ELSEVIER

Alzheimer's & Dementia ■ (2017) 1-13

Alzheimer's & Dementia

Featured Article

Clinical and genetic analyses of familial and sporadic frontotemporal dementia patients in Southern Italy

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Abstract

Introduction: We investigated the clinical differences between familial and sporadic frontotemporal dementia (FTD), screening for mutations in known FTD genes.

Methods: We diagnosed 22 affected individuals belonging to eight families and 43 sporadic cases with FTD in Apulia, Southern Italy, in 2 years. Mutations in common causative FTD genes (*GRN*, *MAPT*, *VCP*, and *TARDBP*) and *C9ORF72* expansions were screened.

Results: Behavioral variant of FTD was the most common clinical subtype (50% and 69% in familial and sporadic cases, respectively). Social conduct impairment/disinhibition, loss of insight, and inflexibility were the most frequent clinical features observed at onset. One new mutation was identified in *GRN* in family A.

Discussion: Disease onset in sporadic FTD was more frequently characterized by a clustering of behavioral symptoms with apathy and loss of personal hygiene. Mutations in common causative FTD genes are not a major cause of familial and sporadic FTD in the Southern Italian population.

Keywords: Frontotemporal dementia; Behavioral variant of FTD; Semantic dementia; Primary progressive aphasia: familial; Sporadic

1. Introduction

Frontotemporal dementia (FTD) is a genetically and pathologically complex disorder [1,2] with a heterogeneous clinical presentation [3]. FTD is characterized by progressive changes in behavior, personality, and/or language functions associated with degeneration of the frontal and temporal lobes [3–5]. FTD occurs both in familial and sporadic forms, with 30%–50% of cases being familial [6]. Mutations in numerous genes have been associated with FTD [7–10]. Mutations in the genes that encode tau (*MAPT*), progranulin (*GRN*), and *C9ORF72* are the most common causes of FTD. Rare mutations have been identified in other genes such as valosin-containing protein

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http://dx.doi.org/10.1016/j.jalz.2017.01.011
1552-5260/

(*VCP*) and transactive response DNA-binding protein 43 (*TARDBP*). Nonetheless, a large proportion of familial and sporadic forms still have an unknown genetic origin.

An earlier age at onset and a more rapid progression of disease have been reported in familial Alzheimer's disease (AD) [11]. For FTD, several studies have compared mutation carriers with noncarriers with the aim to find a genotype–phenotype correlation [12–15]. Nonetheless, the genetic contribution to the clinical phenotype in FTD, including age at onset, symptoms, and progression of disease, is not clear. Familial FTD can present with various extrapyramidal signs in addition to behavioral changes, thus suggesting that familial FTD may differ clinically from sporadic FTD [16]. Conversely, a recent study of 22 FTD families, of which half presented tau gene mutations, reported identical clinical presentations in both tau mutation carriers and noncarriers [17]. Piguet and colleagues reported that familial and nonfamilial FTD cases are similar for age at onset, disease onset-diagnosis interval, and infrequent presence of extrapyramidal signs [12]. Nevertheless, in the same study, psychiatric disorders such as depression, paranoid psychosis, delusions, and hallucinations were more frequently found at onset in sporadic patients, and apathy was reported as less frequent in tau-positive familial cases compared to tau-negative familial and sporadic cases [12]. High prevalence of behavioral variant of FTD (bvFTD) with psychiatric features was also reported in *C9ORF72* expansion carriers [13]. In contrast, GRN mutation carriers more often present primary progressive aphasia (PPA) compared to *C9ORF72* mutation carriers (8%) and patients without mutation (14% of familial FTD; 14% of sporadic FTD). Furthermore, GRN mutations carriers (3% with familial FTD and 6% with sporadic FTD) developed limb apraxia more frequently than *C9ORF72* mutation carriers [13]. In the present study, we aimed to assess the clinical presentation and the genetics of familial and sporadic FTD cases from the population-based Apulia FTD Registry.

2. Methods

2.1. Participants and data collection

Patients were identified through the Apulia FTD Registry, a network of neurologists and geriatricians expert in the care of cognitive disorders including rare dementias, established in Apulia, a region in Southern Italy, with about 4 million inhabitants. The Apulia FTD registry included 13 clinical hospital sites and about 30 clinicians working in outpatient services. A detailed clinical history was obtained from the caregivers, generally the spouse or a first-degree relatives (frequently children or brothers and sisters) using a structured checklist of behavioral and cognitive changes. Family history was defined as the presence of one or more subject(s) with FTD in the same family [18]. Pedigrees were designed based on interviews with family relatives. Patients presented with clinical features matching the diagnostic criteria proposed by Neary and colleagues [19], including initial behavioral changes and/or language problems and relatively preserved memory and orientation. We assessed the following clinical variables: disease duration (onset death or onset end of the study with censoring date, April 2014), age at onset, a complete list of specific features observed by a close relative. We defined the "time of shift" as the interval from behavior symptoms to the first language symptom or vice versa. All patients diagnosed with FTD were evaluated with neuropsychological tests (for bedridden patients or patients in advanced stage of dementia, information about the main investigated domains as memory and attentive–executive functions were obtained from previous neuropsychological examinations or personal history) and electromyography if neurological examination showed evidence of second motor neuron signs. Imaging was obtained through magnetic resonance (MR) 1.5 or 3 Tesla and/or single-photon emission computerized tomography (SPECT).

At the time of enrollment of the probands, many affected family members were deceased. Information about progressive behavior, language, and/or cognitive dysfunctions for these subjects was obtained from both medical records and family reports. Parkinsonism was defined if at least one of the cardinal signs (rigidity, bradykinesia, tremor, postural instability) was present. The presence of pyramidal signs (increased deep tendon reflexes, spastic hypertone, Babinski sign, ankle clonus) was also actively explored. The study was approved by the Ethics Committee on Human Research of all hospitals in Apulia involved in the FTD genetic epidemiologic project. Written consent was obtained from each subject enrolled in the study.

2.2. Genetic analysis

Blood samples were collected from 22 patients and 34 first-degree healthy subjects belonging to 8 families and 43 sporadic cases. DNA was extracted from blood following standard procedures. Mutation screening in *MAPT*, GRN, VCP, and *TARDBP* was performed via Sanger sequencing. C9ORF72 repeat expansions were assessed with a repeat-primed PCR.

2.2.1. Sanger sequencing

All exons and exon–intron boundaries of *MAPT, GRN, VCP*, and *TARDBP* were amplified by PCR. PCR products were purified using the AMPure purification kit (Agencourt Bioscience Corporation, MA, USA) and directly sequenced with ABI BigDye Terminator Cycle Sequencing Kit on an ABI 3730 sequencer. Sequence traces were analyzed using Sequencher (version 4.2; Gene Codes Corporation, Ann Arbor, MI, USA).