Family with Female Predominant FTD

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Abstract

A large kindred was identified with a high prevalence of frontotemporal dementia (FTD), a neurodegenerative disorder that causes primarily language, behavioral, and social dysfunction. The age of onset for this disease ranges from the 40s to the 60s. The disorder appears to have a right frontal onset, which is followed by frontal and temporal lobe dysfunction. Parkinsonism and motor neuron disease have not been observed. Comprehensive neuropsychological testing of affected persons has revealed problems in the cognitive domains of executive function, attention, working and semantic memory, and visuospatial skills. However, medial temporal functions are unaffected. The family appears to be unique in having a higher percentage of affected women than men. Of the family members over the age of 40 who have undergone neuropsychological testing, 86% of the women are affected versus 20% of the men (n=16 and 12, respectively).

Methods

Study Design

The first aim of this study is to characterize this disorder through neuropsychological testing of family members. Neuropsychological testing is used to measure the activity of specific brain areas. Most measures are normalized by age, although some take education, gender, and race into account.

The second aim is to use genetic testing to find a common genetic mutation. Blood samples collected from affected and unaffected family members, as well as spouses, are being analyzed by dideoxy sequencing of exons in the candidate genes *PRESENILIN 1*, *PRESENILIN 2*, and *TAU*, which have been implicated in this and similar neurological disorders. Our collaborator, Pragna Patel, will additionally perform linkage analysis to find common mutations.

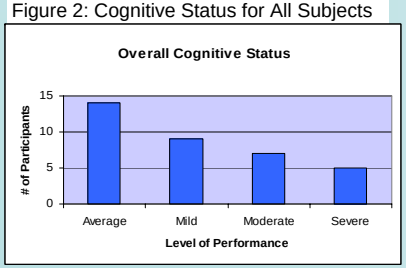
Demographics

Family members were evaluated with a clinical interview and neuropsychological testing. Informed consent was obtained from all participants or their legal representative. The diagnosis of FTD was established using criteria noted in McKhann et al., 2001. Demographics were found (Table 1) and a pedigree was formed based on clinical interviews and histories, and with reconstructed clinical histories of deceased family members (Figure 1). All subjects participating in neuropsychological testing are right-handed.

Table 1: Demographics

	Neuropsychology		Genetic Testing	
	Female	*Male*	*Female*	*Male*
Family Members	16	12	21	18
Spouse Controls	0	0	4	3
Mean Age	42.7 ± 13.2	52 ± 16.4	43.8 ± 12.7	50.1 ± 15.1
Age Range	17 to 62	28 to 83	19 to 55	32 to 53
Education	12.6 ± 2.2	12.3 ± 2.9		
MMSE	27.8 ± 5.2	28.8 ± 1.8		
BDI	7.1 ± 6.3	2.3 ± 2.8		

Figure 2: Cognitive Status for All Subjects



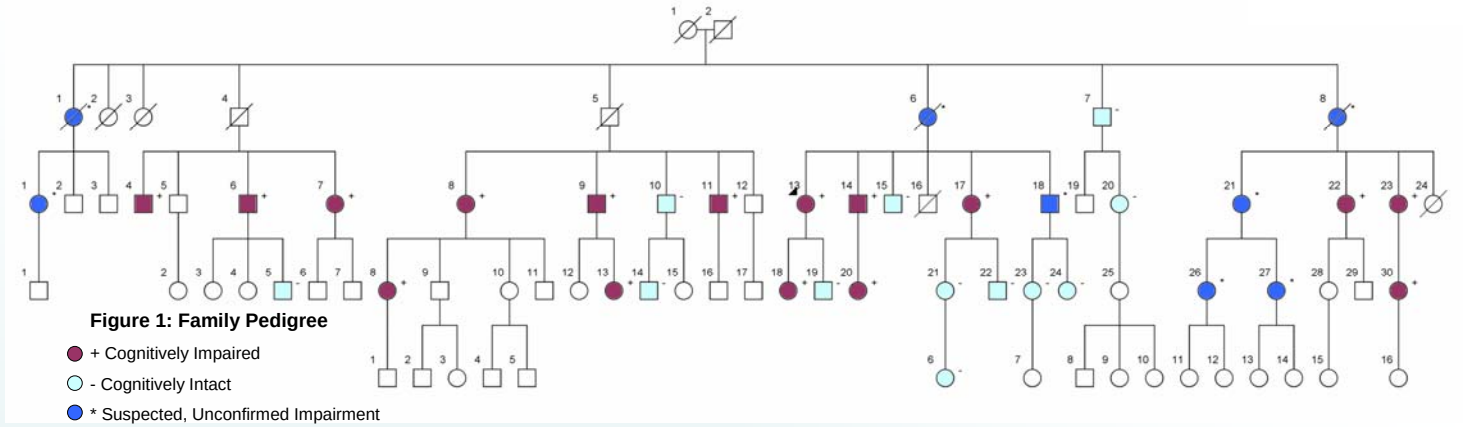


Figure 1: Family Pedigree

+ Cognitively Impaired
- Cognitively Intact
* Suspected, Unconfirmed Impairment

Neuropsychological Measures By Cognitive Domain

Intellectual Function
MMSE, WRAT-R, Information

Language
BNT, Animals

Memory
RAVLT, BVMT, Rey Figure Long Delay

Attention and Information Processing
Digit Span, VSAT, SDM, Trails A

Executive Function
Matrix Reasoning, Similarities, Trails B, FAS, WCST, Stroop, Category Test

Visuospatial
Picture Arrangement, Picture Completion, Benton, JLO, Rey Figure Copy, Block Design

Psychomotor
Grooved Pegboard

Status Classification by Cut-Off Score Analysis

Participants were classified as having mild impairment if composite score from 2 or more cognitive domains was more than 1.5 standard deviations below the norm. Moderate impairment was classified as 1 domain with a composite score 3 standard deviations below the norm. Severe impairment was classified as 2 or more domains with composite scores 3 standard deviations below the norm. Disease status was found for all subjects (Figure 2), and grouped by age (Figure 3).

Results: Characterization by Neuropsychological Measures

Figure 3: Cognitive Status by Age (n=28)

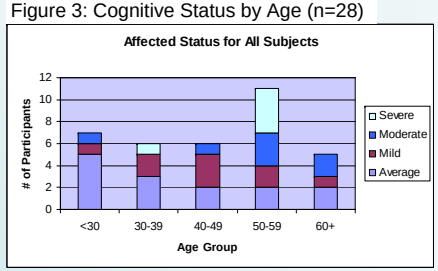


Figure 4: # of Subjects with Impaired Cognition (n=28)

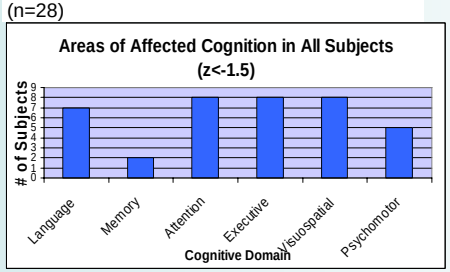


Figure 5: Composite Z-Scores for Domains

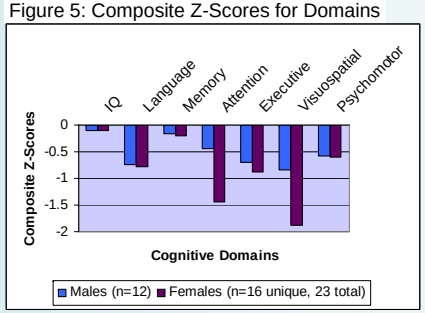


Figure 6: Visuospatial Tests

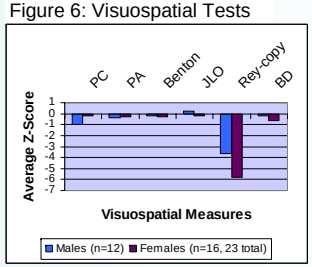


Figure 7: Executive Function Tests

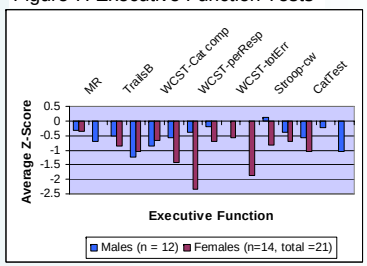


Figure 8: Attention Tests

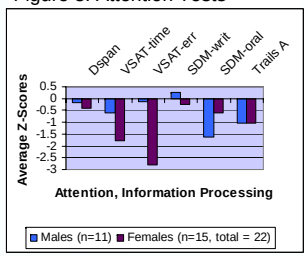
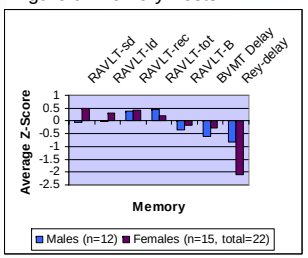


Figure 9: Memory Tests



Results: Genetic Testing

- To date, there have been no mutations found in the exons of *PRESENILIN 1*, *PRESENILIN 2*, and *TAU*, indicating a possible novel mutation

Conclusions

- This disorder appears to affect men and women differently
- The cognitive domains of executive dysfunction and attention tend to be the most affected, while memory is relatively intact
- As mutations were not found in exons of candidate genes linked to FTD and AD, genetic testing will continue
- A behavioral measure (FrSBe), semantic battery, and neuroimaging evaluations will be added
- More longitudinal data needs to be collected to determine whether the cognitive impairment found in the males is the result of a lifelong static disorder or a neurodegenerative process