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Genetics of frontotemporal lobar degeneration

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Frontotemporal lobar degeneration (FTLD), the most frequent neurodegenerative disorder with a presenile onset, presents with a spectrum of clinical manifestations, ranging from behavioral and executive impairment to language disorders and motor dysfunction. Familial aggregation is frequently reported, and about 10% of cases have an autosomal dominant transmission. Microtubule associated protein tau (*MAPT*) gene mutations have been the first ones identified and are associated with early onset behavioral variant frontotemporal dementia phenotype. More recently, progranulin gene (*GRN*) mutations were recognized in association with familial form of FTLD. In addition, other genes are linked to rare cases of familial FTLD. Lastly, a number of genetic risk factors for sporadic forms have also been identified. In this review, current knowledge about mutations at the basis of familial FTLD will be described, together with genetic risk factors influencing the susceptibility to FTLD.

Keywords: genetics, frontotemporal lobar degeneration, autosomal dominant, mutation, risk factor

NEW DIAGNOSTIC CRITERIA OF FRONTOTEMPORAL LOBAR DEGENERATION

Frontotemporal lobar degeneration (FTLD) represents a common cause of dementia in subjects under 65 years. The age at onset is typically 45–65 years, with a mean average in the 50s, and the prevalence is equal among men and women. It is associated with frontal and temporal lobe atrophy, involving the right and left hemispheres, in some cases asymmetrically (Rosen et al., 2006). It can be classified into two main cognitive syndromes (Neary et al., 1998): behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA), whose diagnostic criteria have been recently revised including neuroimaging and genetics (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

Behavioral variant frontotemporal dementia is the most frequent FTLD phenotype, characterized by behavioral alterations, such as disinhibition, overeating, and impulsiveness, and impairment of cognitive functions, with relative sparing of memory (Hou et al., 2004). Changes in social behavior, loss of empathy, and impairment of social insight are early and consistent symptoms of bvFTD, whose importance and role for the early diagnosis has been emphasized in the new consensus criteria (Rascovsky et al., 2011). According to these criteria, bvFTD main feature is the progressive deterioration of behavior and/or cognition by observation or history. If this criterion is satisfied, there are three further levels of certainty for bvFTD: possible, probable, or definite. "Possible" bvFTD requires three out of six clinically discriminating features (disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, and dysexecutive neuropsychological profile). "Probable" bvFTD meets the criteria of "possible" bvFTD plus (1) a significant functional decline (by caregiver report or evidenced at neuropsychological testing) (2) frontal and/or anterior temporal atrophy on MRI or CT, or frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT. "Definite" bvFTD imply the histopathological evidence of FTLD on biopsy or post mortem or the presence of a known pathogenic mutation. These new criteria have a flexible structure to account for the high heterogeneity at initial presentation.

Early and progressive changes in language functions represent the alternative presentation of FTLD. Progressive loss of speech, with hesitant, non-fluent speech output with phonetic/phonological errors, and distortions and/or agrammatism is typical of primary non-fluent aphasia (PNFA) subtype (Scarpini et al., 2006), whereas loss of knowledge about words and objects, anomia and single-word comprehension deficits are core features of the semantic variant of PPA, named semantic dementia (SD; Gorno-Tempini et al., 2011). A third subtype of PPA has been recently described as logopenic or phonological variant (LPA). It is characterized by phonological disorders, defective word retrieval, and sentence repetition deficits. This PPA subtype seems to be associated with underlying Alzheimer's disease (AD) pathology (Rabinovici et al., 2008).

GENETICS: AUTOSOMAL DOMINANT MUTATIONS

The presence of familial aggregation and the autosomal dominant transmission of the disease suggested so far a genetic cause (Snowden et al., 2002; Bird et al., 2003; Goldman et al., 2005). Up to 40% of patients have a family history suggesting FTLD in at least one extra family member (Goldman et al., 2005; Pickering-Brown, 2007), with a percentage of autosomal dominant cases accounting for 13.4% of the total (Goldman et al., 2005).

New criteria for bvFTD diagnosis (Rascovsky et al., 2011) include the presence of a known mutation as a biomarker. The demonstration of an autosomal dominant mutation is

requested for the diagnosis of "definite" bvFTD, and is the only criterion existing so far to make a definite diagnosis during life. Genes demonstrated to be responsible for familial FTLD include: microtubule associated protein tau (*MAPT*) gene, progranulin (*GRN*), valosin-containing protein (*VCP)-1*, chromatin-modifying 2B (*CHMP2B*), TAR-DNA binding protein 43 encoding gene (*TARBDP*), and, very recently, a novel hexanucleotide expansion in chromosome 9 (Dejesus-Hernandez et al., 2011; Renton et al., 2011).

MICROTUBULE ASSOCIATED PROTEIN TAU GENE

The first evidence of a genetic cause for familial FTLD came from the demonstration of a linkage with chromosome 17q21.2 in autosomal dominantly inherited form of FTD with parkinsonism (Lynch et al., 1994) resulting in the label of "frontotemporal dementia and parkinsonism linked to chromosome 17" (FTDP-17). The gene responsible for such association, named *MAPT* gene, was discovered few years later (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998). *MAPT* encodes the microtubule associated protein Tau, which is involved in microtubule stabilization and assembly. To date, more than 40 pathogenic *MAPT* mutations have been described in 134 families (http://www.molgen.ua.ac.be/). *MAPT* mutations can be non-synonymous, deletions, or intronic mutations located close to the splice-donor site of the intron after the alternatively spliced exon 10 (Rademakers et al., 2004). They are mainly clustered in exons 9–13, which contain the microtubule binding regions (Rademakers et al., 2002) and affect the normal function of tau, i.e., the stabilization of microtubules promoting their assembly by binding tubulin. Some mutations increase the free cytoplasmic portion of the protein promoting tau aggregation, whereas others lead to an aberrant phosphorylation of tau protein, which damages microtubule stabilization (Buée and Delacourte, 1999; Goedert and Jakes, 2005). Otherwise, many other mutations affect the alternative splicing, thus producing altered ratios of the different isoforms (3R/4R tau; Goedert et al., 1989). At autopsy, patients with *MAPT* mutations show tau-positive inclusions (Rademakers et al., 2004).

The clinical presentation in *MAPT* mutation carriers in mainly consistent with bvFTD, with a mean onset in the 50s (Yancopoulou and Spillantini, 2003; Villa et al., 2011). Nevertheless, cases of PNFA have been reported as well, with an onset even in the sixth decade of life (Villa et al., 2011).

PROGRANULIN GENE

After the discovery of *MAPT* as causal gene for FTDP-17, there were still numerous autosomal dominant FTLD cases genetically linked to the same chromosomal region of *MAPT* (chr17q21), in which no pathogenic mutations had been identified. A small region rich of genes, localized approximately 6.2 Mb in physical distance to *MAPT* locus, had been recognized as that one containing the gene responsible for the disease in these families. Systematic sequencing of candidate genes within this minimal region was performed and the first mutation in progranulin gene (*GRN*) was identified. It consists of a 4-bp insertion of *CTGC* between coding nucleotides 90 and 91, causing a frameshift and premature termination in progranulin (C31LfsX34; Baker et al., 2006). Cruts et al. (2006), analyzing other families with a FTLD pathology without *MAPT* mutation, found at the same time another mutation of five base pairs into the intron following the first non-coding exon of the *g*ene (IVS0 + 5G–C). This mutation causes the splicing out of the intron 0, leading the retention of mRNA within the nucleus and its degradation.

GRN gene encodes for the growth regulation factor progranulin, belonging to a family of proteins involved in many biological functions including development, wound repair, and inflammation by activating signaling cascades that control cell cycle progression (He and Bateman, 2003). Progranulin is a 593 amino acid protein, rich of cysteine with a molecular weight of 68.5 kDa, subjected to proteolysis by elastase in a process regulated by a secretory leukocyte protease inhibitor (SLPI; Zhu et al., 2002). It is expressed not only in neurons but also is the activated microglia (Baker et al., 2006).

Since the original identification of null-mutations in FTLD in 2006, 69 different mutations have been described so far (http://www.molgen.ua.ac.be/) in 231 families. Most of the known pathogenic *GRN* mutations, including frameshift, splice-site, and nonsense mutations, are predicted to result in a premature stop codon. The resulting aberrant mRNA is degraded through the process of nonsense mediated decay, leading to haploinsufficiency (Gass et al., 2006).

Clinically, mutations in *GRN* are associated with extremely heterogeneous phenotypes, including, besides the classical FTLD presentations, AD (Carecchio et al., 2009), corticobasal syndrome (CBS; Carecchio et al., 2011), or Mild Cognitive Impairment (Pietroboni et al., 2011). Age at disease onset is extremely wide, even in the same family (Pietroboni et al., 2011). In addition, the demonstration of the clinical overlap between psychiatric disorders and genetically determined FTLD comes from the recent description of a patient with heterosexual pedophilia (Rainero et al., 2011), who was a carrier of a *GRN* mutation and developed bvFTD over time, and from a second description reporting two clinically different, apparently sporadic FTLD cases sharing the previously described Thr272fs *GRN* mutation, who had had a premorbid bipolar disorder history (Cerami et al., 2011).

A major contribution to achieve a correct diagnosis independent of the phenotypic presentation is the demonstration that progranulin plasma levels are extremely low in *GRN* mutation carriers, even in asymptomatic subjects (Ghidoni et al., 2008; Finch et al., 2009; Carecchio et al., 2011; Pietroboni et al., 2011).

Notwithstanding the striking proximity of *MAPT* and *GRN* on chromosome 17, at this time, there is no clear link between these two genes, suggesting that their closeness is just a coincidence.

GRN-mutated FTLD cases at the neuropathological examination presented ubiquitin immunoreactive cytoplasmic and intranuclear neuronal inclusions similar to the microvacuolar-type still observed in a large proportion of apparently sporadic FTLD, and differing from the tau-positive inclusions typical of *MAPT* mutated cases. Soon after the identification of *GRN* mutation, truncated, and hyperphosphorylated isoforms of the TAR–DNA binding protein (TDP)-43 were recognized as main components of the ubiquitin-positive inclusions typical of the *GRN*-mutated families, as well as of idiopathic FTLD and of a proportion of amyotrophic lateral sclerosis (ALS) cases (Neumann et al., 2006).

GRN mutations account for about 5–10% of all FTD cases, markedly varying depending on the population considered (Cruts et al., 2006; Gass et al., 2006; Snowden et al., 2006). A collaborative study (Yu et al., 2010) analyzing *GRN* mutations in 434 FTLD patients, clinically ranging from bvFTD to PNFA, FTLD associated with parkinsonism or MND, estimates a frequency of 6.9% of all included FTLD-spectrum cases. In these cases, the 56.2% was represented by FTLD-U-diagnosed subjects with a known familial history of FTD, pathologically confirmed. Clinical information were available for 31 *GRN* mutation-positive patients: the most common phenotype was bvFTD ($n = 24$), while 3 patients were diagnosed with PNFA, 3 with AD, and 1 with CBS (Yu et al., 2010).

CHROMATIN-MODIFYING 2B

Few FTLD families display mutations in the *CHMP2B* gene, which encodes a component of the heteromeric endosomal sorting complex required for transport (ESCRT III complex) involved in the endosomal trafficking and degradation (Skibinski et al., 2005). To date, only four different mutations between or in the exons 5 and 6 have been so far described in five families (http://www.molgen.ua.ac.be/), making *CHMP2B* an extremely rare genetic cause of FTLD pathology. Neuropathologically, patients with *CHMP2B* mutations present FTLD-U with ubiquitin-positive but TDP-43-negative cytoplasmic inclusions (Holm et al., 2007). Behavioral and cognitive impairment associated with extrapyramidal and pyramidal signs are the main clinical manifestations in *CHMP2B* mutation carriers. Myoclonus can occur late in the course of the disease (Gydesen et al., 2002) and motor neuron disorders have been described in only two cases (Parkinson et al., 2006).

VALOSIN-CONTAINING PROTEIN-1

Some familial cases having mutations in the *VCP*-1 gene were reported (Watts et al., 2004). However, the phenotype associated with such mutations is inclusion body myopathy, Paget's disease of bone and less frequently FTD (IBMPFD; Kimonis et al., 2008). Myopathy is the more frequent clinical symptom, present in about 90% of affected subjects, whereas FTD is seen in about 30%, usually many years after the onset of muscle symptoms.

TARDBP

The most common clinical phenotype associated with *TARDBP* mutations is ALS, and aggregates made of TDP-43 have been described in brain and spinal cord of such patients. Nevertheless, *TARDBP* mutated subjects can present also parkinsonism in association with motor neuron dysfunction (see Pesiridis et al., 2009 for review). At present, *TARDBP* mutations have been found in 5% of familiar ALS and only rarely in FTD and FTD–MND subjects (Benajiba et al., 2009; Borroni et al., 2009).

Chr 9 HEXANUCLEOTIDE REPETITION

Lastly, one of the most intriguing discovery in the genetics of FTLD has been the investigation of FTD/MND families linked to a locus on chromosome 9q21-22. The first evidence of linkage with this locus comes from a study carried out in families with FTD–MND (Hosler et al., 2000). After some others reports confirming the linkage to chr9q21-22 in additional FTD–MND families (Morita et al., 2006; Rollinson et al., 2011), and a search lasting more than a decade, in 2011, two groups of researchers identified the gene responsible for the disease, the chromosome 9 open reading frame 72 (*C9ORF72*). Both these studies (Dejesus-Hernandez et al., 2011; Renton et al., 2011) reported a large hexanucleotide (*GGGGCC*) repeat expansion in the first intron of *C9ORF72* as responsible for a high number of familiar ALS or combined FTD–MND phenotype and TDP-43 based pathology. This mutation causes the loss of one alternatively spliced transcript, whose function is still unknown, and the formation of nuclear RNA foci. Wild-type alleles contain no more than 23–30 repeats, whereas mutated alleles have more than 100 repeats. These studies thus demonstrated that *C9ORF72* mutation is at present a major cause of both familiar FTD (12%) and ALS (22.5%) cases (Dejesus-Hernandez et al., 2011), with a higher prevalence in the northern population, reaching a prevalence of 46% of all familiar ALS, 21.1% of sporadic ALS, and 29.3% of FTD in the Finnish population (Renton et al., 2011). Clinically, the large clinical series reported in these studies show that the predominant phenotypes are consistent with bvFTD and ALS, with different phenotypic presentation even in the same family (i.e., FTD, ALS, or a combination of both). From the FTD series reported in Dejesus-Hernandez et al. (2011) study, 26.9% FTLD cases had concomitant ALS and more than 30% had relatives affected with ALS.

CONCLUSIVE REMARKS

In the last few years, it has become clear that there are multiple genetic autosomal dominant mutations leading to the development of FTLD. The most frequent are so far *MAPT* and *GRN* mutations that are associated with high phenotypic variability. Whereas the majority of *MAPT* mutations is characterized by an early onset of symptoms and is associated with a clear segregation across generations, age at disease onset is very wide in *GRN* mutation carriers. According to the most recent discoveries, the large hexanucleotide (*GGGGCC*) repeat expansion in the first intron of *C9ORF72* is not only one of the most frequent mutation associated with ALS and FTD–MND, but is also the second most frequent in FTLD, after *GRN* mutations (Gijselinck et al., 2012). Given the incomplete penetrance of such mutations, a number of cases are apparently sporadic, making more difficult to suspect the presence of a causal mutation. Regarding genetic counseling, at present no international shared guidelines are available.

GENETICS: RISK FACTORS

The first candidate-gene studied in FTLD was the well-known risk factor for late onset sporadic AD, *APOE*. A number of studies suggested an association between FTLD and *APOE∗4* allele (Farrer et al., 1995; Helisalmi et al., 1996; Gustafson et al., 1997; Stevens et al., 1997; Fabre et al., 2001; Bernardi et al., 2006). Nevertheless, other authors did not replicate these data (Geschwind et al., 1998; Riemenschneider et al., 2002; Short et al., 2002). Additional findings demonstrated an association between the *APOE∗4* allele and FTLD in males, but not females (Srinivasan et al., 2006). An increased frequency of the *APOE∗4* allele has been described in patients with SD compared to those with FTD and PNFA (Short et al., 2002).

Concerning the *APOE*2* allele, Bernardi et al. (2006) showed a protective effect of this allele toward FTLD, whereas other authors failed to do so (Riemenschneider et al., 2002; Short et al., 2002; Engelborghs et al., 2003; Srinivasan et al., 2006). A meta-analysis comprising a total of 364 FTD patients and 2671 controls demonstrated an increased susceptibility to FTD in *APOE*2* carriers (Verpillat et al., 2002).

Besides pathogenic mutations, several polymorphisms have been described both in *MAPT* and *GRN*. In Baker et al. (1999), two common *MAPT* haplotypes, named H1 and H2, were identified. They differ in nucleotide sequence and intron size, but are identical at the amino acid level. Homozygosis of the more common allele H1 predisposes to Progressive Supranuclear Palsy and CBS, but not to AD or Pick Disease (Baker et al., 1999; Di Maria et al., 2000).

A contribution of *GRN* genetic variability in sporadic FTLD has previously been shown (Rademakers et al., 2008), even though another study did not confirm these data (Rollinson et al., 2011). A further association analysis demonstrated that a single nucleotide polymorphism (SNP) in the *GRN* promoter influences the risk for FTLD (Galimberti et al., 2010).

A known polymorphism (*A-2518G*) in monocyte chemoattractant-1 (*MCP-1*) gene has been shown to exert a protective effects toward the development of FTLD (Galimberti et al., 2009), whereas Nitric Oxide Synthase (*NOS*)*3 G894T* (Glu298Asp) and *NOS1 C276T* SNPs likely increase the risk to develop FTLD (Venturelli et al., 2008, 2009). Further genetic risk factors, discovered on a candidate-gene basis, include BCL2-associated athanogene 1 (*BAG1*), an anti-apoptotic factor that interacts with tau and regulates its proteasomal degradation (Venturelli et al., 2011), *KIF24* (Venturelli et al., 2010), and defective in cullin neddylation 1 (DCN-1)-domain containing 1 (*DCUN1D1*; Villa et al., 2009).

Van Deerlin et al. (2010) reported the results of the first genome-wide association study (GWAS) on 515 individuals affected by FTLD with autopsy-proven TDP-43 inclusions pathology (FTLD–TDP) compared with 2509 healthy controls, showing an association with three SNPs mapping to a single linkage disequilibrium block on 7p21. This region contains the gene *TMEM106B*, whose variants may increase the risk to develop the disease by increasing *GRN* gene expression.

This association was confirmed in an independent Flanders–Belgian cohort of FTLD patients ($n = 288$; van der Zee et al., 2011). However, these findings were not confirmed by replication study performed in two clinical FTLD cohorts of British origin (Rollinson et al., 2011). Though these authors failed to detect any association of *TMEM106B*, the analysis of chromosome 9 locus revealed strong association in the London FTLD cohort and in the FTLD/ALS cases of the Manchester cohort, later confirmed with the discovery of the *C9ORF72* gene (Dejesus-Hernandez et al., 2011; Renton et al., 2011).

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