Review Article
Genetics and biology of Alzheimer's disease and frontotemporal lobar degeneration

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia in the elderly, whereas frontotemporal lobar degeneration (FTLD) is the most frequent neurodegenerative disorder with a presenile onset. The two major neuropathologic hallmarks of AD are extracellular Amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). Conversely, in FTLD the deposition of tau has been observed in a number of cases, but in several brains there is no deposition of tau but instead a positivity for ubiquitin. In some families these diseases are inherited in an autosomal dominant fashion. Genes responsible for familial AD include the Amyloid Precursor Protein (*APP*), Presenilin 1 (*PS1*) and Presenilin 2 (*PS2*). The majority of mutations in these genes are often associated with a very early onset (40-50 years of age). Regarding FTLD, the first mutations described are located in the Microtubule Associated Protein Tau gene (*MAPT*). Tau is a component of microtubules, which represent the internal support structures for the transport of nutrients, vesicles, mitochondria and chromosomes within the cell. Mutations in *MAPT* are associated with an early onset of the disease (40-50 years), and the clinical phenotype is consistent with frontotemporal lobar degeneration (FTD). Recently, mutations in a second gene, named progranulin (*GRN*), have been identified in some families with FTLD. Progranulin is expressed in neurons and microglia and displays anti-inflammatory properties. Nevertheless, it can be cleaved into granulins which, conversely, show inflammatory properties. The pathology associated with these mutations is most frequently characterized by the immunostaining of TAR DNA Binding Protein 43 (TDP-43), which is a transcription factor. The clinical phenotype associated with *GRN* mutations is highly heterogeneous, including FTD, Progressive Aphasia, Corticobasal Syndrome, and AD. Age at disease onset is variable, ranging from 45 to 85 years of age. The majority of cases of AD and FTLD are however sporadic, and likely several genetic and environmental factors contribute to their development. Concerning AD, it is known that the presence of the e4 allele of the Apolipoprotein E gene is a susceptibility factor, increasing the risk of about 4 fold. A number of additional genetic factors, including cytokines, chemokines, Nitric Oxide Synthases, contribute to the susceptibility for the disease. Some of them also influence the risk to develop FTLD. In this review, current knowledge on molecular mechanisms at the basis of AD and FTLD, as well as the role of genetics, will be presented and discussed.

Keywords: Alzheimer's disease, frontotemporal lobar degeneration, mutation, genetics, amyloid, tau, TDP-43, inflammation, oxidative damage

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with a prevalence of 5% after 65 years of age. The disease was originally described by Alois Alzheimer and Gaetano Perusini in 1906, and it is clinically characterized by a progressive cognitive impairment, including impaired judgment, decision-making and orientation, often accompanied, in later stages, by psychobehavioural disturbances as well as language impairment. The two major neuropathologic hallmarks of AD are extracellular beta-amyloid (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). The production of Aβ, which represents a crucial step in AD pathogenesis, is the result of the cleavage of a bigger precursor, named Amyloid precursor protein (APP), which is over-expressed in AD [1]. Aβ forms highly insoluble and proteolysis resistant

fibrils known as "senile plaques".

Neurofibrillary tangles are composed of the tau protein. In healthy controls, tau is a component of microtubules, which are the internal support structures for the transport of nutrients, vesicles, mitochondria and chromosomes within the cell. Microtubules also stabilize the growing axons, which are necessary for the development and growth of neuritis [1]. In AD, tau protein is abnormally hyperphosphorylated and forms insoluble fibrils, which originate deposits within the cell.

APP gene family

The human *APP* gene was first identified in 1987 by several laboratories independently. The two *APP* homologous, *APLP1* and *APLP2,* were discovered several years later. APP is a type I membrane protein. Two predicted cleavages, one in the extracellular domain (β-secretase cleavage) and another in the transmembrane region (g-secretase cleavage) are necessary to release Aβ from the precursor protein. Notably, *APP* is located on chromosome 21, and this provided an immediate connection to the invariant development of AD pathology in trisomy 21 (Down's syndrome) individuals. The first mutations demonstrated to be causative of inherited forms of familial AD were identified in the *APP* gene [2], providing an evidence that APP plays a central role in AD pathogenesis. Importantly, only *APP* but not its homologous *APLP1* and *APLP2* contain sequences encoding the Aβ domain.

APP processing

Full-length APP undergoes sequential proteolytic processing. It is first cleaved by α-secretase (non-amyloidogenic pathway) or β-secretase (amyloidogenic pathway) within the luminal domain, resulting in the shedding of nearly the entire ectodomain and generation of α- or β-C-terminal fragments (CTFs). The major neuronal β-secretase, named BACE1 (β-site APP cleaving enzyme), is a transmembrane aspartyl protease which cleaves APP within the ectodomain, generating the N-terminus of Aβ [3]. Nevertheless, several zinc metalloproteinases such as TACE/ADAM17, ADAM9, ADAM10 and MDC-9, and the aspartyl protease BACE2, can cleave APP at the α-secretase site [4] located within the Aβ domain, thus precluding the generation of intact Aβ.

The second proteolytic event in APP processing involves intramembranous cleavage of α- and β-CTFs by g-secretase, which liberates a 3kDa protein (p3) and Aβ peptide into the extracellular milieu. The minimal components of g-secretase include presenilin (PS)1 or PS2, nicastrin, APH-1 and PEN-2 [5]. Protein subunits of the g-secretase assemble early during biogenesis and cooperatively mature as they leave the endoplasmic reticulum. Biochemical evidence is consistent with PS1 (or PS2) as the catalytic subunit of the g-secretase. APH-1 and PEN-2 are thought to stabilize the g-secretase complex, and nicastrin to mediate the recruitment of APP CTFs to the catalytic site of the g-secretase. Major sites of g-secretase cleavage correspond to positions 40 and 42 of Aβ.

Amyloidogenic processing is the favoured pathway of APP metabolism in neurons, due to the greater abundance of BACE1, whereas non-amyloidogenic pathway predominates in other cell types. It appears that none of the above mentioned secretases have unique substrate specificity towards APP. Besides APP, a number of other transmembrane proteins undergo ectodomain shedding by enzymes with α-secretase activity. Regarding BACE1, its low affinity for APP lead to the hypothesis that APP is not its sole physiological substrate. Similarly, PS1 and PS2 play a crucial role in intramembranous g-secretase cleavage of several type I membrane proteins other than APP, including Notch1 receptors and its ligands [6].

APP role

A number of functional domains have been mapped to the extra- and intracellular region of APP, including metal (copper and zinc) binding, extracellular matrix components (heparin, collagen and laminin), neurotrophic and adhesion domains. Thus far, a thropic role for APP has been suggested, as it stimulate neurite outgrowth in a variety of experimental settings. The N-terminal heparin-binding domain of APP also stimulates neurite outgrowth and promotes synaptogenesis. In addition, an "RHDS" motif near the extralumenal portion of APP likely promotes cell adhesion, possibly acting in an integrin-like manner. Similarly, APP colocalizes with integrins on the surface of axons at sites of adhesion [7, 8].

Despite APP was initially proposed to act as a cell surface receptor, the evidence supporting this hypothesis has been unconvincing. Only recently, aside of from interactions with extracellular matrix proteins, a candidate ligand has been proposed. In was in fact reported that F-spondin, a neuronal secreted signalling glycoprotein that may function in neuronal development and repair, binds to the extracellular domain of APP as well as of APLP1 and APLP2 [9]. This binding reduces β-secretase cleavage of APP, suggesting therefore that F-spondin binding may regulate APP processing.

APP-deficient animals are a useful model to better understand the role of APP. Deficient APP mice did not show major phenotypic abnormalities [10]. However, *APLP2⁻/⁻/APLP1⁻/⁻* and *APP⁻/⁻/APLP2⁻/⁻* mutants, but not *APP⁻/⁻/APLP1⁻/⁻* animals, showed early postnatal lethality, indicating that members of the APP gene family are essential genes, which exhibit partial overlapping functions. Deficiency of all the *APP* genes lead to death shortly after birth. The majority of animals studied showed cortical dysplasia suggestive of migrational abnormalities of the neuroblasts and partial loss of cortical Cajal Retzius cells [11]. Taken together, these findings presented a convincing picture that members of the *APP* family play essential roles in the development of the nervous system related to synapse structure and function as well as in neuronal migration.

Given the trophyc properties of APP, it would be natural to predict that overexpression of APP would lead to phenotypes related to the enhanced neurite outgrowth and cell growth, which indeed was demonstrated [12]. However, convincing negative phenotypes, in which APP does not act as trophyc factor, has been reported as well. For example, over-expression of APP in cells induced to differentiate into neurons lead to cell death [13]. Genetic in-vivo engineering to over-express APP carrying various familial AD mutations in transgenic mice resulted in the development of Aβ deposition and Aβ associated changes in the brain, including loss of synaptic markers, thus confirming the pathogenic nature of these mutations. A detailed examination also showed axonal swellings and varicosities, which were observed months before any evidence of Aβ-deposition [14].

In this model, tau deposition occurs as a consequence of a deregulation of its phosphorylation induced by Aβ deposition [15]. Basing on this hypothesis, new drugs aimed to block tau deposition are under development.

Tau and Alzheimer's disease

Tau is relatively abundant in neurons but is present in all nucleated cells and functions physiologically to bind microtubules and stabilize microtubule assembly for polymerization. Tau encoding gene (*MAPT: Microtubule Associating Protein Tau*) consists of 16 exons. In the adult brain, alternative splicing of tau nuclear RNA transcribed on exons 2, 3, and 10, results is six tau isoforms, having either three or four peptide repeats of 31 or 32 residues in the C terminal region encoded on exon 10, comprising the microtubule binding domain or differing in the expression of zero, one or two inserts encoded on exon two and three. During neurodegeneration, tau is abnormally phohphorylated. The profile of alternative splicing differs among phatological phenotypes, such that tau accumulation in AD is a mixture of 3R and 4R tau, Pick disease tends to be 3R tau, corticobasal degeneration and progressive supranuclear palsy tends to be 4R tau, and so-called argyrophilic grain disease accumulates small inclusions comprised of 3R tau [16].

Familial Alzheimer's disease

In 1987, a region of linkage with AD was reported on the long arm of chromosome 21, which encompassed a region harboring the *β-APP* gene*,* a compelling candidate for AD [17]. The gene is located at chromosome 21q21.22 and encodes for a transmembrane protein that is normally processed into amyloid fragments. In 1991, the first missense mutation in APP was reported [18].Since then, 32 different mutations have been described in the *β-APP* gene in 89 families (http://molgen-www.uia.ac.be). All these mutations cause amino acid changes in putative sites for the cleavage of the protein, thus altering the APP processing, such that more pathological Aβ42 is produced [15]. Interestingly, the chromosome 21, in which *β-APP* resides, is triplicated in Down syndrome and most of the cases manifest also AD by the age of 50. Post-mortem analyses of Down's patients who die young show diffuse intra-neuronal deposits of Aβ, suggesting that its deposition is an

early event in cognitive decline. The discovery of an extra copy of the *β-APP* gene in familial AD [19] provides further support that increased Aβ production can cause the disease.

The other two genes causing familial AD are Presenilin (*PSEN)1* (14q24.3) and *PSEN2* (1q31 -q42) [20,21]. Presenilins represent a central component of g-secretase, the enzyme responsible for originating Aβ from the C-terminal fragment of the APP protein. Mutations in presenilins also alter APP cleavage, leading to an increased production of Aβ42. So far, 178 mutations in *PSEN1* have been identified and 14 additional mutations have been found in the homologous gene *PSEN2* (http://molgen-www.uia.ac.be).

Most variants in *PSEN1* are missense mutations resulting in single amino-acid substitutions. Some are more complex, for example, small deletions or splice mutations. The most severe mutation in *PSEN1* is a donor-acceptor splice mutation that causes a two-aminoacid substitution and an in-frame deletion of exon 9. However, the biochemical consequences of these mutations for g-secretase assembly seem to be limited [22,23]. All these clinical mutations are likely to cause a specific gain of toxic function for *PSEN1,* determined by an increase of the ratio between Aβ42 and Aβ40 amyloid peptides, thus indicating that presenilins might modify the way in which g-secretase cuts APP.

Mutations in presenilins occur in the catalytic subunit of the protease responsible for determining the length of Aβ peptides therefore generating toxic Aβ fragments. However, presenilins have also non-proteolytic functions [24,25], the disruption of which might also contribute to familial AD pathogenesis.

Despite several carriers develop the disease early (40-50 years of age) with a typical AD phenotype, in some cases patients carrying the same mutation develop signs and symptoms resembling FTD instead of AD [26]. In addition, other mutations are associated with myoclonus, seizures, bilateral spasticity, parkinsonian features or ataxia [27].

Recent data suggest that there are mutations also in ADAM10, a member of disintegrin and metalloprotease family, which is an α-secretase capable of anti-amyloidogenic proteolysis of the APP. In particular, two mutations (Q170H and R181G) were found in 11 out of 16 affected individuals from 7 late-onset AD families. Functionally, both of them significantly attenuated α-secretase activity of ADAM 10 (>70% decrease) and elevated Aβ levels [28].

Sporadic Alzheimer's disease

Risk genes are likely to be numerous, displaying intricate patterns of interaction with each other as well as with non-genetic variables, and-unlike classical Mendelian ("simplex") disorders- exhibit no simple mode of inheritance. Mainly due to this reason, the genetics of sporadic AD has been labeled "complex" [29]. The gene mainly related to the sporadic forms of AD is the Apolipoprotein E (*APOE*) [30], which is located at chromosome 19q13.32 and was initially identified by linkage analysis [31]. The relationship between APOE and AD has been confirmed in more than 100 studies conducted in different populations. The gene has three different alleles, *APOE*2, APOE*3* and *APOE*4*. The *APOE*4* allele is the variant associated with AD. Longitudinal studies in Caucasian populations have shown that carriers for one *APOE*4* allele have a two-fold increase in the risk for AD [32]. The risk increases in homozygous for the *APOE*4* allele, and this allelic variant is also associated with an earlier onset of the disease.

Several linkage studies have been performed, giving rise to additional candidate susceptibility loci at chromosomes 1, 4, 6, 9, 10, 12 and 19. In particular, promising loci have been found at chromosome 9 and 10 [33, 34]. Recently, a wide genome analysis identified variants at *CLU* (which encodes clusterin or ApoJ) on chromosome 8 and *PICALM* in chromosome 11 associated with AD [35]. Data on *CLU* were contemporarily replicated in an independent study, which, in addition, demonstrated that *CR1*, encoding the complement component (3b/4b) receptor 1and locate on chromosome 1, is associated with AD [36].

Also, a large number of candidate genes studies have been performed in order to search a robust risk factor for the sporadic form of the disease. Several studies were mainly focused in genes clearly involved in the pathogenesis of AD such as genes encoding for inflammatory molecules or involved in the oxidative stress cascade.

Polymorphisms in the Interleukin-1 (IL1) complex, which includes *IL1-α, IL1-β,* and IL1R antagonist protein (*IL-1Ra*), are associated with AD in different populations [37-39].Several polymorphisms in *IL-6,* which is a potent inflammatory cytokine but has also regulatory functions, have been investigated as well. The *IL6* gene is located at chromosome 7p21 and polymorphisms exist in the -174 promoter region and in the region of a variable number of tandem repeats (VNTR), which is located in the 3'untraslated region. Both of them have been found associated with AD in case-controls studies [40, 41]. Investigation of Tumor Necrosis Factor-α (*TNFα*) polymorphisms was initiated because genome screening suggested a putative association of AD with a region on chromosome 6p21.3, which lies within 20 centimorgans of the *TNFα* gene. Furthermore, other polymorphisms located in the promoter region of *TNFα* have been associated with autoimmune and inflammatory diseases [42].

Polymorphisms in chemokines have been investigated with regard of susceptibility of AD. In particular, Monocyte Chemoattractant Protein-1 (*MCP-1*) and *RANTES* genes have been widely screened in different neurodegenerative diseases [43]. The distribution of the *A-2518G* variant was determined in different AD populations with concordant results showing no evidence for association of this variant in AD compared with controls [44, 45].

RANTES promoter polymorphism *-403 A/G*, found to be associated with several autoimmune diseases, was examined in AD population, failing to find significant differences between patients and controls [43]. *CCR2* and *CCR5* genes, encoding for the receptors of MCP-1 and RANTES respectively, have been also screened for association with AD. The most promising variants involve a conservative change of a valine with an isoleucine at codon 64 of *CCR2* (*CCR2-64I*) and a 32-bp deletion in the coding region of *CCR5* (*CCR5D32*), which leads to the expression of a non-functional receptor. A decreased frequency and an absence of homozygous for the polymorphism *CCR2-64I* were found in AD, thus suggesting a protective effect of the polymorphic allele on the occurrence of the disease; conversely, no different distribution of the *CCR5D32* deletion in patients compared with controls were shown [46, 47].

Another chemokine recently tested for suscepti-

bility with AD is IP-10. A mutation scanning of the gene coding region has been performed in AD patients searching for new variants. The analysis demonstrated the presence of two previously reported polymorphisms in exon 4 (*G/C* and *T/C*), which are in complete linkage disequilibrium, as well as a novel rare one in exon 2 (*C/T*). Subsequently these SNPs have been tested in a wide case-control study but no differences in haplotype frequencies were found [48].

Other genes under investigation are related to oxidative stress, a process closely involved in AD pathogenesis. In this regard, genes coding for the nitric oxide synthase (NOS) complex have been screened. The common polymorphism consisting in a *T/C* transition (*T-786C*) in *NOS3,* previously reported to be associated with vascular pathologies, has been tested in AD, but no significant differences with controls were found. Nevertheless, expression of *NOS3* in PBMC either from patients or controls seems to be influenced by the presence of the *C* polymorphic allele, and is likely to be dose dependent, being mostly evident in homozygous for the polymorphic variant. The influence of the polymorphism on *NOS3* expression rate supports the hypothesis of a beneficial effect exerted in AD by contributing to lower oxidative damage [49].

An additional variant in *NOS3* gene has been extensively investigated in AD patients, although the results are still controversial. It is a common polymorphism consisting in a single base change (*G894T*), which results in an amino-acidic substitution at position 298 of *NOS3* (Glu298Asp). Dahiyat et al. [50] determined the frequency of the Glu298Asp variant in a two-stage case-control study, showing that homozygous for the wild-type allele were more frequent in late onset AD. However, studies in other populations failed to replicate these results [51-54].

Guidi et al. correlated this variant with total plasma homocysteine (tHcy) levels in patients with AD and controls, demonstrating that the Glu/Glu genotype is correlated with higher levels of tHcy, which represent a known risk factor for AD, and its frequency was increased in AD patients [55]. Thus the mechanism by which this genotype contributes to increase the risk in developing AD could be mediated by an increase of tHcy.

However, *NOS-1* is the isoform most abundantly

expressed in the brain. Recent genetic analyses demonstrated that the double mutant genotype of the synonymous *C276T* polymorphism in exon 29 of the *NOS1* gene represents a risk factor for the development of early onset AD [56], whereas the dinucleotide polymorphism in the 3'UTR of *NOS1* is not associated with AD [57]. The distribution of a functional polymorphisms and a variable number of tandem repeats (VNTR) was analyzed in a case-control study [58]. The functional variant considered is located in exon 1c, which is one of the nine alternative first exons (named 1a-1i), resulting in *NOS1* transcripts with different 5'-untraslated regions [59]. Three SNPs have been identified in exon 1c, but only the *G-84A* variant displays a functional effect, as the *A* allele decreases the transcription levels by 30% in in-vitro models [60]. Regarding exon 1f, a variable number of tandem repeats (VNTR) polymorphism has been recently reported in its putative promoter region, termed *NOS1* Ex1f-VNTR. This VNTR is highly polymorphic and consists of different numbers of dinucleotides (B-Q), which, according to their bimodal distribution, have been dichotomized in short (B-J) and long (K-Q) alleles for association studies. Both Ex1c *G-84A* and Ex1f-VNTR are associated with psychosis and prefrontal functioning in a population of patients with schizophrenia [61]. Both Ex1c and Ex1f transcripts are found in the hippocampus and the frontal cerebral cortex, i.e. brain regions implicated in the pathogenesis of schizophrenia as well as AD. The presence of the short (*S*) allele of *NOS1* Ex1f-VNTR represents a risk factor for the development of AD. The effect is cumulative, as in *S/S* carriers the risk is doubled. Most interestingly, the effect of this allele is likely to be gender specific, as it was found in females only. In addition, the *S* allele was shown to interact with the APOE*4 allele both in males and females, increasing the risk to develop AD by more than 10 fold [58].

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) occurs most often in the presenile period, and age at onset is typically 45-65 years, with a mean in the 50s. Distinctive features in FTLD concern behaviour, including disinhibition, loss of social awareness, overeating and impulsiveness. Despite profound behavioural changes, memory is relatively spared [62]. Conversely to AD, which is more frequent in women, FTLD has an equal distribution among men and women. The current consensus criteria [63] identify three clinical syndromes: Frontotemporal lobar degeneration(FTD), Progressive nonfluent Aphasia (PA) and Semantic Dementia (SD), which reflect the clinical heterogeneity of FTLD. Frontotemporal lobar degenerationis characterized by behavioural abnormalities, whereas PA is associated with progressive loss of speech, with hesitant, nonfluent speech output [64], and SD is associated with loss of knowledge about words and objects. This variability is determined by the relative involvement of the frontal and temporal lobes, as well as by the involvement of right and left hemispheres [65].

Despite the majority of AD and FTLD are sporadic and likely caused by the interaction between genetic and environmental factors, so far it was observed that clinically typical AD and FTLD can cluster in families and be inherited in an autosomal dominant fashion, suggesting a genetic cause.

Familial frontotemporal lobar degeneration

Frontotemporal lobar degeneration is a heterogeneous disease characterized by a strong genetic component in its aetiology as up to 40% of patients report a family history of the disease in at least one extra family member [66]. In 1994 an autosomal dominantly inherited form of FTD with parkinsonism was linked to chromosome 17q21.2. [67]. Subsequently, other familial forms of FTD were found to be linked to the same region, resulting in the denomination "frontotemporal lobar degenerationand parkinsonism linked to chromosome 17" (FTDP-17) for this class of diseases.

In 1998, *MAPT* gene on chromosome 17q21, which encodes the microtubule associated protein tau was described as the cause of the disease in these families [68-70].

Currently, 44 different mutations in the *MAPT* gene have been described in totally 132 families (http://molgen-www.uia.ac.be). *MAPT* mutations are either non-synonimous or deletion, or silent mutations in the coding region, or intronic mutations located close to the splice-donor site of the intron after the alternatively spliced exon 10 [71]. Mutations are mainly clustered in exons 9-13, except for two recently identified mutations in exon 1 [72]. As regards possible ef-

fects on *MAPT* mutations, different mechanisms are involved, depending on the type and location of the mutation. Many of them disturb the normal splicing balance, producing altered ratios of the different isoforms. A number of mutations promote the aggregation of tau protein, whereas others enhance tau phosphorylation [73].

However, after the discovery for MAPT as causal gene for FTDP-17, there were still numerous families with autosomal dominant FTLD genetically linked to the same region of chr17q21 that contains *MAPT* but in which no pathogenic mutations had been identified, despite extensive analysis of this gene [74-76]. The neuropathological phenotype in these families was similar to the microvacuolar-type observed in a large proportion of idiopathic FTD cases with ubiquitin immunoreactive neuronal inclusions. Moreover, clinically, the disease in these families was consistent with diagnostic criteria for FTLD [63]. Sequence analysis of the whole *MAPT* region failed to find a mutation and tau protein appeared normal in these families [77]. Moreover the minimal region containing the disease gene for this group of families was approximately 6.2 Mb in physical distance. This region defined by markers D17S1787 and D17S806 is particularly gene rich, containing around 180 genes. Collectively, these data strongly argued against *MAPT* and pointed to another gene. Systematic candidate gene sequencing of all remaining genes within the minimal candidate region was performed and after sequencing 80 genes, including those prioritized on known function, the first mutation in progranulin gene (*GRN*) was identified. It consists in a 4-bp insertion of *CTGC* between coding nucleotides 90 and 91, causing a frameshift and premature termination in progranulin (C31LfsX34) [78]. These results have been contemporarily replicated by Cruts et al., who analyzed other families with a FTLD-U disease without *MAPT* pathology, finding a mutation five base pairs into the intron following the first non coding exon of the *GRN* gene (IVS0+5G-C). This is predicted to prevent splicing out of the intron 0, leading the mRNA to be retained within the nucleus and subjected to nuclear degradation [79]. At present there is no obvious mechanistic link between the mutations in *MAPT* and *GRN*, currently assuming that their proximity on chromosome 17 is simply a coincidence. Progranulin is known by several different names including granulin, acrogranin, epithelin

precursor, proepithelin and prostate cancer (PC) cell derived growth factor [80]. The protein is encoded by a single gene on chromosome 17q21, which produces a 593 amino acid, cysteine rich protein with a predicted molecular weight of 68.5 kDa. The full-length protein is subjected to proteolysis by elastase and this process is regulated by a secretory leukocyte protease inhibitor (SLPI) [81]. Progranulin and the various granulin peptides are implicated in a range of biological functions including development, wound repair and inflammation by activating signaling cascades that control cell cycle progression and cell motility [80]. Excess progranulin appears to promote tumour formation and hence can act as a cell survival signal. Despite the increasing literature on the function of progranulin, its role in neuronal function and survival remains unclear. In the human brain, *GRN* is expressed in neurons but significantly is also highly expressed in activated microglia [78], with the result that *GRN* expression is increased in many neurodegenerative diseases.

Since the original identification of null-mutations in FTLD in 2006, numerous novel mutations have been reported, spanning most exons, and to date 68 *GRN* mutations have been described (http://www.molgen.ua.ac.be/).

The majority of mutations identified create functional null alleles, causing premature termination of the *GRN* coding sequence. This leads to the degradation of the mutant RNA by nonsense mediated decay, creating a null allele [78, 79]. The presence of a null mutation causes a partial loss of functional progranulin protein, which in turn leads eventually to neurodegeneration (haploinsufficency mechanism), although how loss of *GRN* causes neuronal cell death remains unclear. Estimates of the frequency of *GRN* mutations in typical FTD patient populations suggests that they account for about 5-10% of all FTD cases, although numbers vary markedly depending on the nature of the populations considered [79,82,83].

Neuropathology analysis revealed that ubiquitin immunoreactive neuronal cytoplasmic and intranuclear inclusions were present in all cases with FTDP-17, where pathological findings were available [84]. Furthermore, soon after the identification of mutations in *GRN*, biochemical analyses demonstrated that truncated and hyperphosphorylated isoforms of the TAR-DNA

binding protein (TDP-43) are major components of the ubiquitin-positive inclusions in families with GRN mutations as well as in idiopathic FTD and a proportion of Amyotrophic Lateral sclerosis (ALS) cases [85]. TDP43 is a ubiquitously expressed and highly conserved nuclear protein that can act as a transcription repressor, an activator of exon skipping or a scaffold for nuclear bodies through interactions with survival motor neuron protein. Under pathological conditions, TDP-43 has been shown to relocate from the neuronal nucleus to the cytoplasm, a consequence of which may be the loss of TDP-43 nuclear functions [85]. The mechanism by which loss of progranulin leads to TDP-43 accumulation and whether this is necessary for neurodegeneration in this group of diseases is still to be clarified.

In conclusion, the function of progranulin in the brain is currently unclear and why loss of this protein leads to neurodegenerative diseases in mid-life remains to be established, and its possible role as regulator of a repair activity in the central nervous system, as it is well known to happen in periphery, remains a challenge for science. The gene encoding for TDP-43, named TARDBP, has been extensively studied and a number of mutations found in its C-terminal glycine rich region. Unexpectedly, the clinical phenotype of carries was ALS, and aggregates made of TDP-43 have been described in brain and spinal cord of such patients [86].

A recently published collaborative study [87] analyzed GRN in a population of 434 patients with FTLD, including FTD, PA, SD, FTD/ALS, FTD/MND, CBD and PSP. Fifty eight variants were identified, including 24 pathogenic variants. The frequency of GRN mutations was 6.9% of all FTLD-spectrum cases, 21,4% of cases with a pathological diagnosis of FTLD-U, 16% of FILD-spectrum cases with a family history of a similar neurodegenerative disease, and 56.2 of cases of FTLD-U with a family history. Clinical information were available for 31 GRN mutation-positive patients from 28 different families. The most common clinical diagnosis was FTD (n=24); 3 patients were diagnosed with PA, 3 with AD and 1 with CBD. The majority of GRN mutations introduced a premature termination codon, suggesting that their corresponding mRNA will be degraded through nonsense mediated decay, supporting the hypothesis that most GRN mutations create functional null al-

lele [87].

Two additional genes have been shown to cause FTLD. In 1995 Brown et al. [88] reported linkage to the pericentromeric region of chromosome 3 in a large multigenerational family with FTLD from Denmark. Nevertheless, the aberrant gene in this family has only recently been identified [89]. It consists in a mutation of the splice acceptor site of exon 6 of CHMP2B (charged multivescicular body protein 2B), which is part of the endosomal ESCRTIII-complex. The change from G to C results in an alteration of the splice acceptor site of exon 6, causing aberrant mRNA splicing of this transcript, which leads to the insertion of 201 base pairs of the intron between exons 5 and 6. In addition, a further transcript was identified, resulting from the use of a cryptic splice site consisting of 10 base pairs from the 5' end of exon 6. Anyway, mutations in CHMP2B appear as a rare genetic cause of FTLD mainly due to their rare frequency of occurrence, showing moreover that the CHMP2B locus does not increase the risk for FTLD [90].

Lastly, the first evidence of linkage with chromosome 9q21-22 comes from a study carried out in families with Motor Neuron Disease (MND) and FTD [91]. Despite the evidence of linkage to chr9q21-22 in several additional FTD-MND families, the gene responsible for the disease in this locus has yet to be identified [92-94].

Sporadic Frontotemporal Lobar Degenerartion

The best well-known risk factor for late onset SAD, Apo E4, has also been considered as a risk factor for sporadic FTLD. A number of studies suggested an association between FTLD and APOE*4 allele [95-100]. Other Authors however, did not replicate these data [101-103]. Recent findings demonstrated an association between the APOE*4 allele and FTLD in males, but not females [104], possibly explaining the discrepancies previously reported. An increased frequency of the APOE*4 allele was described in patients with SD compared to those with FTD and PA [102].

Concerning the APOE*2 allele in the development of FTLD, heterogeneous data have been obtained in different populations. Bernardi et al. [100] showed a protective effect of this allele towards FTLD, but data were nor replicated. A recent meta-analysis comprising a total of 364

FTD patients and 2671 controls demonstrated an increased susceptibility to FTD in *APOE*2* carriers [105].

Besides pathogenic mutations, several polymorphisms have been reported to date, both in *MAPT* and *GRN*. An association between Progressive Supranuclear Palsy (PSP) and a dinucleotide repeat polymorphism in the intron between *MAPT* exons 9 and 10 was described in 1997 [106]. The alleles at this locus carry 11 to 15 repeats. Subsequently, two common *MAPT* haplotypes, named H1 and H2, were identified [92]. Homozygosity of the more common allele H1 predisposes to PSP and Corticobasal Degeneration (CBD), but not to AD or Pick Disease [107,108]. Regarding *GRN*, an association of a SNP located in the promoter and an increased risk to develop FTLD in patients who did not carry causal mutations has recent been demonstrated [109].

Lastly, a known polymorphism in *MCP-1 (A-2518G)* has been shown to exert a protective effects towards the development of FTLD, whereas *NOS3 G894T* (Glu298Asp) and *NOS1 C276T* SNPs likely Increases the risk to develop FTLD [110-112].

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