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# Frontotemporal Dementia: What About Genetic Forms?

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***Abstract***
*Frontotemporal lobar degeneration (FTLD) is the second most common cause of dementia in adults, after Alzheimer's disease. They are characterized by progressive impairment of cognitive functions, behavioral, language, and/or motor disorders, resulting from degenerative damage that affects the frontal and lateral temporal lobes to a greater extent. DLFTs are characterized by remarkable clinical, neuropathological, and genetic heterogeneity. The major clinical phenotypes are the behavioral variant of FTLD (or frontotemporal dementia, FTD, proper) and the non-fluent/agrammatic and semantic variants of primary progressive aphasia. These cognitive syndromes may be associated with motor neuron damage in amyotrophic lateral sclerosis (ALS). In addition, there are overlaps with atypical Parkinsonian syndromes, such as corticobasal syndrome and progressive supranuclear palsy. FTLDs are underpinned by different neuropathological substrates, with two distinctly more represented forms: the TDP-43 (transactive response DNA binding protein of 43 kDa) and TAU (tubulin associated unit) proteinopathies. Each of these forms presents specific clinical and genetic associations. A genetic cause can be found in up to a third of patients with FTLD. Of the many genes currently identified, the three most important are GRN, C9orf72, and MAPT.*

***Keywords:*** *frontotemporal lobar degeneration, dementia, genetic associations*

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## I. Introduction

Dementia, also known as major neurocognitive disorder, is characterized by a loss of mental faculties that reduces a person's ability to care for themselves independently. There is a decline in performance in one or more cognitive domains, such as memory, complex attention, executive functions (e.g., planning, organization, abstraction), language, visual-motor, functions or social skills. Degenerative dementias, marked by progressive neuronal death, are the most frequent category, with Alzheimer's disease (AD) the leading cause.

Although the majority of dementias, particularly degenerative dementias, are sporadic, they can also run in families. The causative mutations in certain genes are sufficiently penetrating to cause the disease, and are transmitted in a Mendelian or sex-linked fashion. There are also multiple genetic risk factors, which confer a higher risk than the general population, but are neither necessary nor sufficient to induce the disease. The number of such factors discovered is increasing every year, thanks to large-scale genetic case-control studies.

While the identification of dementia-causing genes is essential for a better understanding of these diseases and their pathophysiological mechanisms, it also makes it possible to define new therapeutic targets, and remains indispensable for accurate genetic counseling in these families, with the possibility of presymptomatic diagnosis. The main degenerative dementias that have been genetically identified are:

- Alzheimer's disease.
- Frontotemporal dementia.
- Huntington's disease.

Frontotemporal lobar degeneration (FTLD) includes several clinical forms of the disease: the behavioral form, sometimes associated with amyotrophic lateral sclerosis (FTLD-ALS), non-fluent/agrammatic and semantic variants of primary progressive aphasia, progressive supranuclear palsy (PSP), and cortico-basal syndrome (CBS).

Like most neurodegenerative diseases, DLFTs are associated with the aggregation of insoluble proteins in neurons. Three main pathological subtypes are described according to the protein present in these neuronal inclusions:

- Neuropathological forms characterized by the presence of cytoplasmic or intranuclear neuronal inclusions immunoreactive for TDP-43 (transactive response DNA binding protein 43), make up the FTLD-TDP subclass. These are the most common (50-60%) [1].
- FTLD with TAU protein inclusions (FTLD-TAU) account for 30-40% of pathological series.
- FTLD-FUS, characterized by the presence of FUS-positive inclusions (Fused in Sarcoma), are rarer forms (10%) [50].

- More rarely, proteins linked to the ubiquitin-proteasome system may also aggregate (FTLD-UPS).

TDP-43 and FUS are DNA- and RNA-binding proteins of the heterogeneous nuclear ribonucleoprotein (hnRNP) family. They are involved in various stages of RNA metabolism: regulation of transcription, splicing of pre- messenger RNAs, transport of messenger RNAs, and biosynthesis of micro RNAs [2].

The TAU protein plays an important role in microtubule assembly, stabilization, and axonal transport.

FTLDs are genetically heterogeneous. Today, 19 genes are implicated in familial forms of DLFT associated or not with ALS; the most frequent genetic forms are linked to mutations in three genes, C9ORF72, GRN/PGRN, and MAPT [3].

The genes identified explain almost 80% of familial forms, but also 10-15% of sporadic forms. Knowledge of the different genetic forms of DLFT and their associated phenotypes is now essential in order to offer patients a targeted genetic diagnosis and provide families with appropriate genetic counseling.

## II. Genetics Of DLFT And Associated Clinical Forms

**Phenotype associated with mutations in the C9ORF72 gene:**

The C9ORF72 gene is a major gene that, on its own, explains around 40% of autosomal dominant forms of ALS, 20% of familial forms of DLFT and almost 80% of familial forms combining the two pathologies [3].

The average age of onset is 60, but can vary from 30 to over 80, even within the same family [4]. Although it is an expanding disease, there is no clear correlation between the size of the expansion and the age of onset [5], unlike in other expanding diseases. Nor is there any evidence to date of clinical or molecular anticipation in mutated families [4].

Most mutated patients present with behavioral DLFT, ALS, or FTLD-SLA [4]. Particular "DLFT phenocopy " forms have been described, characterized by remarkably slow progression of cognitive and behavioral disorders, mildly altered neuropsychological scores, and mild atrophy lasting several years. Forms beginning with progressive non-fluent aphasia or a semantic form are much less frequent [4].

ALS differs little from non-genetic cases, although initial bulbar symptoms and cognitive deterioration (47%) are more frequent [5]. Psychiatric symptoms are remarkably frequent in patients with the C9ORF72 mutation [6]. Visual or auditory hallucinations, obsessive-compulsive disorders or a psychotic picture (hallucinatory or schizophreniform psychosis, bipolar disorder or hypomania) precede or appear at the same time as the first symptoms of DLFT, in 10% to 53% of mutated patients [3].

More rarely, the disease is revealed by a parkinsonian syndrome suggestive of Parkinson's disease or a Parkinsonian syndrome [7], or by isolated episodic memory disorders mimicking Alzheimer's disease, in which case it is the negativity of CSF biomarkers and the presence of a family history of FTLD/SLA that guide the diagnosis.

Neuropathological lesions associated with C9ORF72 gene expansions consist of TDP-43-positive neuronal inclusions (type A or B), associated with UPS "p62"-positive /TDP-43-negative inclusions, particularly in hippocampal and cerebellar neurons [8]. The function of the C9ORF72 protein and the pathogenic effect of the atypical non-coding expansion remain unclear.

**Phenotype associated with progranulin gene mutations (GRN/PGRN):**

GRN mutations were identified in 2006 in patients with an autosomal dominant form of FTLD associated with TDP-43-positive intranuclear and cytoplasmic neuronal inclusions [9,10].The GRN gene encodes progranulin, a growth factor with multiple functions in the inflammatory response, tumorigenesis, and tissue repair.

The function of progranulin in the central nervous system is still largely speculative. It promotes neuritic growth and survival of cortical and motor neurons in culture, and could therefore have a neurotrophic effect.

It also plays a role in neuroinflammatory mechanisms. The mechanisms of neurodegeneration in FTLD with GRN mutations are not known. Mutations in the GRN gene produce mutated RNA, which is degraded without being translated [9,10]. The result is a partial loss of function of progranulin, which is expressed at only 50% of its physiological level. Neuronal degeneration could be linked to the loss for progranulin function and, in particular, its neurotrophic function or its role in neuroinflammation.

Mutations in the GRN gene represent the second most frequent cause of autosomal dominant FTLD since the identification of abnormal expansions in the C9ORF72 gene. The types of mutations (nonsense, small insertions or frame-shifting deletions, splice-site mutations) point to a loss-of-function mechanism. This has been confirmed by the demonstration of reduced plasma progranulin levels in patients with mutations [11].

In this genetic form, the age of onset varies between 40 and 85 years, with an average of 65 years. Penetrance is not complete, with an estimated 90% at 75 years of age [12].

Clinical presentations are extremely variable, even within the same family. The most frequent

presentations are a behavioral form of FTLD [9,10], progressive non-fluent aphasia [13], or cortico-basal syndrome [14]. More rarely (5%), the clinical picture may be suggestive of AD.

Progranulin is a secreted protein that can be measured in the plasma. When low, progranulinemia is a good predictor of GRN mutations [15]. This assay is used in clinical practice to identify patients for whom confirmatory molecular analysis is warranted.

**Phenotypes associated with mutations in the MAPT gene:**

Mutations in this gene, which directly encodes the Tau (tubulin associated unit) protein, both a microtubule stabilizer and a major constituent of the intraneuronal inclusions of tauopathies, are responsible for DLFT of autosomal dominant transmission. The disease begins earlier than in other genetic forms, on average at the age of 55. Penetrance is almost complete by the age of 65.

Patients with MAPT mutations present two major phenotypic forms dominated by behavioral disorders or an atypical parkinsonian syndrome [16]. The most common presentation is behavioral DLFT, often associated with verbal semantic disorders early in the disease. In other cases, MAPT mutations may produce a clinical picture of PSP or a cortico-basal syndrome [16]. Brain imaging shows bilateral, often symmetrical, frontal, and temporo- polar involvement.

**Phenotypes associated with VCP gene mutations:**

Mutations in the VCP gene are responsible for a particular syndrome of autosomal dominant inheritance, named IBMPFD for inclusion body myopathy (IBM), the most common phenotype, Paget disease of bone (P), and frontotemporal dementia (FD) [17]. These clinical syndromes may be present in the same person or family, but the classic triad is rarely complete in a single patient [18]. Diagnosis can be difficult, as the most frequent presentation is muscular at an average age of 42 years, which may mimic limb-girdle myopathy, and Paget's disease of the bone may be asymptomatic. The family genetic investigation and radiological/biochemical work-up of Paget's disease are therefore decisive in identifying a mutation in this gene.

More recently, VCP mutations have been identified in families with ALS phenotypes [19], further enriching the phenotypic spectrum. Some authors now prefer the term multisystem proteinopathy, encompassing IBMPFD and ALS due to VCP mutations or with comparable phenotypes in hnRNPA2B1 and hnRNPA1 gene mutations [20]. Pathologically, VCP mutations are responsible for TDP43-positive DLFT-Us, and in muscle, the presence of bordered vacuoles leads to the diagnosis of inclusion myopathy.

## III. Genetic Risk Factors For FTLD

The first gene to be investigated as a risk factor for DLFT was APOE, well known for its impact on AD. Indeed, some studies have shown that there is also an increased risk of developing DLFT in individuals carrying APOE4 [21]. Apart from causative mutations, certain MAPT variations, notably synonymous ones, i.e., those that do not change the amino acid composition of the protein, could be involved as a risk factor for FTLD [22].

Finally, as in AD, genome-wide association studies (GWAS) have been carried out in DLFT and have identified TMEM106B [23], leading secondarily to modulation of GRN expression, and very recently two loci [24]: 6p21.3, including the HLA locus (involved in the immune system), and 11q14, including RAB38/CTSC (involved in trafficking within the lysosome).The change in DLFT risk associated with these loci remains very moderate, but reinforces the involvement of the immune system and lysosomal pathways in the pathological processes involved.

## IV. Diagnostic Approach To FTLD

Because of the diversity of FTLD expression, Le Ber et al. under the aegis of the national center for references on rare dementia [15], have proposed a decision tree for clinically-based genetic testing (Cf. Fig.1).

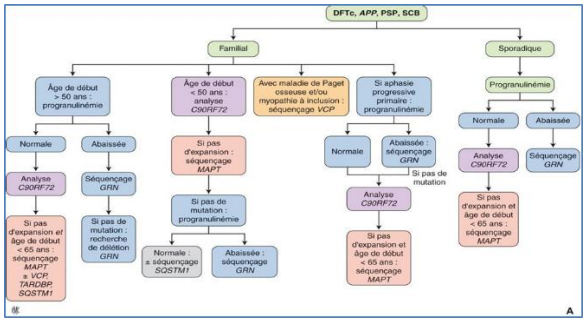


**Figure 1: Genetic investigations for the molecular diagnosis of frontotemporal lobar degeneration.**

## V. Conclusion

FTLD are complex and heterogeneous diseases. This term covers a wide spectrum of clinical disorders (bvFTD, PNFA, SD, PSP, CBDS, and FTLD-ALS), establishing a continuum with ALS on the one hand and parkinsonian syndromes on the other. The high intrafamilial variability of phenotypes underlines the necessity of a careful interview concerning the family history of patients, not only regarding the FTLD spectrum of disease but also other neurodegenerative and extra-neurological disorders. The identification of several FTLD genes during the last decade has increased our knowledge of biological mechanisms.

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