Genetic Background Predicts Poor Prognosis in Frontotemporal Lobar Degeneration

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Key Words

Frontotemporal lobar degeneration • Frontotemporal dementia • Progranulin • MAPT haplotype • VEGF polymorphisms • APOE

Abstract

Background: Ruling out predictors of survival in frontotemporal lobar degeneration (FTLD) is a clinical challenge for defining disease outcomes and monitoring therapeutic interventions. Little is known about determinants of survival in FTLD. **Objective:** The aim of the present study was to identify whether genetic determinants are key, not only as risk factors but as predictors of survival in FTLD. **Methods:** Ninety-seven FTLD patients were considered in the present study. A clinical evaluation and a standardized assessment were carried out. Each patient underwent blood sampling for genetic testing, and mutations within the progranulin (*PGRN*) gene, microtubule-associated protein tau (*MAPT*) haplotype, apolipoprotein E (*APOE*) genotype and 4 vascular endothelial growth factor (*VEGF*) polymorphisms were evaluated. Discrete-time survival models were applied. **Results:** Mono-

genic FTLD due to *PGRN* mutations [odds ratio (OR) = 3.62, 95% confidence interval (CI) = 1.12–11.7; $p = 0.032$], and *MAPT* *H2 haplotype (OR = 3.23, 95% CI = 1.08–9.69; $p = 0.036$) were associated with an increased hazard risk of poor outcome. Conversely, *APOE* genotype, and *VEGF* polymorphisms were not associated with survival risk in the FTLD sample. **Conclusions:** Genetic background is not only crucial in disease pathogenesis, but it also modulates disease course. Genetic factors influencing prognosis should be taken into account to include homogeneous groups in future clinical trials and to monitor efficacy of future interventions.

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Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common form of neurodegenerative dementias in adulthood, after Alzheimer's disease [1]. The improving knowledge of neuropathological hallmarks and disease mechanisms suggests new possible therapeutic targets to be tested in the near future [2]. However, to assess

the beneficial effect of therapeutic interventions and to include homogeneous patients in clinical trials, a better definition of natural disease course and factors related to higher mortality risk is mandatory [3].

The common experience of clinicians who follow patients with FTLT is the existence of large heterogeneity in the course of the disease not merely explained by clinical phenotypes [4]. A subgroup of these patients shows a benign prognosis over years, others progress to institutionalization with a malignant course. Previous studies demonstrated that FTLT progresses to death faster than Alzheimer's disease [5], but the current literature has still not recognized significantly associated factors at the time of diagnosis to be used in clinical practice as markers of survival risk. Demographic characteristics, age at symptom onset, or family history of dementia do not help in identifying patients with higher risk of mortality [5–11]. More recently, it has been suggested that a positive family history and older age at onset might be predictive of worse prognosis [12]. In the same way, clinical presentation, except for motor neuron disease, is not associated with different patterns of progression over time [5, 6, 8, 13]. Notwithstanding, patients with definite FTLT have a worse prognosis if language deficits are also present [14].

The few available works on survival risk in FTLT have not considered certain variables yet. In this view, as FTLT is recognized as having a stronger genetic background compared to other neurodegenerative dementias, the role of genetic factors should inevitably be analyzed further.

FTLT may present an autosomal dominant pattern of inheritance, and mutations within progranulin (*PGRN*) [15, 16] and microtubule-associated protein tau (*MAPT*) [17] are recognized as the most common forms of known genes.

However, despite several efforts to identify monogenic causes of FTLT, less interest has been shown in the understanding of the genetic risk factors associated with the disease, and no study has tested the effect of genetic variations of possible candidate genes on disease survival.

It has been demonstrated that *MAPT* H1/H2 haplotype influences clinical FTLT presentation [18] and short-term prognosis in FTLT spectrum [11]; on the other hand, apolipoprotein E (*APOE*) genotype, beyond being the most recognized genetic risk factor for late-onset Alzheimer's disease, might modulate the FTLT clinical picture [19, 20]. More recently, vascular endothelial growth factor (*VEGF*) polymorphisms have been associated with increased risk of FTLT [21].

With these caveats in mind, we sought to test whether genetic background, namely *PGRN* mutations and genet-

ic variations within *MAPT*, *APOE* and *VEGF* (–2578C/A, –1190G/A, –1154G/A, and –634G/C), might be associated with higher risk of mortality in FTLT. To this end, we applied discrete-time survival models, and we considered demographic characteristics and disease presentation as possible contributors.

Methods

Subjects

This study is part of an ongoing research program aimed at evaluating the core feature of FTLT and predictors of prognosis at the Center for Aging Brain and Neurodegenerative Diseases, University of Brescia, Italy, between 2001 and 2010. Ninety-seven subjects who fulfilled the Neary and McKhann criteria for FTLT [22, 23], including behavioral frontotemporal dementia, semantic dementia, and progressive nonfluent aphasia variants, and who met inclusion/exclusion criteria were considered in the present study.

Specifically, inclusion criteria were: (a) full consensus agreement by at least 2 experienced reviewers on FTLT diagnosis; (b) follow-up for at least 2 years after diagnosis, and diagnosis confirmation; (c) blood sampling and genetic test availability. Stringent exclusion criteria were applied as follows: (a) cerebrovascular disorders, previous stroke, hydrocephalus, and intracranial mass documented by MRI; (b) a history of traumatic brain injury or other neurological diseases; (c) significant medical problems (e.g. poorly controlled diabetes or hypertension; cancer within the past 5 years; clinically significant hepatic, renal, cardiac, or pulmonary disorders); (d) major depressive disorder, bipolar disorder, schizophrenia, substance abuse disorder, or mental retardation according to criteria of the DSM-IV; (e) FTLT with motor neuron disease.

Variables

All subjects underwent a somatic and neurological evaluation, and routine laboratory examinations, a brain structural MRI and/or brain functional study by single photon emission tomography. The diagnostic assessment involved a review of full medical history, a semi-structured neurological examination, and a complete mental status evaluation.

All patients underwent a cognitive, behavioral and functional examination according to a standardized FTLT assessment, as previously published [11].

In the present study, age at onset, clinical features, and genetic variables were considered. Briefly, the age at onset of symptoms was based on a family report of the earliest persistently abnormal clinical feature in the domains of language, social function or personality change, or executive functioning. Patients considered to have a positive family history were those who had a first-degree relative with dementia. In regard to comorbidities, history of hypertension, diabetes mellitus, hypercholesterolemia and cardiomyopathy were assessed in each subject. Hypertension was considered present either if systolic blood pressure was >140 mm Hg and diastolic pressure >90 mm Hg in more than 3 separate measurements, or if the subject was treated with antihypertensive drugs before recruitment. The diagnosis of diabetes mellitus was

established according to WHO criteria. Hypercholesterolemia was considered present either if cholesterol serum levels were >220 mg/dl or if the subject was under treatment with cholesterol-lowering drugs. The presence of atrial fibrillation, ischemic cardiomyopathy or hypertensive cardiomyopathy was also considered according to common clinical criteria.

Blood sampling was carried out after informed consent for genetic analyses. In each patient, mutations within *PGRN* gene were analyzed, as well as *MAPT* haplotype, *APOE* genotype and 4 different *VEGF* polymorphisms (–2578C/A, –1190G/A, –1154G/A, and –634G/C). FTLD patients were screened for *MAPT* mutations; in the present analysis, *MAPT* pathogenetic mutations were not considered, because only 1 patient carried monogenic *MAPT* disease.

All participants were made fully aware of the research goals, and the signature of an informed consent was required from all subjects. The work was conducted in accordance with local clinical research regulations and in conformity with the Declaration of Helsinki.

Genetic Analyses

Total genomic DNA was prepared from peripheral blood according to standard procedures.

PGRN Sequencing. All the 12 exons plus exon 0 of *PGRN* and at least 30 base pairs (bp) of their flanking introns were evaluated by polymerase chain reaction (PCR). PCR primers were designed to optimize denaturing high-performance liquid chromatography (dHPLC) conditions, following previously provided primer pairs, as previously published [24]. The dHPLC method was adopted to screen, and samples with an altered dHPLC profile were purified with Microcon centrifugal filter devices (Amicon Bioseparation – Millipore) and sequenced. Sequencing was performed in duplicate from purified PCR on the 310 DNA sequencer ABI Prism (Applied Biosystems, Italy), according to the manufacturer's instructions. Sequences were compared with those available in public databases.

MAPT Haplotype Analysis. *MAPT* haplotype was evaluated by saito-hin gene (*STH*) amplification using the forward primer 5' CCA AGT TCA GTT GCC ATC TCC 3' and reverse primer 5' CTC TTG TGC ATG GAC CCT GTA 3'. PCR product consisted of a fragment of 795 bp. PCR was performed using 200 ng of genomic DNA in 50 µl of reaction mixture consisting of 0.2 mM of each primer, 5 mM of deoxynucleotide triphosphate, 2.5 mM of MgCl₂, 5 nl of 10× PCR buffer and 2.5 U of *Taq* polymerase. After initial denaturation at 95°C for 5 min, the reaction mixture was subjected to 35 cycles of 40-second denaturation at 95°C, 2-min annealing at 56°C, 1-min extension at 72°C, followed by a final 10-min extension step at 72°C. Genotyping of the *STH* single nucleotide polymorphism was performed by digesting the PCR product with *Hinf* I restriction enzyme (New England Biolabs). The *STH**Q allele was characterized by 5 fragments of 261, 243, 194, 54, and 30 bp, while the *STH**R allele was characterized by 2 fragments of 97 bp, a fragment of 261 bp and 1 of 243 bp.

APOE Genotyping. Genetic variation at the *APOE* locus was determined by restriction isotyping using PCR amplification and subsequent digestion with *Hha* I (Qbiogene). The nucleotide substitutions that result in Arg-Cys interchange at position 112 and 158 alter *Hha* I cleavage sites: each genotype can be distinguished by unique combinations of *Hha* I fragment sizes in all homozygotic and heterozygotic combinations.

VEGF Genotyping. Two genomic DNA regions containing portions of the *VEGF* promoter were amplified by PCR. The amplification protocol was as follows: 5 min at 94°C for the first cycle, denaturation at 94°C for 30 s, annealing at 60°C for 30 s, extension at 72°C for 30 s for the subsequent 35 cycles, and a final extension at 72°C for 5 min. To detect the polymorphism C(–2578)A, fragments were directly electrophoresed on a 3% agarose gel because of an 18-nucleotide insertion always associated with the –2578A allele, whereas CC homozygotes do not contain this insertion. –1190G/A and –1154G/A variants were detected through direct sequencing analysis of PCR fragments using Big-Dye Terminator protocol on an automated 3100 ABI Prism Genetic Analyzer (Applied Biosystem, Foster City, Calif., USA). The polymorphism G(–634)C (rs2010963) was detected by allelic discrimination through a TaqMan SNP genotyping assay (ID: C_8311614_10) on an ABI Prism 7000 instrument (Applied Biosystem).

Follow-Up Outcomes

Each patient was followed up over a 9-year period from the time of the study enrolment/diagnosis, and the survival times were recorded in years from the age at onset of symptoms. The binary endpoint was determined as the entry to nursing home or other long-term care facility (institutionalization) and death (outcome = 1), and otherwise (no institutionalization/death, outcome = 0). Endpoints were determined by clinical periodic follow-up when possible, or by a semi-structured telephone interview.

Statistical Analysis

Results are given as means ± standard deviation (SD). All statistical tests were 2-sided, and p values less than 0.05 were considered statistically significant. FTLD groups were compared by means of one-way ANOVA or χ^2 test, as appropriate.

Since the continuous times were replicated in many patients, and the number of time values is less than 20, discrete-time survival analysis models (for an overview, see Singer and Willett [25]) were performed using six time intervals of the follow-up period: 1–2, 3–4, 5–6, 7–8, 9–10, and >10 years.

Only time-independent covariates have been considered, thus only covariates whose values remain constant during follow-up. The survival analysis investigated demographic features (age at onset, and gender), clinical variables (diagnosis, family history, history of hypertension, hypercholesterolemia, diabetes, and cardiomyopathy) and genetic background (*PGRN* mutation and *MAPT* haplotype, *APOE* genotype, *VEGF* polymorphisms). Univariate models (single predictor entered in the multiple models) and one multivariate model (all predictors entered in a single model) were fitted. In the multivariate model, total number of comorbidities (from 0 to 4), and total number of *VEGF* polymorphisms (from 0 to 4) were considered for reducing multicollinearity.

The maximum likelihood estimates of model parameters (= hazard odds ratios, OR), 95% confidence intervals (95% CI), and p values of the t test (= parameter estimate/standard error) using 'robust' standard error were reported.

Data analysis and discrete-time survival modeling were performed using the SPSS (version 15.0) software (www.spss.com), and Mplus (version 6.0) software (www.mplus.com), respectively.

Table 1. Demographic and clinical characteristics of included FTLN patients

	FTLD overall (n = 97)	bvFTD (n = 80)	SD (n = 8)	PNFA (n = 9)	p value ²
Age at onset, years	63.6 ± 7.8	63.5 ± 7.8	68.6 ± 9.0	60.5 ± 7.5	0.094
Age at diagnosis, years	65.6 ± 7.8	65.6 ± 7.5	70.3 ± 9.0	63.1 ± 8.6	0.146
Female gender, %	51.5 (50)	48.8 (39)	75.0 (6)	55.6 (5)	0.335
Family history, %	42.3 (41)	43.8 (35)	25.0 (2)	44.4 (4)	0.587
<i>Clinical variables</i>					
Hypertension, %	36.6 (34)	37.7 (29)	28.6 (2)	33.3 (3)	0.872
Hypercholesterolemia, %	39.4 (37)	42.9 (33)	25.9 (2)	22.2 (2)	0.334
Diabetes, %	12.9 (12)	14.3 (11)	0.0	11.1 (1)	0.612
Cardiomyopathy, %	16.0 (15)	17.9 (14)	0.0	11.1 (1)	0.424
Comorbidities, n	1.05 ± 0.98	1.13 ± 0.98	0.50 ± 0.54	0.77 ± 1.28	0.218
<i>Genetic background</i>					
PGRN mutations, n	7.2 (7)	5.0 (4)	0.0	33.3 (3)	0.006
APOE ¹ ε4, %	29.0 (27)	30.3 (23)	37.3 (3)	11.1 (1)	0.380
MAPT ¹ H2 haplotype, %	40.0 (36)	37.3 (28)	71.4 (5)	37.5 (3)	0.210
VEGF ¹					
-2578 C/A, AA, %	22.6 (19)	23.9 (17)	14.3 (1)	16.7 (1)	0.790
-1190 G/A, AA, %	25.0 (21)	28.2 (20)	0.0	16.7 (1)	0.230
-1154 G/A, AA, %	17.9 (15)	19.7 (14)	0.0	16.7 (1)	0.428
-634 G/C, CC, %	10.0 (8)	9.0 (6)	14.3 (1)	16.7 (1)	0.771
VEGF polymorphisms, n	0.78 ± 1.00	0.85 ± 1.04	0.28 ± 0.48	0.66 ± 0.81	0.353

bvFTD = Behavioral variant of frontotemporal dementia; SD = semantic dementia; PNFA = progressive nonfluent aphasia. Number of subjects are given in parentheses.

¹ Differences in the total are due to missing values: smoking habits = 81 cases, APOE and MAPT = 90 cases, VEGF polymorphisms = 84 cases available.

² F test of one-way ANOVA or χ^2 test, as appropriate.

Results

Among 180 FTLN patients, 97 subjects fulfilling inclusion and exclusion criteria and with genetic testing available were considered in the present analysis.

Demographic, clinical and genetic features according to clinical diagnosis are reported in table 1. FTLN patients were homogeneous across clinical diagnoses. The average time delay between age at diagnosis and age at onset of symptoms was equal to 2 years (SD = 1.7 years). Seven out of 97 patients carried PGRN mutations (7.2%), namely T272SfsX10 (n = 6) and Q341X (n = 1). Forty percent of patients carried at least one MAPT*H2 allele (H1/H2 or H2/H2), and 29% the APOE ε4 allele. Thirty-two out of 97 FTLN patients had been institutionalized or died throughout the follow-up observation. In the overall group, the average survival time from the onset of symptoms was 6.2 years (SD = 2.9 years), and the failure rate was about 5 events per 100 person-years at risk.

The univariate (crude) and multivariate (adjusted for) hazard OR estimates from discrete-time survival models are reported in table 2. There was no significant evidence to suggest that gender, positive family history of dementia, and comorbidities, i.e. history of hypertension, hypercholesterolemia, diabetes, and cardiomyopathy, significantly correlated with the rate of survival. Clinical diagnoses and age at onset of symptoms predicted the survival rate in FTLN only when either the crude OR or multivariate model were considered, respectively.

Conversely, as shown in table 2, genetic background significantly predicted the survival rate in FTLN patients in both the univariate and multivariate models. In particular, monogenic cases due to PGRN mutations (OR = 5.11, 95% CI = 1.83–14.2, p = 0.002 for univariate model, and OR = 3.62, 95% CI = 1.12–11.7, p = 0.032 for multivariate model), and patients carrying the MAPT*H2 haplotype (OR = 2.67, 95% CI = 1.10–6.46, p = 0.029 for

Table 2. Hazard OR estimates of prognostic factors according to univariate and multivariate discrete-time survival models

Prognostic factor	Univariate model		Multivariate model	
	OR (95% CI)	p value	OR (95% CI)	p value
Age at onset (years)	1.04 (0.99–1.09)	0.104	1.09 (1.03–1.16)	0.005
Gender (1 = female)	0.76 (0.34–1.68)	0.495	0.80 (0.36–1.78)	0.577
<i>Clinical variables</i>				
Diagnosis (1 = bvFTD)	0.45 (0.21–0.98)	0.045	0.85 (0.32–2.23)	0.739
Family history (1 = yes)	1.03 (0.45–2.34)	0.952	1.57 (0.64–3.84)	0.325
Hypertension (1 = yes)	0.54 (0.19–1.54)	0.252	–	–
Hypercholesterolemia (1 = yes)	0.50 (0.20–1.25)	0.137	–	–
Diabetes (1 = yes)	1.23 (0.39–3.87)	0.719	–	–
Cardiomyopathy (1 = yes)	0.60 (0.12–3.00)	0.538	–	–
Comorbidities	0.67 (0.42–1.08)	0.097	0.58 (0.31–1.07)	0.081
<i>Genetic background</i>				
PGRN mutations	5.11 (1.83–14.2)	0.002	3.62 (1.12–11.7)	0.032
APOE ϵ 4	1.24 (0.54–2.84)	0.615	0.95 (0.32–2.81)	0.920
MAPT H2 haplotype	2.67 (1.10–6.46)	0.029	3.23 (1.08–9.69)	0.036
VEGF				
–2578 C/A, AA	0.81 (0.28–2.36)	0.703	–	–
–1190 G/A, AA	1.17 (0.40–3.49)	0.772	–	–
–1154 G/A, AA	0.61 (0.15–2.48)	0.491	–	–
–634 G/C, CC	1.33 (0.50–3.52)	0.568	–	–
VEGF mutations	0.92 (0.59–1.43)	0.699	1.24 (0.80–1.94)	0.332

bvFTD = Behavioral variant of frontotemporal dementia.

univariate model, and OR = 3.23, 95% CI = 1.08–9.69, $p = 0.036$ for multivariate model) had a 3-fold increased hazard risk of mortality/early institutionalization compared to the reference ('wild') genotypes. Conversely, APOE genotype and those VEGF polymorphisms previously associated with increased risk for FTLT [21] were not associated with survival in the FTLT sample.

Figure 1 displays the estimated discrete-time survival probabilities of the multivariate model for the four PGRN $\times$ MAPT groups at the mean value for age at onset (= 64 years), and at the reference category (= 0) for the other covariates.

Discussion

The evaluation of predictors of survival in FTLT is essential for a number of reasons. First of all, it allows the identification of factors that can be targeted to reduce the mortality risk, and to define faster decliners eligible for therapeutic interventions. This would allow clinicians to

Fig. 1. Estimated discrete-time survival probabilities in patients with different genetic backgrounds. Blue = Patients with PGRN pathogenic mutations and carrying MAPT *H2 haplotype; green = patients carrying MAPT *H2 haplotype without PGRN pathogenic mutations; red = patients carrying PGRN pathogenic mutations without MAPT *H2 haplotype; orange = no at-risk genetic background.

meet caregivers' and patients' expectations and counsel on disease course and disease progression. Moreover, the estimate of mortality risk might be of help in reducing the number of patients needed in clinical trials, and in establishing the effects of a disease-modifying drug within a reasonable time frame.

Up to now, only a few studies on natural disease course and survival predictors are available. It is well demonstrated that neither demographic characteristics, nor comorbidities, nor family history of dementia can help clinicians to predict the mean survival rate [5, 6, 10, 26]. It has previously been suggested that a data-driven approach on neuropsychological data might be of help in identifying patients at higher risk of progression [10]. On the other hand, no data on the role of genetic background in modulating survival rate are available.

In the present work, we suggest that genetic background is not only a significant determinant in monogenic and polygenic FTLN, but that it influences disease course. Both pathogenic *PGRN* mutations and *MAPT* *H2 haplotype were significantly associated with poor prognosis over time.

Only one previous study has reported the effect of *PGRN* mutations on survival in FTLN patients, arguing that patients bearing *PGRN* mutations had a shorter survival (5 years) than patients without *PGRN* mutation-associated disorder [27]. Accordingly, it has been demonstrated that patients carrying *PGRN* mutations have more generalized atrophy and smaller brains at postmortem compared to patients without *PGRN* mutations, therefore suggesting that *PGRN* results in a more rapid, 'malignant' form of FTLN [28].

Beyond the key role of autosomal dominant inherited disorder, our findings also demonstrated a significant association between the presence of *H2 allele within *MAPT* gene and worse prognosis. The mechanism by which *MAPT* gene polymorphisms contribute to the modulation of FTLN in these patients is currently un-

clear; it could be related to an effect on tau expression or to an association with other disease-modifying factors. In fact, H1 and H2 alleles have different transcriptional activity in human cell lines with H1 being more efficient at driving *MAPT* gene expression than H2 allele [29]. In the same way, functional brain imaging studies have supported the claim of a more severe frontal impairment in *H2 compared to H1 carriers in FTLN, thus leading to a faster progression [30, 31].

These findings add to the growing body of literature that argues that the clinical course of FTLN is heterogeneous. The observations of the present study might be of help in clinical practice, but we recognize that they entail some limitations. It is noteworthy that the results of this study need to be replicated in other work, and neuropathological confirmation would be necessary to further confirm the present findings. Furthermore, one of the drawbacks of the present study is that we considered both institutionalization and death as an outcome measure, this being able to influence the final results.

In conclusion, the present work argues that genetic background is not only crucial in disease pathogenesis and disease onset, but it modulates disease course. Establishing disease-modifiable and nonmodifiable factors of poor prognosis is mandatory to define homogeneous patient groups to include in future clinical trials and to monitor efficacy of future interventions. Future studies comparing prognosis in the different autosomal dominant FTLNs would be of interest.

Acknowledgements

The authors wish to thank the patients and their families for taking part in this study. The authors are indebted to Drs. Chiara Agosti, Antonella Alberici, and Maura Cosseddu for clinical assistance. This study was supported by grants of Ente Universitario Lombardia Orientale (EUO) to A. Padovani.

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