FTD+/-MND with TDP-43 Pathology Genome Wide Association Study

Description

The Alzheimer's Disease Center and the Center for Neurodegenerative Disease Research at the University of Pennsylvania are coordinating an international collaborative effort to conduct a genome wide association study (GWAS) on patients with a clinical diagnosis of frontotemporal dementia (FTD) with or without motor neuron disease (MND), and with autopsy confirmed TDP-43 neuropathology. This project is a recommendation from a FTD workshop held in Miami in January 2007, supported by NINDS and NIA.

This study will be conducted at Penn and supported by resources from the University. We will collect as many cases as possible, with an initial goal of about 500. With more than 30 sites already on board, we are well on our way towards this goal. However, group effort is essential in this project, since the statistical power of the analysis (which is key to GWA studies) will be significantly increased if we are able to collect every sample that is available from both US and international sites. Dr. Vivianna Van Deerlin, a faculty member in our Pathology Department, who is a member of our Center and is also the Director of the Molecular Pathology Lab, will coordinate all aspects of this important study.

The inclusion criteria and shipping information are included in this document (see back). Cases with clinical diagnoses of FTD+/-MND and autopsy proven TDP-43 pathology, as well as living patients with progranulin (*GRN*) mutations will be included. Samples from affected family members (autopsy confirmed or living with a *GRN* mutation) are also welcome, and will be used for subsequent confirmatory analysis.

Of note, we will collect high quality DNA from blood or brain samples, as well as frozen tissue if DNA is not available. Importantly, we can provide assurance that all samples received will ONLY be used for the purpose of this study and that all contributing sites will be a part of any publication that results from this study. In addition, after the initial data analysis, all data will be available for further analysis.

Summary of collaborators to date

As of September 2007, this is the number of sites, from the United States, Europe and Australia that have been contacted or are already enrolled in the project. Since only 7 ADCs have responded so far, this presentation aims to increase awareness and participation of additional ADCs in this GWAS.

- Number of sites enrolled and actively participating 34
- Number of sites previously contacted and still pending on decision 23

In terms of samples, the numbers reflect that we are close to our initial goal of 500:

- Number of samples currently received, from 7 different sites 153
- Number of samples expected from 15 sites that have provided an estimate 288
- Number of samples from 12 sites that have not provided an estimate yet ?
- Total number of received + expected samples 441

Instructions for TDP-43 screening at Penn

If staining of tissue sections for TDP-43 can not be performed in your Center or cannot be performed in a timely manner, we will be more than happy to carry out the TDP-43 immunohistochemistry on your cases in our lab.

We will ask for at least 5 unstained slides from each of 3 different regions for each patient, including hippocampus, frontal or temporal cortex and striatum; with this sampling we believe we will be able to detect TDP-43 pathology if it is present in the case.

Criteria and Information

Clinical, Genetic and/or Pathologic Criteria:

1) Clinical FTD+/-MND with autopsy confirmed FTLD-U TDP-43 neuropathology, both sporadic and familial (with or without GRN mutations)
2) Clinical FTD+/-MND with known pathogenic GRN mutation in living individual

Family members of proband:

1) Affected family members who have had autopsy confirmation of TDP-43 pathology or who are living but have a known GRN mutation will also be accepted but will be used for confirmation studies; they will NOT be counted as study cases and will NOT be included in the initial analysis.

Exclusion criteria:

1) Clinical diagnosis of pure ALS without concomitant FTD
2) Dementia other than FTD due to other known mutations or pathologies

Sample requirements:

1) DNA
    a. Extracted from blood or brain tissue
    b. Concentration preferably >50 ng/µl (but at least >20 ng/µl)
    c. Total of at least 2 µg if possible
    d. Must be pure and of high quality (A260/280 >1.6)
    e. 96-well plates (very well sealed) or individuals tubes
2) Frozen brain tissue
    a. Cerebellum preferred (less affected, better yield), but other regions accepted
    b. 250 mg or greater of tissue
    c. Avoid freeze-thawed tissue
    d. Aliquot of DNA sample can be returned at conclusion of study if desired by tissue submitter and sufficient DNA remains
3) Additional sample information
    a. A spreadsheet will be provided to collect sample information (see below)
    b. All samples should be clearly labeled (typed or clearly printed)

Information collected

We will provide you with a datasheet in order to gather demographic, clinical, and pathologic information from all your samples. This spreadsheet will include the following fields:

DEMOGRAPHICS	***CLINICAL/PATH***	***GENETICS***	***SAMPLE INFO***
Sample ID	*Clinical diagnosis*	*Family History? (y/n)*	*Source*
Race/ethnicity	*Age of onset*	*Screened for GRN mutation? (y/n)*	*DNA concentration in ng/ul*
Gender (M/F)	*MND present (y/n)*	*GRN mutation (y/n)*	*If DNA sent: extraction method*
Is this a family member of another sample? (y/n)	*Age at death*	*If GRN mutation present what is it?*	*If frozen tissue sent, brain region*
If family member, ID of proband	*Neuropath diagnosis*		
	TDP-43 pathology confirmed (y/n)		

Shipping Information

- Please use an overnight delivery (or 2-3 day for international shipments). Send tracking code by email to us along with any electronic files when sample is being shipped so we are alerted to receive the sample.
- The contact person in the lab is Maria Martinez-Lage (marmaria@mail.med.upenn.edu). Questions can be addressed to her or to Vivianna Van Deerlin vivianna@mail.med.upenn.edu 215-662-6957 (office) or 610-291-4331 (cell)
- Shipping address:

    Vivianna Van Deerlin, MD, PhD
    University of Pennsylvania, Center for Neurodegenerative Disease Research
    6 Maloney Building, 3600 Spruce Street, Philadelphia, PA 19104
    215-615-4715