Genetic Contributors to Frontotemporal Lobar Degeneration: Beyond Monogenic Disease

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Abstract: Frontotemporal Lobar Degeneration (FTLD) is a genetically and pathologically heterogeneous disorder characterized by behavioral change, executive dysfunction and language impairment associated with frontal and temporal lobe degeneration. Three major clinical subtypes have been identified so far, namely behaviour variant Frontotemporal dementia (bvFTD), Semantic Dementia (SD) and Progressive Non-Fluent Aphasia (PNFA). FTLD might also overlap with atypical parkinsonisms or motor neuron disease. Several pathogenetic mutations have been associated with specific pathological and clinical correlates. FTLD associated with either *Microtuble Associated Protein Tau* (*MAPT*) or *Progranulin* (*PGRN*) mutations is recognised as the most common form of autosomal dominant inherited disorder. However, monogenic mutations account for only about one third of all FTLD cases. Several studies have evaluated the contribution of genetic background in non-monogenic forms of FTLD, with the attempt to establish its role in increasing disease risk and in modulating clinical phenotypes. Specific *MAPT* and *PGRN* polymorphisms have been demonstrated to affect disease onset, clinical features and prognosis of FTLD, and genetic variations within other genes appear to play a role in influencing disease risk and clinical expression of FTLD.

The aim of the present review is to discuss the impact and the role of genetic background in non-monogenic forms of FTLD, to highlight new potential pathogenetic and therapeutic targets.

Keywords: Frontotemporal lobar degeneration, frontotemporal dementia, genetics, polymorphism, risk factors.

INTRODUCTION

Frontotemporal Lobar Degeneration (FTLD) is a clinically and pathologically heterogeneous syndrome, characterized by impairment in executive functions, behavioral disturbances and language deficits associated with degeneration of the frontal and anterior temporal lobes [1-2].

According to current clinical criteria [1-2], three distinct variants have been described: behavioral variant Frontotemporal Dementia (bvFTD), Progressive Non-fluent Aphasia (PNFA), and Semantic Dementia (SD). bvFTD is characterized by behavioral disturbances and personality changes, PNFA is associated with progressive loss of speech, with hesitant, nonfluent speech output, and SD is associated with loss of knowledge about words and objects [1].

Neuropathologically, two distinct molecular subtypes may be recognized, and either FTLD with tau-positive inclusions (FTLD-tau) or TAR DNA-binding protein 43 (TDP-43)-positive inclusions (FTLD-TDP) represent the most common forms [3].

Up to 40% of patients have history that suggests familial transmission, with roughly 10% showing an autosomal dominant inheritance pattern [4-6]. This familial recurrence has suggested a strong genetic component in disease etiology. Despite several efforts to identify monogenic causes of the disease, genetic predisposing factors have not been considered for a long time.

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Only in the last few years, have genetic variations increasing disease risk or modulating disease phenotype been considered. Moreover, the recently performed genome wide scans have reported interesting findings and have highlighted new candidates in the pathogenesis of the disease.

Given these premises, in the present review, we have summarized the current literature on genetic contributors to FTLD, focusing the attention on genetic risk factors and disease modulators beyond monogenic causes.

GENES CAUSING AUTOSOMAL DOMINANT INHERITED FTLD

In recent years, important progress has been made towards understanding the genetic causes of FTLD.

In 1994, the first linkage analysis of familial cases of FTLD with parkinsonism reported linkage to chromosome 17q21 [7]. This finding was then further confirmed [8-13], and the collective name of Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17) was adopted for all the cases linked to this chromosomic region and showing an autosomal dominant pattern of inheritance [14].

In 1998, the seminal works by Spillantini *et al.* and Hutton *et al.* permitted the identification of mutations within *Microtubule Associated Protein Tau* (*MAPT*) gene as the cause of FTDP-17 [15-17]. Tau protein, encoded by *MAPT* gene, is abundantly expressed in the central nervous system; it interacts with the microtubules to regulate the microtubule assembly and stabilization, being involved in signal transduction and axonal transport [18]. Since the first findings,

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more than 40 pathogenic mutations have been reported (http://www.molgen.ua.ac.be/FTDmutations/).

The prevalence of *MAPT*-related disorder is highly variable, ranging from 0% [19] to 17.8% [20-26].

MAPT mutations show 100% penetrance, with variable phenotypic presentation; disease onset is between the fourth and the sixth decade, even though both very early onset [27] or late onset dementia [28] has occasionally been reported.

Interestingly, since the first reports of *MAPT* mutations in FTDP-17 familial cases, there have been numerous findings of families with linkage to chromosome 17q21 with no evidence of *MAPT* pathogenetic mutations [9, 12, 29-33]. The neuropathological phenotype in these patients was characterized by ubiquitin immunoreactive neuronal inclusions, with no evidence of tau aggregates. In 2006, in these families the identification of pathogenetic mutations in the gene encoding *Progranulin* (*PGRN*) opened a new avenue in the study of FTLD [34-35]. Progranulin is a 593 aminoacid cysteine rich protein expressed in neurons and microglia and is implicated in cellular and tissue development, wound repair, and inflammatory regulation. Concomitantly with the identification of *PGRN* as related to monogenic FTLD, it has been demonstrated that the neuropathological hallmark of these cases is defined by TAR DNA-binding protein (TDP-43) inclusions [36].

The prevalence of *PGRN* mutations in FTLD patients ranges from 5% to 10% of all FTLD cases, and from 20% to 25% if familial cases are considered [37-43]. Up to now, 68 different mutations have been described (http://www.molgen.ua.ac.be/FTDmutations/). *PGRN* mutations, which lead to haploinsufficiency, show variable disease penetrance and wide range of age at onset. *PGRN* mutations encompass different disease phenotypes, although language deficits are frequently present [44-46].

MAPT and *PGRN* mutations cover the majority of known FTLD mutations, but rare forms of autosomal dominant disorder have also been demonstrated. Mutations within *Chromatin Modifying Protein 2B* (*CHMP2B*) gene, which is involved in the endosomal-lysosomal pathway [47-49] and mutations within the *Valosin-Containing Protein (VCP*) gene, which is deputed to degradation in the endoplasmic reticulum [50], have been characterised. More recently, it has been demonstrated that mutations in the *TAR DNA-Binding Protein (TARDBP)* gene are not only associated with sporadic and familial forms of amyotrophic lateral sclerosis (ALS)[51-54], but are responsible for FTLD cases with or without signs of motor neuron disease [55-57]. Another gene previously associated with monogenic ALS, namely the *Fused in Sarcoma gene (FUS*) [58], is believed to be pathogenetic in a patient with pure FTLD [59].

POLYMORPHISMS WITHIN *MAPT* AND *PGRN* GENES: BEYOND MONOGENIC DISEASE

MAPT and *PGRN* genes are characterized by a number of genetic variations, which do not cause monogenic disorder, but whose function is still to be elucidated. Several studies have investigated whether these polymorphisms might act as risk factors for FTLD or modulate the clinical phenotypic presentation.

Several polymorphisms throughout the *MAPT* gene are in complete linkage disequilibrium with each other and are inherited as two separate haplotypes, namely *H1* and *H2*, which can be delineated *via* a 238 bp insertion/deletion polymorphism within intron 9 [60-61].

The most frequently inherited haplotype in general population, i.e. *H1/H1*, has found to be associated with a higher risk of Progressive Supranuclear Palsy and Corticobasal Syndrome [60-61]; however, works assessing association with FTLD yielded contrasting results. Some reports suggested no significant association between increased risk of FTLD and *MAPT* haplotype [62-63], while others found a correlation with *H1/H1* [64]. Interestingly, *MAPT* haplotype seems to affect disease presentation, as **H2* (*H1/H2* or *H2/H2*) carriers had a lower age at onset [65-66]. Moreover, there is evidence that *MAPT* genetic variability affects brain changes over disease course, **H2* haplotype being associated with greater frontotemporal hypoperfusion and hypometabolism compared to *H1* carriers [67-68]. These findings suggest that *MAPT* is not only one of the key-players of monogenic disorder, but it may modulate the disease course when the pathology is overt. The mechanism by which *tau* gene polymorphisms contribute to the modulation of FTD is currently unclear; it could be related to an effect on *tau* expression or to an association with other disease-modifyng factors; moreover it has been shown that the *H1* and *H2* alleles have different transcriptional activity in human cell lines, with *H1* being more efficient at driving tau gene expression [69]. In order to make results reproducible studies should be extended to larger cohorts of patients, from a wide range of different geographical locations, population groups, and ethnic origins.

The other actor in autosomal dominant disease, i.e. *PGRN*, shows several Single Nucleotide Polymorphisms (SNPs), the more frequent being *rs17523519, rs3859268, rs9897526, rs34424835, rs25646, rs850713, IVS+7G>A*, and *rs5848* [70]. Genetic variations within *PGRN* have been shown to contribute to increasing the risk of Alzheimer's disease [71-72], ALS and hippocampal sclerosis in the elderly [73-74].

However, the role of *PGRN* as genetic risk factor of FTLD has not been extensively explored yet.

Recently, Rademakers and colleagues demonstrated that *rs5848* located in the 3'-untranslated region (3'-UTR) of *PGRN* is significantly associated with the development of FTLD. The study was conducted in a homogeneous series of patients with autopsy-confirmed FTLD-TDP [75] . It was suggested that carrying T allele increased the affinity for the micro-RNA miR-659 and the binding of this to the 3'-untranslated region, thus suppressing translation of the protein. Accordingly, *PGRN* TT carriers showed an increased number of lentiform intranuclear inclusions, which are always seen in patients with nullmutations of *PGRN*. Moreover, protein levels were decreased in brain tissue from patients with the TT compared with those with the CC genotype. Finally, when miR-659 was transfected into M17 cells this led to a decrease in PGRN protein compared with control micro-RNAs [75].

Conversely, studies evaluating *rs5848* polymorphism, conducted on clinical-based diagnosis, did not yield significant results [76-77]. Notwithstanding, Galimberti *et al*. found an increased frequency of the *rs4792938 CC* genotype in FTLD as compared to healthy controls (17.4% versus 10.4%, OR: 1.81, 95%CI: 1.15-2.85) [78].

Another association study carried out in the Manchester cohort, analyzing several SNPs covering the *PGRN* locus, failed to demonstrate any effect on disease risk either at the genotype or haplotype level [26]. However, it has been reported that carrying the A allele of *rs9897526* delayed the age at onset by nearly 4 years on average [26].

Further studies are needed to better clarify the role of *PGRN* genetic variability in affecting disease risk or disease phenotype. A summary of the available works evaluating the role of either *MAPT* or *PGRN* genetic variations in FTLD are reported in Table **1** and Table **2**, respectively.

Finally, a few studies have evaluated the direct sequencing of *VCP*, *CHMP2B*, *TARDBP*, *FUS* genes in small-number cohorts, but no polymorphism linked to sporadic FTLD has been identified [79-82].

THE OVERLAP BETWEEN FTLD AND ALZHEIMER'S DISEASE: THE CASE OF APOLIPOPROTEIN AND GENOTYPE

The human *Apolipoprotein E* (*APOE*) is a 299 amino acid glycoprotein that is expressed in several organs, in particular the liver and the brain; within the brain the highest expression of *APOE* is found in astrocytes and microglia [83-84]. The *APOE* gene is mapped to chromosome 19 and contains several SNPs distributed across the gene. The most common SNPs lead to the three isoforms of *APOE*, namely ε2, ε3 and ε 4, which have different structures and functions [85].

It is well established that *APOE* ε4 allele is a risk factor for Alzheimer's disease [86]. Though the effect on Alzheimer Disease risk may be reconducted to the varying influence that *APOE* isoforms play on amyloid-β metabolism,

Table 1. Studies Evaluating the Role of *MAPT* Haplotypes in FTLD

Authors	Diagnostic criteria	% NP	n	Results	Ref.
Russ *et al*. 2001	AC	100	33	Negative finding on disease risk.	[141]
Morris *et al*. 2002	AC	100	34	Negative finding on disease risk.	[143]
Verpillat *et al*. 2002	AC/CC	3	100	Positive finding on disease risk. H1 haplotype and APOE ε2 allele interact and increase the risk of FTLD.	[94]
Sobrido *et al*. 2003	AC/CC	25	48	Negative finding on disease risk.	[63]
Borroni *et al*. 2005	AC/CC	15	86	Negative finding on disease risk. Positive finding on disease modulation. H2 allele is associated with an earlier age of onset.	[65]
Kaivorinne *et al*. 2008	AC/CC	8	59	Positive finding on disease risk. Positive association between the H2 haplotype and FTLD.	[19]
Ingelson *et al*. 2001	CC	0	36	Positive finding on disease risk. H1 haplotype and APOE ε4 interactively increase the risk of FTLD	[142]
Short *et al*. 2002	CC	0	63	Positive finding on disease modulation. Clinical subtypes of FTLD showed specific *MAPT* haplotypes.	[144]
Huges *et al*. 2003	CC	0	113	Positive finding on disease risk. Positive association between the H1 haplotype and FTLD. No effect on age at onset.	[64]
Panegyres *et al*. 2002	CC	0	48	Negative finding on disease risk.	[145]
Sobrido *et al*. 2003	CC	0	25	A significant overrepresentation of the H1/H1 genotype in Primary Progressive Aphasia	[146]
Johansson *et al*. 2005	CC	0	96	Negative finding on disease risk.	[147]
Bernardi *et al*. 2006	CC	0	100	Negative finding on disease risk.	[62]
Laws *et al*. 2007	CC	0	142	Negative finding on disease risk. Positive finding on disease modulation. H2 haplotype was associated with younger age at onset and greater decline of glucose utilization in frontal brain areas.	[67]
Borroni *et al*. 2008	CC	0	48	Positive finding on disease modulation. H2 haplotype carriers showed greater hipoperfusion in frontal areas.	[68]
Laws *et al*. 2008	CC	0	171	Negative finding on disease risk.	[66]

NP: neuropathological confirmation. AC: autopsy confirmed; CC: Clinical Criteria for FTLD.

Table 2. Studies Evaluating the Role of *PGRN* Polymorphisms in FTLD

Study	Diagnostic criteria	% NP	n	Results	Ref.
Rademakers *et al.*2008	AC/CC	17	339	Positive finding on disease risk in FTLD-TDP (*rs5848*)	[75]
Pickering-Brown *et al.* 2008	AC/CC	20	223	Positive finding on disease modulation in clinically diagnosed FTLD. *rs9897526 A* allele delayed mean age at onset by nearly 4 years	[26]
Simòn-Sànchez *et al.* 2009	AC/CC	9	256	Negative finding on disease risk. *(rs5848)*	[77]
Rollinson *et al.* 2009	AC/CC	18	467	Negative finding on disease risk. (*rs5848*)	[76]
Galimberti *et al.* 2010	CC	0	265	Negative finding on disease risk. (*rs5848, rs2879096, rs3785817*, and *rs9897526*). Positive finding on disease risk in clinically diagnosed FTLD. (r*s4792938)*	[78]

NP: neuropathological confirmation. AC: autopsy confirmed; CC: Clinical Criteria for FTLD.

it remains to be fully clarified how *APOE* may influence neurodegeneration in other diseases.

Indeed, conflicting reports on the role of *APOE* genetic variations in FTLD are available, some showing positive findings, others claiming negative results. As shown in Table **3**, some authors argued for higher prevalence of *APOE ε4* allele in FTLD than in controls in either autopsy or clinical-defined series [19, 62, 87-91]. Conversely, other authors have suggested that the *APOE ε2* allele, rather than the *ε4*, could be a risk factor for FTLD [92-95]. In a large series of FTLD patients, Verpillat and colleagues established that the *H1* haplotype of the *MAPT* gene and the *ε2* allele of *APOE* interactively increase the risk of FTLD (*ε2 + H1H1* carriers, OR: 1.39, 95%CI: 0.53-3.67; *ε2 + H1H2 or H2H2* carriers, OR: 3.48, 95%CI: 1.21-10.00; *ε2* non carriers + *H1H1*, OR: 2.64, 95%CI: 1.52-4.60) [94].

Beyond evaluating the role of *APOE* genotype on disease risk, several studies have explored whether this may influence its phenotypic expression.

It was reported that *APOE* ε4 allele modulates amyloid deposition in patients with FTLD; in a series of 54 autopsy cases, Mann and colleagues found that about 26% of FTLD patients showed cerebral amyloid deposition and that this occurred mostly in patients who were homozygous for ε4 allele [96].

Neurimaging studies have also demonstrated that *APOE* ε4 may affect regional brain damage, and greater right frontal atrophy [97-98] or greater hippocampal and parahippocampal hypoperfusion [99] were reported. These findings were corroborated by neuropsychological data, arguing for higher prevalence of aggressiveness [100] and memory deficits [99] in FTLD patients carrying *APOE ε4* allele.

Finally, it has been suggested that *APOE ε4* may be associated with earlier disease onset [100] or worse short-term prognosis [102].

THE GENETIC RISK FACTORS IN SPORADIC FTLD

In the last few years, it has been claimed that new candidate genes are involved in the multi-factorial sporadic forms (see Table **4**).

The most interesting work is a genome-wide association study by Van Deerlin and colleagues [103] carried out on 515 individuals with a pathological or genetic *(PGRN* mutation) diagnosis of FTLD-TDP. Three SNPs (*rs6966915, rs1020004* and *rs1990622*), mapping on chromosome 7p21.3, reached the statistical significance. These SNPs belong to *TMEM106B* gene, which encodes an uncharacterized transmembrane protein of 274 aminoacids. The association was replicated in 89 independent FTLD-TDP cases *vs.* 553 controls. mRNA expression analysis in lymphoblastoid cell lines and in the autopsy brain showed higher gene expression in risk-allele carriers. Moreover, an effect of *rs1020004* on disease duration was observed, AA carriers having worse prognosis compared to non-carriers (*P*=0.03), thus suggesting that *TMEM106B* may act as a disease modifier gene. Additionally, considering sporadic cases (n= 426), this study also demonstrated a trend of association with other locus including one on chromosome 9p21.2. This is in line with previous findings on pedigrees affected by FTLD with motor neuron disease that demonstrated a linkage disequilibrium mapping on this locus [104-106] [Morita, 2006, Vance 2006, Le Ber 2009]. Based on the above observations, Rollinson and colleagues have recently conducted a linkage study to assess the role of 9p21 region, by SNPs analysis covering the single haplotype block on 9p21 for a total of 133 genes [76]. The authors evaluated 214 cases clinically diagnosed as having FTLD, and found a possible association of three different genes, namely *Ubiquitin Associated protein 1* (*UBAP1)* (*P*=0.0005), *Endothelial Thyrosin Kinase* (*TEK)* (*P*=0.02), and *reversion-inducing-cysteine-rich protein with kazal motifs (RECK)* (*P*=0.0052). Fifty additional SNPs covering the interest region finally identified 3 different *at-risk* polymorphisms (*rs7018487, rs10814079*, and *rs10814083*), including and surrounding the *UBAP-1* gene. This association was further replicated in other independent FTLD cohorts. T-G-C haplotype was confirmed as being associated with FTLD in the Manchester cohort (n=214; OR: 1.42, 95%CI: 1.08 – 1.88) and in the Dutch cohort (n=214; OR: 1.33, 95%CI: 1.04–1.69). Similarly, G-C-T haplotype showed a higher prevalence in the American cohort (n=176; OR: 1.4, 95%CI: 1.02–1.92) and in the Spanish cohort (n=75; OR: 1.45, 95%CI: 0.97–2.17). These results failed to be replicated in a

Table 3. Studies that Have Evaluated the Role of *APOE* Genotype in FTLD (Studies with at Leat 50 FTLD Patients are Reported)

Study	Diagnostic criteria	% NP	N	Results	Ref
ε4 as a risk factor for FTLD					
Rosso *et al*. 2002	AC/CC	17	98	The frequency of *APOE* ε4 was 21.9% in FTLD compared to 15.3% in controls (*P*=0.02).	[90]
Kaivorinne *et al*. 2008	AC/CC	8	59	The frequency of *APOE* ε4 was 42.4% of the FTLD patients compared to controls (*P*=0.002).	[19]
Fabre *et al*. 2001	CC	0	65	The frequency of *APOE* ε4 was 52% in FTLD compared to 21% in controls (OR=3.9, 95% CI=1.7-8.9; *P*=0.0012).	[91]
Short *et al*. 2002	CC	0	63	Patients with anomic aphasia had increased *APOE* ε4 frequency (30.4%) compared with patients with bvFTD (14.8%) and controls (11.1%).	[144]
Bernardi *et al*. 2006	CC	0	54	The frequency of *APOE* ε4 was 19.0% in FTLD compared to 8.6% in controls (OR=2.68, 95% CI=1.51-4.76; *P*=0.001).	[62]
Srinivasan *et al*. 2006	CC	0	198	The frequency of *APOE* ε4 was 19.4% in FTLD compared to 14.1% in controls (*P*=0.01).	[89]
Mehta *et al*. 2007	CC	0	64	In *VCP* mutation carriers *APO* ε4 is more frequent in FTLD phenotype (70.0%) than in Inclusion-body phenotype (27.5%) or Paget's disease phenotype (26.6%) (*P*=0.002).	[148]
ε2 as a risk factor for FTLD					
Verpillat *et al*. 2002	CC	0	100	*APOE* ε2 and *MAPT* H1 haplotype interactively increase the risk of FTLD (ε2 + H1H1 carriers, OR=1.39, 95% CI=0.53-3.67; ε2 + H1H2 or H2H2 carriers, OR=3.48, 95% CI=1.21-10.00; ε2 non carriers + H1H1, OR=2.64, 95% CI=1.52-4.60).	[93]
Verpillat *et al*. 2002	CC	0	94	The ε2ε2 genotype frequency was more than 10-fold higher in patients than in controls (3.2% in FTLD patients and 0.3% in controls; *P*=0.041).	[94]
Negative findings					
Pickering-Brown *et al*. 2000	AC/CC	56	88	ε4 allele frequency was 19.3% in FTLD and 14.3% in controls.	[149]
Riemenschneider *et al*. 2002	CC	0	52	ε4 allele frequency was 9.6% and 9.9% in controls.	[150]
Hughes *et al*. 2003	CC	0	113	No difference in ε4 frequency in FTLD vs. Controls (15% vs. 14%; *P*=0.776).	[64]
Studies that have shown phenotypic modulation of APOE genotype					
Mann *et al*. 2001	AC	100	54	26% of all patients with FTLD showed some deposition of Aβ in their brains; deposition occurs mostly in those patients who are homozygous for ε4 allele.	[152]
Borroni *et al*. 2006	CC	0	52	ε4 carriers showed worse performances in Short Story recall (6.3 ± 3.9 vs. 10.1 ± 4.2, *P*=0.004) and had greater bilateral hypoperfusion in uncus and parahippocampal gyrus and in medial frontal cortex compared to ε4 non-carriers	[99]
Borroni *et al*. 2010	CC	0	127	ε4 heterozygous patients had almost 3-fold times increased risk (OR=2.86, 95% CI=1.14-7.86), and ε4 homozygous patients had 8-fold times increased risk (OR=8.18, 95% CI=1.18-6.19) to have worse short-term prognosis.	[102]

%NP: % of neuropathological confirmation. AC: autopsy confirmed; CC: clinical consensus criteria for FTD.

Table 4. Genes Associated with FTLD Risk or FTLD Presentation

Author	Gene	Results	SNPs	Number of patients	OR	Association with other disease	Ref.
Li *et al*. 2005	PRNP	Risk factor	M129V	39 PPA	8.47	Prion disease	[116]
Venturelli *et al*. 2008	NOS1	Risk factor	C276 T	71	1.96	Alzheimer's disease	[129]
Borroni *et al*. 2008	VEGF	Risk factor	-2578C/A	161	2.14 (AA)	Amyotrophyc Lateral Sclerosis, Alzheimer disease	[125] [126]
			1190G/A, -	161	1.83 (AA)		
			1154G/A	161	1.32 (A allele)		
Venturelli *et al*. 2009	NOS3	Risk factor	G894T	222	1.65	Alzheimer's disease	[130]
Villa *et al*. 2009	DCUN1D1	Risk factor, GG genotype	rs4859147	220	4.39	Squamous cell carcinoma	[113]
Rollinson *et al*. 2009	UBAP1	UK	T-G-C haplotype	214	1.42	Nasopharyngeal Carcinoma	[76]
		NED		214	1.33		
		USA	G-C-T haplotype	176	1.4		
		London		158	NO association		
		ESP		75	1.45		
Van Deerlin *et al*.2010	TMEM106B	Risk factor and disease modifier both in FTLD-TDP	rs1990622 C rs 1020004	515 FLTD	0.61		[103]
				89 GWS-replication cohort			
Venturelli *et al*. 2010	KIF24	Risk factor	rs17350674	284	3.63	-	[110]
Galimberti *et al*. 2010	MCP-1	Protective factor	A2518G	212	0.59	HIV- dementia Alzheimer disease	[132]
Padovani *et al*. 2010	FOXP2	Disease modifier, language	rs1456031	210		Hereditary speech loss Schizofrenia	[138]

PRNP: prion protein; NOS1: neuronal nitric oxide synthase 1; VEGF: Vascular endothelial growth factor; NOS3: nitric oxide synthase 3 (endothelial cell); DCUN1D1: defective in cullin neddylation 1 domain containing 1; UBAP1: Ubiquitin Associated protein 1; TMEM106B: transmembrane protein 106B ; KIF24: kinesin family member 24; MCP-1: Monocyte Chemotactic Protein; FOXP2: forkhead boxP2.

fifth cohort (n=158) from the UK. Additionally, it was reported that levels of *UBAP1* expression were significantly reduced in the *at risk-allele* carriers.

UBAP1 is a member of the ubiquitin-activated enzymes family and it contains two ubiquitin-associated domains (UBA), found in several proteins and in certain TDP-43 pathological inclusions [107]. The UBA are involved in multiple cell functions such as cell signaling, DNA excision repair and in ubiquitine/proteosome pathway [108], pivotal in protecting the central nervous system from the accumulation of toxic protein [109]. The genetic variability within *UBAP1* gene might increase FTLD risk by lowering UBAP1 expression. This is consistent with one of the putative identified mutations (*S391Afs21X*) which removes both of ubiquitin-associated domains thus altering protein function.

Venturelli and colleagues focused on *UBAP-1* and another two candidate genes in the same chromosome region, i.e. Ubiquitin Associated protein 2 (*UBAP-2)* and kinesin family member 24 (*KIF24)* [110]. Nine different SNPs were tested and *KIF24 rs1735067* AA genotype showed a significant association with FTLD (OR: 3.63, 95%CI: 1.58–8.35) and bvFTD (OR: 3.26, 95%CI: 1.40–7.57). *KIF24* encodes for an ATP-kinesin protein, involved in axonal transport, microtubule dynamics and neuronal survival [111]. From a functional point of view, *rs1735067* leads to a non-synonymous aminoacid change (*W218L*), which may affect

protein function. Notwithstanding, the study did not confirm the association between FTLD and *UBAP-1* and no association with *UBAP-2* was found.

DCUN1D1 (defective in cullin neddylation 1, domain containing 1), another gene involved in protein degradation [112], has been described as linked to sporadic FTLD [113]. The study was based on 220 unrelated FTLD patients, and showed an association between *rs4859146* GG genotype and an increased risk for FTLD (OR: 4.39, 95%CI: 1.40–13.78). However, this SNP was not in Hardy-Weinberg equilibrium in the control group and there was no significant allelic association. Additionally, the genetic variation does not lead to an aminoacidic change, thus not affecting the aminoacid sequence.

Further, a common polymorphism (Methionine [M] or Valine [V]) at codon 129 of the prion protein *(PRNP)* gene is known to be a strong susceptibility and disease-modifier factor for human prion disease [114], and influences the three-dimensional conformation of the pathogenic isoform of PrP [115]. Li and colleagues analysed this polymorphism in a cohort of patients with neurodegenerative disorders, including Alzheimer's disease (n=281), ALS (n=256) and patients with Primary Progressive Aphasia (PPA, n=39) [116]. MV genotype was seven times more frequent in PPA patients compared to controls (age-adjusted OR: 8.47, 95%CI: 3.42–21.0). The polymorphism might influence protein function, primarily involved in delivery of copper, cell signalling, and cell-death pathway control [117]. However, these findings have not been confirmed by a study on 66 FTLD patients [118].

Vascular endothelial growth factor (VEGF) is a neurotrophic-vascular factor with a recently discovered key–role in neurodegeneration, beyond its well-known angiogenetic effects [119-121]. Several polymorphisms/haplotypes in the *VEGF* promoter region have been associated with Alzheimer's disease and ALS risk [122-124]. Based on these data, *VEGF* role has been tested in FTLD and an overrepresentation of the A-G-G haplotype (-2578C/A, -1190G/A, -1154G/A) in cases compared to controls was reported [125]. Subsequently, it has been demonstrated that A-G-G haplotype increased the risk of Progressive Supranuclear Palsy and Corticobasal Syndrome [126].

The neuronal nitric oxide synthase 1 (nNOS), coded by *NOS1* gene, is the most abundant isoform expressed in the brain [127]. An overexpression of NOS1 in neuron loss in enthorinal cortex and hippocampus of Alzheimer's disease patients has been showed [128]. Studying *NOS* genetic variations in 71 sporadic FTLD, Venturelli *et al.* [129] suggested a significant increase of T allele among patients (OR: 1.94, 95%CI: 1.15–3.27). This variant is located in an untranslated region of the gene, thus the possible mechanism underlying the association could consist in an alterated nNOS expression. Further studies will be able to explain these preliminary findings.

In the same protein family, the endothelial form of NOS, coded by *NOS3* gene, seems to be involved in different forms of neurodegeneration, and the *NOS3 G894T* polymorphism has recently been associated with FTLD (OR:1.65, 95%CI:1.13–2.42) [130]. The polymorphism results in an aminoacidic substitution at position 298, demonstrated as altering the structural properties and cleavage susceptibility of protein [131].

The effect of inflammation was evaluated in one study, testing the *Monocyte Chemotactic Protein* (*MCP-1*) gene. The authors described the protective role of the *A2518G* polymorphism (OR: 0.59, 95%CI: 0.40-0.87) [132]. This polymorphism, acting in regulatory region of the gene, has been shown to influence MCP-1 expression in response to inflammation stimulus [133-134]. According to this, in the study the presence of G allele was associated with significantly higher MCP-1 cerebrospinal levels [132]. MCP-1 protein could play a role in counterbalancing the neurodegeneration in FTLD.

Finally, *forkhead box P2* (*FOXP2)* is a gene deeply involved in the mechanism facilitating human spoken language [135]. Causative mutations have been found in families with abnormalities of expression and articulation of language [136] and several polymorphisms have been associated with language impairment in patients with schizophrenia [137]. Recently, two different *FOXP2* SNPs have been studied in 211 FTD patients [138]. Although the study did not show any association between these polymorphisms and the risk of FTLD development, *rs1456031* TT and *rs17137124* TT carriers showed worse language performances and greater cerebral hypoperfusion in language-related areas. Thus, it has been suggested that *FOXP2* may be a disease-modifier gene, affecting language impairment in FTLD.

Several other candidate genes have been studied in FTLD patients, with negative results [140-141]. A complete list of studies with negative findings is reported in Table **5**.

CONCLUSIONS

Since the first description of FTLD by Arnold Pick in 1892, great progress has been made in our understanding of the clinical, pathological and genetic mechanisms underlying this heterogeneous disease.

FTLD has been of particular interest to genetists due to its high rate of hereditability with up to 40% of patients reporting a family history. The discovery of genes involved in monogenic forms and their pathological correlation are mandatory for understanding the specific FTLD-neurodegenerative bases. Indeed, besides being the most frequent causes of monogenic FTLD, *MAPT* and *PGRN* polymorphisms are also crucial in increasing FTLD- risk and modifying the disease course.

Variability in genes involved in rarer forms (*CH2MP, VCP, TARDBP, FUS*) has not been demonstrated as playing a significant role in sporadic forms, but studies performed on large samples are still lacking.

It has been claimed that genes involved in other neurodegenerative diseases play a role in FTLD too. First of all, *APOE*, the main recognised genetic risk factor for late-onset Alzheimer disease, has been extensively studied in FTLD with discordant findings. However, even if *APOE* may partially contribute to the pathogenesis of neurodegenerative disorders, it is not a specific determinant for FTLD risk.

Table 5. Negative Studies on at-Risk Genetic Polymorphisms in FTLD

Authors	Gene	SNPs	FTD Case number	Ref
Nicosia *et al*. 2001	A2M	A2M-2 deletion	39	[153]
Fehèr *et al*. 2009	BDNF	Val66Met	39	[154]
Johansson *et al*. 2007	CDC2	Ex6 + 7 II Ex6 + 7I	70	[155]
Ghanim *et al*. 2010	CHMP2B	Sequencing	198	[82]
Villarino-Guell *et al*. 2010	DCTN1	Sequencing	87	[156]
Villa *et al*. 2009	DCUN1D1	rs4859146 rs4859147	220	[113]
Padovani *et al*. 2010	FOXP2	rs2396753 rs1852469	210	[138]
Cantoni *et al*. 2010	FUS/TLS	rs1052532 rs741810	251	[80]
Van Langenhoven *et al*. 2010	FUS	Sequencing	122	[59]
Schaffer *et al*. 2008	GSK3B	IVS2−68G>A g.26161412G>	64 FTD + 47 AD	[157]
Rollinson *et al*. 2009	KIF24	rs34282855	214	[76]
Venturelli *et al*. 2010	KIF24	rs10814083	284	[110]
Hernandez *et al*. 2005	LRRK2	G2019S	40	[158]
Reif *et al*. 2008	MAOA	u-VNTR	62	[140]
Venturelli *et al*. 2009	NOS 3	T786C	222	[130]
Rollinson *et al*. 2009	NUDT 2	rs11788425	214	[76]
Rohrer *et al*. 2006	PRNP	M129V (SNP)-1368	66	[118]
Rollinson *et al*. 2009	RECK	rs1359885	214	[76]
Schumacher *et al*. 2009	TARDBP	10 different SNPs	173	[79]
Rollinson *et al*. 2009	TEK	rs664513	214	[76]
Fenoglio *et al*. 2007	TREM2	rs2234252 rs2234253 rs2234255 rs2234256	56	[139]
Venturelli *et al*. 2010	UBAP1	rs7018487	284	[110]
Rollinson *et al*. 2009	UBAP 2	rs10453201	214	[76]
Venturelli *et al*, 2010	UBAP2	rs307658 rs1785506	284	[110]
Schumacher *et al*. 2009	VCP	27 different SNPs	198	[79]
Borroni *et al*. 2008	VEGF	634(G/C)	161	[125]

A2M: alpha-2-macroglobulin; BDNF: brain-derived neurotrophic factor; CDC2: cell division cycle 2; CHMP2B: chromatin modifying protein 2B; DCTN1: dynactin 1; DCUN1D1: defective in cullin neddylation 1 domain containing 1; FOXP2: forkhead boxP2; FUS/TLS: fused in sarcoma; GSK3B: glycogen synthase kinase 3 beta; KIF24: kinesin family member 24; LRRK2: leucine-rich repeat kinase 2; MAO: monoamine oxidase A; NOS3: nitric oxide synthase 3 (endothelial cell ; NUDT2: nudix (nucleoside diphosphate linked moiety X)-type motif 2; PRNP: prion protein; RECK: reversion-inducing-cysteine-rich protein with kazal motifs; TARDBP: TAR DNA binding protein; TEK: Endotelial Thyrosin Kinase; TREM2: triggering receptor expressed on myeloid cells 2; UBAP1: Ubiquitin Associated protein 1; UBAP2: Ubiquitin Associated protein 2; VCP: valosin-containing protein; VEGF: Vascular endothelial growth factor.

New genetic risk factors have been identified, some modulating disease phenotype.

Proteasome-associated proteins, inflammation determinants, growth factors and proteins involved in speech function have been shown to increase the risk of sporadic FTLD, and to affect clinical presentation, underlying the heterogeneity of the disease. These studies have opened a new chapter in the study of FTLD, but most of them were based on single-center data and relatively small numbers of patients. Additionally, only a few studies used pathological criteria, fundamental for a sub-classification of disease.

The advances in high-throughput and high-density genotyping technology have led to the emergence of genome-wide association studies. Contrary to candidate gene studies, no *a priori* hypothesis studies are needed, making them promising and powerful tools to identify susceptibility genes. In FTD history, the first genome-wide association study has been recently carried out, producing unexpectedly important findings. This is the first step of a new understanding era. However, these data must be validated and replicated in appropriately large patient populations.

The functional characterization of the new associated genes could lead to a better understanding of the pathophysiology of FTLD, opening new therapeutic approaches.

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