cycle sequencing in forward and reverse directions will be performed on purified PCR products and run on an ABI 3730 genetic analyzer (Applied Biosystems, Foster City, CA). Sequence chromatograms will be viewed and genotypes determined using Sequencher (Genecodes).

Genetic Testing: Subjects will not receive DNA results as part of the current study. However, all subjects who wish to pursue commercial genetic testing are required to receive genetic counseling from our genetic counselor, Jill Goldman, MS, MPhil. After counseling, the subjects can decide if they would like to pursue commercial genetic testing. All subjects are offered genetic counseling. This expense will be covered by the study. If a subject pursues commercial genetic testing, he or she will submit samples to a CLIA-certified laboratory and receive follow-up counseling.

History and Physical (Neurological) exam: A physician on the protocol will examine subjects to obtain their medical history and administer the standardized neurological exam and psychiatric evaluation. As part of this procedure, we will administer the Clinical Dementia Rating Scale.

Clinical characterization: We will assess behavior, cognition, mood, diet, exercise, and substance use in this study. Cognitive testing will estimate intellectual, memory, visuospatial, attentional, language, executive, and motor abilities. All tests will be administered by trained research staff. Test instructions are given to subjects prior to each task. Adequate comprehension of the instructions for each test is insured by the test examiner before a test is formally administered. Subjects will not be administered any task if they don't understand its instructions. Subjects will be allowed to end participation on any test if they feel fatigued or frustrated. Research staff is trained to be supportive and responsive to the subject's needs. Testers are usually in the room with the participant or in the room just outside of the testing room. Cognitive testing will be audio-recorded with the subjects' permission. Some participants may also be interested in receiving the results from cognitive testing. A summary of the results from the cognitive testing may be shared with the participant, upon request. As part of the feedback process, we will assist individuals who are interested in seeking clinical evaluation for cognitive deficits.

Neuroimaging: Participants will undergo one hour of scanning in a 3.0 T magnet during which structural MRI will be acquired to assess brain volume and cortical thickness, arterial spin labeling (ASL) will be acquired to measure cerebral blood flow, T2 Flair and Diffiusion Tensor Imaging to measure white matter integrity, and 10 minutes of resting bold fMRI to assess default network activation. Freesurfer software will be used to comprehensively assess the structural and functional integrity of various brain regions. Dr. Brickman, an expert in image analysis, will conduct all freesurfer analyses. Covariance analyses will be used to detect quantitative and qualitative differences in structural and functional networks across distributed brain regions, and ultimately to investigate the prognostic power of such

networks in predicting future cognitive decline. Dr. Habeck, an expert in covariance analysis, will conduct all multivariate analyses.

Lumbar Puncture: A lumbar puncture (LP) will be performed by a trained physician as per ADNI procedures in the Irving Center for Clinical and Translational Research at the Columbia Medical Center, in the clinical research center of The Dublin Neurological Institute, and in the University of Michigan Medical Center. Up to 30 ml of Cerebrospinal Fluid (CSF) will be collected and stored in 0.5 ml aliquots in a -80 degree freezer. Samples will be tested locally for white blood count, red blood count, glucose and protein. If the laboratory analyses of the CSF reveal clinically relevant abnormalities, subjects will be notified so that they may seek further clinical assessment. We will assist individuals in seeking further evaluation if this is recommended. A portion of the samples will also be sent to the NINDS Repository. CSF will be collected at the baseline visit and year 5 of the study to maximize the amount of time between collections.

Skin biopsy: A skin biopsy will be performed by a trained physician in the Irving Center for Clinical and Translational Research at the Columbia Medical Center, in the clinical research center of The Dublin Neurological Institute, and in the University of Michigan Medical Center. At the Columbia site, the skin biopsy procedure will be performed by the principal investigator, Dr. Edward Huey. For the first subject undergoing the skin biopsy, Dr. Huey will perform the procedure under the supervision of another physician experienced in the skin biopsy procedure. This physician will then provide a letter of certification indicating that Dr. Huey can perform the procedure independently. This letter will be submitted to the IRB.

A small piece of skin and underlying tissue (1/8th inch diameter by 1/16th-1/8th inch thick) will be removed from the skin, usually of the forearm. A portion of the samples will be sent to the NINDS Repository. These skin biopsies will be used to create pluripotent stem cells. These stem cells can be induced to differentiate into specialized cell lines, including neurons which are then used to study the effects of the exon 10 +14 C>T MAPT mutation of on neuron development and morphology.

Home visits: Willing participants who are unable to participate on-site can choose to have an in-home visit as an alternate arrangement for participation. Participants must sign the consent form indicating informed consent for a home visit. In a home visit, the research staff and study physician will visit the participant in their home to complete a subset of the study procedures which may include: cognitive testing, questionnaires, a neurological examination, and a blood draw. The neurological examination and blood draw will be conducted by the study physician. Some study procedures, including the MRI scan and the lumbar puncture, will not be performed as these can only be done on-site. The in-home visit will involve no greater risk than participation on-site.

Subjects not entering their Year 5 follow-up window in time for evaluation prior to the termination of the grant may be scheduled for their final follow-up prior to their Year 5 period, as deemed appropriate by the investigators on a case-by-case basis.

Cookie Theft Collaboration: In order to externally share voice-only audio recordings of subjects completing the cookie theft measure, staff will need to contact subjects to obtain explicit consent to the sharing of these files with external research collaborators. The following plan for re-consenting subjects is proposed, as it is most feasible, given the unique nature of the cohort: Study staff will contact subjects by phone to obtain verbal consent for sharing audio files with external collaborators. If the subject is deceased, or if there is doubt as to subject's capacity to provide consent, then staff will contact the informant (typically spouse or sibling) that was identified by the subject at their most recent assessment in which they had capacity. If a subject is living and believed to have capacity to consent based on the last assessment, but is unreachable after 2 attempts (i.e. unanswered voicemails), then staff will contact the informant. If a subject's informant is unreachable after 2 attempts at contact (with no response from subject to what would be a total of 4 voicemails at this point), then staff will proceed with full data sharing/usage, as an effort in good faith has been

made to obtain consent.

Biological Specimens

Add an individual entry for each human specimen type that will be collected or utilized for the proposed study. For each specimen type, indicate the source or sources from which you will obtain the specimens.

The use of specimens for research purposes may require that informed consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) be obtained from subjects.

Type:
Saliva
Source:
[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

[x] Specimens will be prospectively collected specifically for this research.
[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.
[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.

[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia
Description of Specimen and Method of Obtaining:
A saliva sample will be obtained using a mouth swab for participants when we are unable to obtain a blood sample.
Indicate the manner in which the specimens will be labeled:
[ ] Specimens will be labeled with direct identifiers
[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:
Cerebrospinal Fluid

The Anatomic Pathology approval request form and guidance on requirements to attach the form can be found on the HRPO website, in the "Biospecimen Research" section of the Human Research Policy Guide page: https://research.columbia.edu/human-research-policy-guide

Source:
[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

[x] Specimens will be prospectively collected specifically for this research.

[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.
[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.

[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

A lumbar puncture (LP) will be performed by a trained physician as per ADNI procedures in the Irving Center for Clinical and Translational Research.

Indicate the manner in which the specimens will be labeled:

[x] Specimens will be labeled with direct identifiers

[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier

[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain

[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:

Tissue

The Anatomic Pathology approval request form and guidance on requirements to attach the form can be found on the HRPO website, in the "Biospecimen Research" section of the Human Research Policy Guide page: https://research.columbia.edu/human-research-policy-guide

Source:

[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

[x] Specimens will be prospectively collected specifically for this research.
[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.
[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.

[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

A skin biopsy will be performed by a trained physician in the Irving Center for Clinical and Translational Research.

Indicate the manner in which the specimens will be labeled:

[ ] Specimens will be labeled with direct identifiers

[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier

[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain

[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will

need to be included in the respective sections of this Rascal submission.

Type:

Blood

Source:

[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

[x] Specimens will be prospectively collected specifically for this research.

[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.

[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.

[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.

[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

Blood will be collected from study participants for DNA and plasma at each of the 3 study visits. Up to 12 tablespoons of blood will be collected at each visit, including citrate tubes for DNA isolation (Year 1), and heparin tubes for plasma isolation (Year 1, 3 and 5).

The blood draw will be performed by the phlebotomist at the Irving Institute, for participants seen on-site.

For participants seen in a home visit, a study physician (the principal investigator) will perform the blood draw.

Indicate the manner in which the specimens will be labeled:

[ ] Specimens will be labeled with direct identifiers

[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier

[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain

[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:

Urine

Source:

[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

[x] Specimens will be prospectively collected specifically for this research.

[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.

[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.

[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.

[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

A urine pregnancy test will be performed on any woman of child bearing age prior to lumbar puncture.

Indicate the manner in which the specimens will be labeled:

[ ] Specimens will be labeled with direct identifiers

[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier

[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Future Use

For what materials do you anticipate future research use? Select all that apply.

[x]Data
[x]Biological Specimens

Please indicate how data and/or specimens will be retained for future use:

[ ]Some or all data and/or specimens, as applicable, will be retained by Columbia researchers for future use.
[x]Some or all data/specimens will be released to a non-Columbia entity for future use and Columbia researchers will not have direct control.

Indicate to whom the data/specimens will be released

[ ]Sponsor
[x]Non-Columbia repository
[x]Other

Describe

Cognitive and clinical data will be entered into a Uniform Data Set (UDS) database managed by the National Alzheimer's Coordinating Center (NACC). Biospecimens and clinical data will also be submitted to the NINDS Repository at Indiana University, a research resource supported by the NIH/NINDS.

Describe plans for release of data and/or specimens.

Cognitive and clinical data collected as part of the study will be shared with the NIH-funded repository. Cognitive data will be entered into a Uniform Data Set (UDS) database managed by the National Alzheimer's Coordinating Center (NACC).

A portion of the biological samples collected from participants enrolled in this study at US sites will be submitted to the NINDS Repository, a research resource supported by the NIH/NINDS. Volumes submitted to the NINDS repository for each biospecimen collected will include the following: up to 30 ml of CSF, up to 12 tablespoons of whole blood and a skin and underlying tissue sample obtained from a punch biopsy. A limited de-identified data set will be sent to the NINDS repository for cataloging with the biospecimen samples. Biospecimens collected by the clinical site in Ireland and the University of Michigan will submit samples to CUMC every 3 months. The samples will be submitted under standard collection operating procedures developed with the Principal Investigators of this study and the NINDS repository. The samples will be stored indefinitely. No personal identifiers will be sent to the Repository as the sample will be identified by a number assigned by the Principal Investigators or study coordinator. The specimens will be used for preparation of DNA and may be used for cell culture from which DNA will be prepared. The DNA and cell culture will be distributed to scientists for use for cell culture from which DNA will be prepared. The DNA and cell culture will be distributed to scientists for use in research and teaching only, and as such the Repository does not return results to donors. The sample could be used for research in any type of disease and other genetic factors, not just FTD. The skin biopsy sample may also be used to create a cell line. The cells from the samples may be isolated and modified so that they divide forever. These modified cells may be maintained in culture indefinitely. In addition, various techniques may be

used to return the cells to a stem cell-like state, from which they can be turned into other cell types. These cells would also be maintained indefinitely for use in experiments researching the development of FTD. These cell lines will be deidentified from the subjects from whom the biopsies were taken. The sample and unidentified data will be available to researchers at hospitals, universities, and commercial organizations.

Subjects will also be assigned a Global Unique Identifier (GUID) which will be given to the NINDS Repository. The GUID is a global identifier which will serve to identify duplicate samples that were collected from one subject, but submitted to multiple repositories, if for instance a subject co-enrolls in another study that submits biospecimens to a different repository. The GUIDs will be generated by study staff through a secure GUID Generator Tool managed by the NINDS. The record of GUIDs will be maintained in a password protected database in a firewall-protected server accessible only to authorized study staff.

Researchers requesting to use study samples from the NINDS Repository would first be reviewed by an FTD Biospecimens Review Access Committee (BRAC) which would include the study's Principal Investigator. If approved to receive samples, the researcher would initially receive the requested samples under randomized IDs, not the GUIDs. The researcher would not be informed of the associated study/site or date of sample collection, only whether the sample was collected at an initial or follow up evaluation. After the researcher performs their tests and returns results to the Repository, NINDS would at that point release the GUID and the aforementioned limited de-identified dataset to the researcher for analysis. Researchers receiving samples from the NINDS Repository must agree not to attempt to identify the donor of a sample, as a condition of sample usage. The Material Transfer Agreements document used by the BioSEND Repository in sending requested samples to researchers is included as an attachment to this protocol.

Research data may be shared with collaborators at outside academic institutions, including the University of Pennsylvania. All data shared with external collaborators will include NO personal identifiers, only a subject ID.

Imaging Procedures/Radiation Therapy

Will a contrast agent (e.g. gadolinium) be used in conjunction with radiation exposure that goes beyond the parameters established for the applicable standard of care (SOC), or will a contrast agent be administered for research purposes only?
No

For each type of radiation exposure (e.g., ionizing: CT, X-ray; non-ionizing: MRI), identify the procedure and whether the administration (e.g., radiation dosage, number or type of scans) is clinically indicated and in accordance with the parameters established for the applicable standard of care (SOC), or is "beyond" these parameters (i.e., includes procedures or exposure for research purposes only).

Procedure(s) Involving Ionizing Radiation
No data to display

Procedure(s) Involving Non-Ionizing Radiation

Procedure	The exposure to:
MRI	As established for the applicable SOC

Recruitment And Consent

Recruitment:

Will you obtain information or biospecimens for purposes of screening or determining eligibility?

No

Describe how participants will be recruited:

All subjects will receive a recruitment letter in the mail detailing the purpose of the study (see attached). Those subjects who participated in the pilot phase of this study from 2009 to 2011 will also be re-contacted about potential participation in the current phase of the study. Subjects and/or informants will facilitate participation of other family members by contacting family members about the study. Family members who wish to participate may contact the research team directly or may give permission to other family members to allow the study coordinator or research assistants to contact them. For individuals who do not respond to the recruitment letter, we will call them only if we have been given permission to contact them from a relative, and that relative has received permission from the person of interest. We will not contact an individual who has not given us permission through a relative, and who does not know that we will be approaching them. All subjects will be encouraged to arrive with an informant. If no informant is present, research staff will attempt to complete informant-based measures by telephone. We will only contact an informant if given permission by the participant.

Select all methods by which participants will be recruited:

[ ] Study does not involve recruitment procedures
[x] Person to Person
[ ] Radio
[ ] Newspapers
[x] Direct Mail
[x] Website
URL: URL exceeds Rascal character limit. Please see attached document titled "Website Recruitment URL"
[x] Email
[ ] Television
[x] Telephone
[ ] Flyer/Handout
[ ] Newsletter/Magazine/Journal
[ ] ResearchMatch
[ ] CUMC RecruitMe

Additional Study Information: Please add a description of your study as you would like it to be displayed on the RecruitMe website.

Informed Consent Process:

Informed Consent Process, Waiver or Exemption: Select all that apply

[x] Informed consent with written documentation will be obtained from the research participant or appropriate representative.

Documentation of informed consent is applicable to:
The study in its entirety

Identify the portion of the study (e.g., prospective portion, focus groups, substudy 2) or subject population for which documentation of consent will be obtained::

Documentation of participation will be obtained from::
[x] Adult participants
[ ] Parent/Guardian providing permission for a child's involvement
[x] Legally Authorized Representatives (LARs)

Describe how participants' written consent will be obtained:
Consent will be obtained by research staff in person using the IRB-approved consent form prior to the start of study procedures. The proposed study, including the potential risks and benefits, will be discussed with the potential subjects, and they will be given copies of the consent form to read. Decision-making capacity to provide informed consent, including understanding the purpose of the study and the risks and benefits of participating, will be assessed by the evaluating physician, psychologist, or trained personnel and documented in the chart. Individuals with intact decision-making capacity will sign the consent form. We expect the majority of subjects to have capacity to provide informed consent.

All subjects with impaired capacity to provide informed consent will be evaluated by a physician or psychologist for their ability to assign a surrogate. Subjects who demonstrate capacity to assign a surrogate will identify a surrogate for the remainder of the study. Surrogates permitted are designated family members (only parent, spouse, or adult child), or may be another individual chosen by Patient Chosen Surrogate (PCS) method. The study will be explained to each potential subject and surrogate, and written informed consent must be obtained from the surrogate. If the participant does not have the capacity to assign a surrogate, he or she will not be allowed to participate in the study. The consent process will be repeated at each evaluation, and the above procedures will be followed for any individual that loses capacity during the course of the study.

The consent process described above will be carried out in the same manner for both on-site and in-home visits. Every effort will be made to evaluate all subjects in person. If an individual is unable to be seen in person, we will mail that person a consent form and complete both the capacity assessment and consent process by telephone.

Subjects (and/or their study partners, if applicable - see Modification Information section of this submission) will be contacted to be reconsented for explicit consent to share audio recordings with external collaborators, as detailed below. Study staff will contact subjects by phone to obtain verbal consent for sharing audio files with external collaborators. If the subject is deceased, or if there is doubt

as to subject's capacity to provide consent, then staff will contact the informant (typically spouse or sibling) that was identified by the subject at their most recent assessment in which they had capacity. If a subject is living and believed to have capacity to consent based on the last assessment, but is unreachable after 2 attempts (i.e. unanswered voicemails), then staff will contact the informant. If a subject's informant is unreachable after 2 attempts at contact (with no response from subject to what would be a total of 4 voicemails at this point), then staff will proceed with full data sharing/usage, as an effort in good faith has been made to obtain consent.

Following the above procedure, the participant or informant will be emailed a link to the informed consent form REDCap page at https://redcap.sac-cu.org/ and asked to complete all sections including signatures.

The Mater Misericordiae University Hospital Research Ethics Committee will review and approve the consent form at the Irish site.

The University of Michigan Institutional Review Board will review and approve the consent form at the Michigan site.

[ ] Informed consent will be obtained but a waiver of written documentation of consent (i.e., agreement to participate in the research without a signature on a consent document) is requested.

[ ] A waiver of some or all elements of informed consent (45 CFR 46.116) is requested.

[ ] Planned Emergency Research with an exception from informed consent as per 21 CFR 50.24.

[ ] This is exempt research.

Subject Language

Enrollment of non-English speaking subjects is not expected.

During the course of the study, if non-English speaking subjects are encountered, refer to the IRB's policy on the Enrollment of Non-English Speaking Subjects in Research for further details (http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc

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Capacity to Provide Consent:

Do you anticipate using surrogate consent or is research being done in a population where capacity to consent may be questionable?

Yes

Who will be enrolled?

Those with and/or without capacity to provide their own consent (surrogate consent is proposed)

Describe the process that will be in place to identify an appropriate surrogate to provide consent:

All subjects with impaired capacity to provide informed consent will be evaluated by a physician or psychologist for their ability to assign a surrogate. Subjects who demonstrate capacity to assign a surrogate will identify a surrogate for the remainder of the study. Surrogates permitted are designated

family members (only parent, spouse, or adult child), or may be another individual chosen by Patient Chosen Surrogate (PCS) method. The study will be explained to each potential subject and surrogate, and written informed consent must be obtained from the surrogate. If the participant does not have the capacity to assign a surrogate, he or she will not be allowed to participate in the study. The consent process will be repeated at each evaluation, and the above procedures will be followed for any individual that loses capacity during the course of the study.

Describe the plan to assess capacity both at the time of enrollment and, if applicable, throughout each subject's participation:

At each visit, an evaluating physician or psychologist will assess participants for capacity as well as ability to assign a surrogate, in cases of impaired capacity.

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):

This protocol will examine the extent to which carriers of a MAPT mutation, in the offspring generation of a family with a known genetic risk for frontotemporal dementia, display subtle cognitive and behavioral deficits in comparison to non-carrier family members.

Scientific Abstract:

FTD is a debilitating neurodegenerative disease. This study seeks to identify its earliest clinical features, in an effort to improve early detection of the disease and ultimately facilitate timely intervention and treatment. Mutations in the microtubule-associated protein tau (MAPT) and progranulin (PGRN) genes are two of the most common established genetic causes of frontotemporal lobar degeneration (FTLD). MAPT mutations on chromosome 17 account for 10-20% of familial cases, and are associated with disruption of the normal function of the tau protein. Abnormal deposits of tau are associated with approximately 40% of FTLD cases, familial or sporadic. This study seeks to identify the earliest indicators of disease in MAPT mutation carriers and to characterize lifestyle factors and their potential effects on symptom onset and course. At the Taub Institute, we have unique access to the offspring generation of a large family with an exon 10 +14 C>T MAPT mutation in whom the FTLD syndrome was first linked to chromosome 17. This project will provide us with the unique opportunity to recruit all branches of the offspring cohort (n >=104), determine carrier status, and conduct longitudinal assessments including neuroimaging, cognitive testing, behavioral characterization, plasma and cerebrospinal fluid collection, and psychiatric evaluation to examine the earliest features of FTLD. Moreover, examination of early and current lifestyle features will inform the extent to which specific behaviors may modify symptom onset and course.

Lay Abstract:

This study will examine individuals in a family with a known genetic mutation for frontotemporal dementia (FTD). We will use cognitive tests, behavioral measures, blood and cerebrospinal fluid samples, and neuroimaging to evaluate the earliest signs of FTD. We will also examine the extent to which lifestyle variables such as diet, physical activity and substance use, modify age of disease onset and/or disease course. Participants who are able to come into the medical center for

evaluation will be seen for a daylong visit. Those who cannot will be seen in their home. During the visit, they will receive a battery of cognitive tests designed to estimate memory, visuospatial, attentional, language, and executive, abilities. They will also complete questionnaires that ask about mood and behavior. In addition, they will undergo a full neurological examination, and will undergo structural and functional neuroimaging. Furthermore, with the participants' permission, we will ask someone who knows them well to complete several questionnaires regarding their functioning. Participants will also undergo a lumbar puncture and blood draw. We will evaluate participants approximately once every two years.

Risks, Benefits & Monitoring

Abbreviated Submission:
The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives. .
If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Potential Risks:
Provide information regarding all risks to participants that are directly related to participation in this protocol, including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in past studies should be provided.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Blood draw: Subjects may experience slight pain at the site when blood is drawn, a bruise which could last several days, and slight discomfort for a few days after blood is drawn.

Cognitive testing: The cognitive tests are not harmful, but may be frustrating or stressful. If subjects do not wish to do a particular test, that test will not be administered.

Interviews and questionnaires: Subjects and/or informants may be uncomfortable and/or embarrassed answering questions regarding their psychiatric and substance abuse history. If subjects do not wish to complete particular questionnaires or interviews, those will not be administered.

Neuroimaging: There is no evidence that radio waves associated with MRI are harmful. However, it may be the case that some people will feel the need to leave the MRI scanner due to claustrophobia or discomfort lying on their back. In this case we will stop the study without any

disadvantages for the subject. People with magnetic metallic implants are at increased risk for harmful interactions between the implant and the magnetic field and therefore will be excluded from participation. Additional contraindications include: pacemakers, AICDs, vagus nerve stimulators, and deep brain stimulators. If the subject is pregnant, we will not scan her.

Lumbar Puncture: The LP is performed under local anesthesia by an experienced physician while the subject is lying on his/her side, or sitting upright in bed. The procedure is generally accompanied by little pain other than the pinprick of the anesthetic needle and the discomfort of lying or sitting in one position for the 10 to 15 minutes while the cerebrospinal fluid is collected. The subjects are then instructed to stay in bed for up to 60 minutes to assess their general tolerability to the procedure. Local discomfort in the area of the LP is a relatively common untoward effect of an LP. This reaction generally improves in a few days and may be minimized through routine doses of nonsteroidal anti-inflammatory medications. In the situation where a headache is severe, or persists beyond a few days, the subject is offered a “blood patch”. This procedure involves the injection of a small portion of the patient’s own blood into the area of the LP to help stop the leak of spinal fluid thought to be responsible for the continuing headache. This technique is generally performed by an anesthesiologist on staff and is most often effective within hours. Rare ophthalmologic complications including VIth nerve palsy have also been encountered following the LP procedure. Conservative treatment, including eye patching, has been all that is required, as the palsy remits spontaneously in several days to three weeks. Women of child-bearing age will be tested for pregnancy prior to a lumbar puncture. If the subject is pregnant, we will not perform the lumbar puncture.

Skin Biopsy: We will use sterile techniques. The risks of this procedure are, as in any procedure, infection or minor bleeding into the wound with some blood-clot formation. Infections are very rare after this procedure. Participants may experience mild to moderate pain or discomfort following the procedure.

Confidentiality: Genetic research studies collect personal information and genetic research participation could be misunderstood by health care providers, insurers, or employers, and misused in cases of discrimination.

Cognitive data collected as part of the study will be shared with the NIH and the National Alzheimer’s Coordinating Center (NACC). The biological samples collected from participants enrolled in this study at US sites will be submitted to the NINDS Repository, a research resource supported by the NIH/NINDS. There is a risk that someone could use the information from the submitted sample, via DNA, to identify the
participant if it were matched with another DNA sample provided by the same participant. To ensure confidentiality, any user of this sample must agree to not use it for that purpose.

Genetic Testing: There is a risk that subjects will become distressed as a result of undergoing genetic testing. However, subjects will not receive DNA results as part of the current study. Rather, all subjects will receive initial genetic counseling from our genetic counselor, Jill Goldman, MS, MPhil. After counseling, the subjects can decide if they would like to pursue commercial genetic testing. If a subject pursues commercial genetic testing, he or she will submit samples to a CLIA-

certified laboratory and receive follow-up counseling. A member of our study will notify the subject of the availability of the results, at which time they may speak to our genetic counselor to obtain them.

Potential Benefits:

Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Potential benefits of the current study include the receipt of information regarding the presence of clinically relevant findings. Results from the MRI scan and CSF testing will be shared with participants on a regular basis. As soon as the results are available, a radiologist will read the MRI scan for evidence of irregularities that may require clinical follow-up. Subjects will receive a letter that summarizes the safety review. Similarly for the CSF diagnostic testing, as soon as the results are available, a study physician will read the results for evidence of irregularities that may require clinical follow up. Subjects will receive the summarization of the CSF safety review should any abnormalities be detected. If they choose, the results of the safety reviews can be shared with their doctor. If they do not have a physician, we will assist them by referring them to a physician at Columbia University Medical Center.

Some participants may also be interested in receiving the results from cognitive testing. A summary of the results from the cognitive testing may be shared with the participant, upon request. As part of the feedback process, we will assist individuals who are interested in seeking clinical evaluation for cognitive deficits.

Finally, while results from the research based genetic testing will not be shared, participants and their family members will be offered genetic counseling services and assisted in the process of pursuing commercial genetic testing if desired.

An indirect benefit of participation is that results are likely to yield generalizable knowledge applicable to improving the understanding of frontotemporal dementia.

Alternatives:

If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Subjects do not receive any treatment in this study or forgo any treatment in order to participate in this study. The alternative, therefore, is not to participate.

Data and Safety Monitoring:

Describe how data and safety will be monitored locally and, if this is a multi-center study, how data and safety

will be monitored across sites as well.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Plans for data and safety monitoring:

Several steps will be taken to ensure standardization of data collection methods across sites. First, a five-day training meeting will be held at the start of the study by Drs. Cosentino, Huey, and Asllani to train and certify all research staff in the collection and coding of all genetic, imaging, clinical, and lifestyle data. Staff certification in the administration of all instruments will be required prior to data collection, and will be achieved through in-person observation by Drs. Huey, Cosentino, and Asllani. Certification procedures will consist of the PIs observing staff members administer full research batteries to one another. Following this initial meeting, investigators at CUMC and Ireland will have monthly conference calls to review data collection procedures and ensure that consent procedures at the Dublin site are conducted in accord with the approved IRB, and that informed consent is being documented properly. Formal quality control checks will be conducted at both sites, three times a year in each data collection year (1, 3, and 5) to evaluate the integrity of the data collected and any systematic differences across sites. A second in-person meeting will be conducted in Year 3 to identify and correct any drift in methods between sites over time and to re-certify all staff in data collection procedures. A final in-person meeting will be conducted in Year 5 to identify and correct any drift in methods between sites over time and to re-certify all staff in data collection procedures.

Standardization of imaging procedures across NY, Ireland, and Michigan is a critical component of this study and will be conducted in person by Dr. Asllani. Dr. Asllani has demonstrated the capability to standardize scanning procedures across multiple centers, and will assess and reconcile differences between the 2 scanners using methods previously used in an ASL reproducibility study that examined the SNR properties of the ASL signal across 28 laboratories located in Asia, Europe and North America.

Each participant's identity and participation in this study will be kept confidential in our database, including data collected from participants in Ireland. All records will be stored in a computer file and access will be restricted to research staff. All questionnaires and other forms generated from the data collection will be kept in locked file cabinets, and only the investigators will have access to this information. Participant names will not be used. Rather, we will assign a code number that will be associated with all information collected. Data that has been stripped of all identifying information from genetic analysis will be kept separate from the clinical and demographic data stored at the Taub Institute Human Genetics Resources Core and can only be accessed by authorized individuals. The Irish site will be responsible for ensuring subject and data confidentiality and protection and subject safety as reviewed by the Mater Misericordiae University Hospital Research Ethics Committee. The Michigan site will be responsible for ensuring subject and data confidentiality and protection and subject safety as reviewed by the Institutional Review Board at the University of Michigan. Data transmitted electronically between these sites will be limited to contain the minimum necessary subject identifying information, and will be conducted by research study personnel using encrypted and protected information-storage devices and endpoint devices.

Subjects

Unless otherwise noted, the information entered in this section should reflect the number of subjects enrolled or accrued under the purview of Columbia researchers, whether at Columbia or elsewhere.

Target enrollment:

75

Number enrolled to date:

63

Number enrolled since the last renewal or, if this is the first renewal, since the initial approval:

0

Number anticipated to be enrolled in the next approval period:

0

Does this study involve screening/assessment procedures to determine subject eligibility?

No

Of the number of subjects enrolled, or the number accrued for interventional studies with a screening process:

How many remain on the study?

0

How many are off study?

63

How many completed the study?

32

Have any withdrawn of their own initiative?

No

Have any been removed by PI?

Yes

How many?

3

Please explain:

Reported previously: 2 subjects were unable to schedule Visit 2, and were thus "removed by the PI" after multiple unsuccessful attempts at scheduling. Both subjects postponed scheduled visits at least 5 times over the course of several months and efforts to reschedule were discontinued after subjects were significantly out of their window evaluation. A 3rd subject seen at the Ireland study site was removed, as she was too ill for follow-up evaluation [note this subject passed away May 2019].

Have any been lost to follow-up?

Yes

How many?

26

Have any died while on study?

Yes

How many?

2

Please explain, including whether death was related to participation in this study:

Reported previously: One subject who had completed a baseline visit in 2014 passed away in 2016 before completing Visits 2 and 3, and was thus technically "on the study" at the time of death.

New: One subject who had completed a baseline visit in 2015 at the Michigan site passed away in May 2019 before completing Visit 3.

Is this a multi-center study?

Yes

Target number of eligible subjects to be included at all sites:

75

Does this study have one or more components that apply to a subset of the overall study population (e.g. Phase 1/2, sub-studies)?

No

Of the number enrolled, or the number accrued for interventional studies with a screening process, indicate:

Population Gender

Females	Males	Non Specific
59%	41%	0%

Population Age

0-7	8-17	18-65	>65	Non Specific
0%	0%	97%	3%	0%

Population Race

American Indian/Alaskan Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	More than One Race	Non-Specific
0%	0%	0%	0%	100%	0%	0%

Population Ethnicity

Hispanic or Latino	Not Hispanic or Latino	Non-Specific
0%	100%	0%

Vulnerable Populations as per 45 CFR 46:

Will children/minors be enrolled

No

Will pregnant women/fetuses/neonates be targeted for enrollment?

No

Will prisoners be targeted for enrollment?

No

Other Vulnerable Populations:

[x]Individuals lacking capacity to provide consent

Are the procedures this population will be exposed to minimal risk?

Yes

Please ensure that your plan for assessing capacity to provide consent is described on the Informed Consent page.

[ ]CU/NYPH Employees/Residents/Fellows/Interns/Students

[ ]Economically disadvantaged

[ ]Educationally disadvantaged

[ ]Non-English speaking

[ ]Other Vulnerable populations

[ ]None of the Populations listed above will be targeted for Enrollment

Subject Population Justification:

Inclusion criteria: Members of families with established MAPT mutations, who either have the capacity or have designated a surrogate/proxy to consent to participate in the protocol

Exclusion criteria: Unwillingness to participate

Safeguards for vulnerable populations: Please see attached document entitled: "Safeguards for vulnerable populations"

Does this study involve compensation or reimbursement to subjects?

Yes

Describe and justify reimbursement/compensation:

Subjects who come into the medical center will receive $350 as: 1)compensation for participating in the full study (clinical evaluation, cognitive testing, blood draw, imaging, and lumbar puncture); and 2) reimbursement for parking and transportation expenses. Subjects who do not complete the lumbar puncture portion of the study will receive $150. Subjects who do not undergo lumbar puncture and imaging but participate in all other parts of the study will receive $50. Subjects may also be reimbursed for their meals during the visit, up to $10 for breakfast, $15 for lunch, and $30 for dinner.

Are subjects eligible for compensation of $600 or more in a calendar year?

No

Attached Attestation

Principal Investigator	Date Created
Edward Huey (edh2126)	07/21/2020

Attached HIPAA Forms

Number	Type	Title	Status
AAAH6108	A	Sponsored Form A	Approve

Attached Consent Forms

Number	Copied From	Form Type	Title	Active/InActive	Initiator
AABX0450	AABX0450	Consent	Early Symptoms of FTLD	Active	Masood Manoochehri (mm2626)

Documents

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	PCS Forms	Consent Form/Addendum	PCS Forms.pdf	Y	No	08/23/2011	Masood Manoochehri (mm2626)
No	Narrative from grant	Funding/Grant Application/Subcontract	AAAI2809 AFTD Science.pdf	Y	No	07/20/2011	Brenda Ruotolo (blr2102)
No	Telephone Script_Audio Reconsent_Cookie Theft	Information Sheet/Verbal Script	Telephone Script_Audio Reconsent_2020-02-03.pdf	Y	No	02/25/2020	Masood Manoochehri (mm2626)
No	Telephone Script_Audio Reconsent_Cookie Theft	Information Sheet/Verbal Script	Telephone Script_Audio Reconsent_2020-02-03.pdf	Y	No	02/25/2020	Masood Manoochehri (mm2626)
No	Telephone Script_Audio Reconsent_Informant_Cookie Theft	Information Sheet/Verbal Script	Telephone Script_Audio Reconsent_Informant_2020-02-03.pdf	Y	No	03/13/2020	Masood Manoochehri (mm2626)
No	AAAI2809 - Ireland Site's Ethics Committee Approval 2016	Local IRB/Ethics/Site Approval	AAAI2809 - Ireland Site's Ethics Committee Approval 2016.pdf	Y	No	11/04/2016	Melissa Scotti (ms5269)
No	AAAI2809 - Ireland Site's Ethics Committee Approval	Local IRB/Ethics/Site Approval	AAAI2809 - Ireland Site's Ethics Committee Approval.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	AAAI2809 - Ireland Site's Ethics ext of approval 2015	Local IRB/Ethics/Site Approval	AAAI2809 - Ireland Site's Ethics ext of approval 2015.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	AAAI2809 - Michigan Site's IRB Approval Letter	Local IRB/Ethics/Site Approval	AAAI2809 - Michigan Site's IRB Approval Letter.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	AAAI2809 Michigan Site Approval Letter 2016	Local IRB/Ethics/Site Approval	AAAI2809 Michigan Site Approval Letter 2016.pdf	Y	No	11/04/2016	Melissa Scotti (ms5269)
No	Mater Misericordiae Uni. Study Site Ethics Approval	Local IRB/Ethics/Site Approval	Ethics ext of approval 2015.pdf	Y	No	01/14/2015	Gayathri Cheran (gc2646)
No	University of Michigan Study Site IRB Approval	Local IRB/Ethics/Site Approval	IRBMED Approval_MAPT_Study_UM_PI-Heidebrink.pdf	Y	No	01/14/2015	Gayathri Cheran (gc2646)
No	BioSEND_Master MTA	Material Transfer Agreement	BioSEND_Master MTA_ESFTLD_IU#170943_FE_2020-02-13.pdf	Y	No	02/25/2020	Masood Manoochehri (mm2626)
No	BioSEND_MTA Appendix A	Material Transfer Agreement	BioSEND_MTA Appendix A_ESFTLD_2.9.2020_FE.pdf	Y	No	02/25/2020	Masood Manoochehri (mm2626)
No	Fully Executed Fibroblast MTA Duff Yoo Collaboration	Material Transfer Agreement	FE MTA Washington Univ. Duff.pdf	Y	No	05/14/2019	Gayathri Cheran (gc2646)
No	Fibroblast MTA Duff Yoo Collaboration	Material Transfer Agreement	Fibroblast MTA Duff Yoo Collaboration.pdf	Y	No	05/01/2019	Gayathri Cheran (gc2646)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	UPenn_DUA_Cookie Theft	Material Transfer Agreement	UPenn DUA_ESFTLD Cookie Theft_2019-11-14.pdf	Y	No	03/13/2020	Masood Manoochehri (mm2626)
No	NIH Progress Report June 2014	Other	2014 RPPR.pdf	Y	No	12/09/2014	Stephanie Cosentino (sc2460)
No	AAAI2809 - BioSEND Letter regarding NINDS Repository Move	Other	AAAI2809 - BioSEND Letter regarding NINDS Repository Move.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	AAAI2809 - Consent Form with Changes Tracked	Other	AAAI2809 - Consent Form Changes Tracked.pdf	Y	No	12/22/2015	Gayathri Cheran (gc2646)
No	AAAI2809 - Correspondance from IRB on 12/22 with comments	Other	AAAI2809 - Correspondence following the 12.16.2015 meeting with comments.pdf	Y	No	12/22/2015	Gayathri Cheran (gc2646)
No	AAAI2809 - Ireland Site's Consent Form 2017 signatures page	Other	AAAI2809 - Ireland Site's Consent Form 2017 signatures page.pdf	Y	No	10/03/2017	Gayathri Cheran (gc2646)
No	AAAI2809 - Ireland Site's Consent Form 2017	Other	AAAI2809 - Ireland Site's Consent Form 2017.pdf	Y	No	10/03/2017	Gayathri Cheran (gc2646)
No	AAAI2809 - Ireland Site's Ethics Committee Approval 2017	Other	AAAI2809 - Ireland Site's Ethics Committee Approval 2017.pdf	Y	No	10/03/2017	Gayathri Cheran (gc2646)
No	AAAI2809 - Ireland Site's Patient Consent form 2016	Other	AAAI2809 - Ireland Site's Patient Consent form 2016.pdf	Y	No	11/04/2016	Melissa Scotti (ms5269)
No	AAAI2809 - Michigan Site's IRB Approval Letter [2017]	Other	AAAI2809 - Michigan Site's IRB Approval Letter [2017].pdf	Y	No	10/02/2017	Gayathri Cheran (gc2646)
No	AAAI2809 - Michigan Site's IRB Consent Form 2017	Other	AAAI2809 - Michigan Site's IRB Consent Form 2017.pdf	Y	No	10/02/2017	Gayathri Cheran (gc2646)
No	AAAI2809 - Violations Log	Other	AAAI2809 - Violations Log.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	AAAI2809 Approval letter for Michigan site 2019	Other	AAAI2809 Approval letter for Michigan site 2019.pdf	Y	No	03/28/2019	Gayathri Cheran (gc2646)
No	Article	Other	AAAI2809 knopman.pdf	Y	No	07/20/2011	Brenda Ruotolo (blr2102)
No	AAAI2809 Michigan Site Consent 2016	Other	AAAI2809 Michigan Site Consent 2016.pdf	Y	No	11/04/2016	Melissa Scotti (ms5269)
No	Explanation of PCS	Other	AAAI2809 Patient Chosen Surrogate Consent.PDF	Y	No	07/20/2011	Brenda Ruotolo (blr2102)
No	AAAI2809 Y1M2 031212.pdf	Other	AAAI2809 Y1M2 031212.pdf	Y	No	03/14/2012	Sharon Leary (sl2785)
No	AAAI2809 Y2M0 012313 - approved documents	Other	AAAI2809 Y2M0 012313.pdf	Y	No	02/08/2013	Challace Pahlevan-Ibrekic (cdp2109)
No	Behavioral Knowledge Statements	Other	Behavioral Knowledge Statements.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	Material Transfer Agreement used by BioSEND	Other	BioSEND MTA OUT Final 2-4-2016 Highlighted for IRB.pdf	Y	No	07/26/2016	Gayathri Cheran (gc2646)
No	Other Study Sites Federalwide Assurance Numbers	Other	Federalwide Assurance numbers for other study sites.pdf	Y	No	01/14/2015	Gayathri Cheran (gc2646)
No	NACC FTD Initial Visit Packet	Other	FTD NACC Initial Visit.pdf	Y	No	11/27/2012	Sarah Cines (sc3311)
No	NACC FTD Neuropsych Battery	Other	FTD NACC UDS Battery.pdf	Y	No	11/27/2012	Sarah Cines (sc3311)
No	FTD Tests	Other	FTD tests.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	How-to social knowledge task	Other	HOW-TO_social knowledge task.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	Log of Incidental Findings	Other	Incidental Findings Log.pdf	Y	No	12/19/2014	Gayathri Cheran (gc2646)
No	IRB Approval Resubmission	Other	IRB approval resubmission 1.7.13.docx	Y	No	01/14/2013	Sarah Cines (sc3311)
No	IRB approval resubmission 1.7.13	Other	IRB approval resubmission 1.7.13.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	Edits/changes tracked on Consent Form	Other	IRB-AAAI2809 Edited Consent Form approved March 2015_MM edits.pdf	Y	No	07/14/2015	Gayathri Cheran (gc2646)
No	March 2015 IRB Correspondence	Other	IRB-AAAI2809 March 2015 IRB Correspondance.pdf	Y	No	07/14/2015	Gayathri Cheran (gc2646)
No	Safeguards for Vulnerable Populations	Other	IRB-AAAI2809 Safeguards for Vulnerable Populations.pdf	Y	No	07/14/2015	Gayathri Cheran (gc2646)
No	Lifetime Total Physical Activity Questionnaire	Other	Lifetime Total Physical Activity Questionnaire.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	March 2015 Modification Data Sheet	Other	March 2015 Data Sheet AAAI2809.pdf	Y	No	07/14/2015	Gayathri Cheran (gc2646)
No	Memo to IRB_8_16_2019_ Response to_8_13_2019_C orrepondence	Other	Memo to IRB_8_16_2019_ Response to_8_13_2019_C orrepondence.pdf	Y	No	08/16/2019	Masood Manoochehri (mm2626)
No	MRI Level 1 Letter	Other	MRI Level 1 Letter.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	MRI Level 2 Letter	Other	MRI Level 2 Letter.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	MRI Level 3 Letter	Other	MRI Level 3 Letter.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	NIH recruitment letter final	Other	NIH recruitment letter final.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	Consent Note	Other	Offspring FTD Consent Note.pdf	Y	No	01/08/2013	Sarah Cines (sc3311)
No	Pathology Approval Form	Other	pathology.approval.form.pdf	Y	No	01/09/2013	Sarah Cines (sc3311)
No	Subject Accrual Description	Other	Rascal_sbjs_renewal 1.6.14.pdf	Y	No	01/06/2014	Sarah Cines (sc3311)
No	SCID Drug List	Other	SCID Drug List.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SCID Mood Episodes	Other	SCID Module A Mood Episodes.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SCID Mood Disorders	Other	SCID Module D Mood Disorders.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	SCID Substance Use	Other	SCID Module E Substance Use.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SCID Anxiety Disorder	Other	SCID Module F Anxiety Disorders.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SCID Optional Disorders	Other	SCID Module J Optional Disorders.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SCID Psychotic Screen	Other	SCID Modules B and C NP or P Psychotic Screen.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SCID Modules G,H,I	Other	SCID Modules G, H, I Somatoform, Eating, Adjustment.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SCID Non-Patient	Other	SCID Non Patient Score Sheet and Overview.pdf	Y	No	12/19/2012	Sarah Cines (sc3311)
No	SRT Recognition Record Forms	Other	SRT Recognition Record Forms.pdf	Y	No	02/23/2015	Gayathri Cheran (gc2646)
No	Violations Log	Other	Violations Description Final 1.6.14.pdf	Y	No	01/06/2014	Sarah Cines (sc3311)
No	Web text from recruitment URL	Other	Web Text for IRB.pdf	Y	No	03/02/2015	Gayathri Cheran (gc2646)
No	Web text from recruitment URL on Association for Frontotempo	Other	Web text from recruitment URL on Association for Frontotemporal Degeneration website.pdf	Y	No	01/14/2015	Gayathri Cheran (gc2646)
No	AAAI2809 - Annual Report to NIH 2016	Progress Report	5R01NS07683705AnnualReportSectionB2.pdf	Y	No	11/01/2016	Gayathri Cheran (gc2646)
No	AAAI2809 - AFTD Progress Report July 2015	Progress Report	AAAI2809 - AFTD Progress Report July 2015.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	AAAI2809 - NIH Progress Report 2015	Progress Report	AAAI2809 - NIH Progress Report 2015.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	ESFTLD Final Annual Report 2016	Progress Report	ESFTLD Final Annual Report 2016.pdf	Y	No	10/03/2017	Gayathri Cheran (gc2646)
No	AAAI2809 - Website Recruitment URL	Recruitment Material	AAAI2809 - Website Recruitment URL.pdf	Y	No	12/03/2015	Gayathri Cheran (gc2646)
No	Recruitment letters	Recruitment Material	Recruitment letters.pdf	Y	No	06/23/2011	Masood Manoochehri (mm2626)
No	Cookie theft	Study Material/Instrument	AAAI2809 Cookie Theft.pdf	Y	No	07/20/2011	Brenda Ruotolo (blr2102)
No	Twenty Questions Instructions	Study Material/Instrument	AAAI2809 Twenty Questions.pdf	Y	No	07/20/2011	Brenda Ruotolo (blr2102)
No	Food Related Problems Questionnaire	Study Material/Instrument	FRPQ published version for use and distribution.pdf	Y	No	10/24/2012	Sarah Cines (sc3311)
No	Lifetime Drinking History	Study Material/Instrument	LDH-Administration and Scoring Guidelines.pdf	Y	No	11/05/2012	Sarah Cines (sc3311)
No	Harvard Semiquantitative Food Frequency Questionnaire	Study Material/Instrument	willett.dietaryassessment.pdf	Y	No	10/24/2012	Sarah Cines (sc3311)