

Review

Role of Genetics and Epigenetics in the Pathogenesis of Alzheimer's Disease and Frontotemporal Dementia

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Abstract. Alzheimer's disease (AD) and frontotemporal dementia (FTD) represent the first cause of dementia in senile and pre-senile population, respectively. A percentage of cases have a genetic cause, inherited with an autosomal dominant pattern of transmission. The majority of cases, however, derive from complex interactions between a number of genetic and environmental factors. Gene variants may act as risk or protective factors. Their combination with a variety of environmental exposures may result in increased susceptibility to these diseases or may influence their course. The scenario is even more complicated considering the effect of epigenetics, which encompasses mechanisms able to alter the expression of genes without altering the DNA sequence. In this review, an overview of the current genetic and epigenetic progresses in AD and FTD will be provided, with particular focus on 1) causative genes, 2) genetic risk factors and disease modifiers, and 3) epigenetics, including methylation, non-coding RNAs and chromatin remodeling.

Keywords: Alzheimer's disease, epigenetics, frontotemporal dementia, genetics

INTRODUCTION

Most neurological disorders, including Alzheimer's disease (AD) and frontotemporal dementia (FTD), are multifactorial diseases. Despite a small percentage of these diseases occurring in families with an autosomal dominant pattern of transmission, the majority of cases are sporadic, and derive from complex interactions between a number of genetic and environmental factors. Therefore, these diseases are defined as “multifactorial” or

“complex” [1]. The familial clustering can be explained by recognizing that family members share a greater proportion of their genetic information and environmental exposures than do individuals chosen randomly in the population. Thus, the relatives of an affected individual are more likely to experience the same gene-gene and gene-environment interactions that led to disease in the first place than are individuals who are unrelated to the patient. The multifactorial inheritance pattern represents an interaction between the collective effect of the genotype at one or, more commonly, multiple loci (polygenic or multigenic effects) either to increase or to decrease the susceptibility to the disease, combined with a variety of environmental exposures that may trigger, accelerate, or protect against the disease altered mechanisms.

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The gene-gene interactions in polygenic inheritance may be simply additive or more complicated. Gene-environment interactions, including systematic exposures or chance encounters with environmental factors in one's surroundings, add even more complexity to individual disease risk and the pattern of disease inheritance.

Herein, main genetic variations, either causative or conferring risk for AD and FTD will be described, together with epigenetic factors.

GENETICS: BASIC CONCEPTS AND METHODOLOGIES

Genetic background differs from thousands to millions of genetic variants that are the differences in DNA sequences within the genome of individuals in the population. These variations can take many forms, including single nucleotide polymorphisms (SNPs), tandem repeats (short and variable), small insertions and deletions, duplications or deletions that change the copy number of a large segment of a DNA sequence (≥ 1 kb), i.e., copy number variations (CNVs), and other chromosomal rearrangements such as inversions and translocations (also known as copy-neutral variations) [1–3].

Common variants are synonymous with polymorphisms, defined as genetic variants with a minor allele frequency (MAF) of at least one percent in the population, whereas rare variants have a MAF of less than 1% [1]. The large majority of genetic variants are hypothesized to be neutral [4], as they do not contribute to phenotypic variation.

Four strategies have been applied so far in genetic studies: genetic linkage analysis, candidate gene studies, genome wide association studies (GWAS), and next generation sequencing (NGS) technology based studies: whole genome sequencing (WGS) and whole exome sequencing (WES).

Linkage analyses were the first kind of strategy used to unravel the genetic basis of Mendelian traits, involving families presenting autosomal dominant inheritance. Genetic linkage studies led to the identification of chromosomal regions associated with the disease segregation, but does not identify the causal gene associated, which requires fine mapping [5].

The candidate gene approach aims to determinate whether frequencies of genetic variants of people with a specific disease differ significantly from a control population. Susceptibility genes are defined when cases and controls showed significant differences

in occurring genetic variants frequencies. Candidate gene approach led to the identification of the Apolipoprotein E gene (*APOE*) risk alleles implicated in late onset AD (LOAD). Thousands of genes were tested in this way on the basis of existing knowledge on disease pathogenesis, quite often giving inconsistent results, particularly because most of the candidate gene association studies could not be replicated, due to the small sample size, which did not allow adequate statistical power [6].

The advent of microarray technology era revolutionized genetics research, allowing the contemporaneous determination of millions of SNPs in thousands of samples. GWAS are based on the testing common genetic variants in a hypothesis-free manner. Thus, it provides information on how common genetic variability confers risk for common diseases [7]. Several susceptibility genes for common neurodegenerative disorders have been revealed by GWAS studies, although the odds ratios associated with these risk alleles are relatively low [8].

Recent advances, collectively referred to as NGS, allowed for high-throughput sequencing, giving massive data results, that need to be analyzed by specific bioinformatics software. Moreover, in opposition to the first generation sequencing, NGS can produce the same genome sequence within a few weeks and with reduced costs. This allows for simultaneous investigation of multiple genes and has been demonstrated to be an effective alternative for establishing the genetic base for Mendelian diseases in the research setting [9, 10] and recently also in clinical settings [11, 12]. NGS relies upon multiple, short, overlapping reads of fragmented DNA that can be aligned against a reference genome or assembled “de novo” if no information on the reference genome is available. If just the protein-coding regions are amplified when sequencing all the genes, the method is referred to as WES, whereas when the target is the whole genome, it is known as WGS.

GENETICS OF ALZHEIMER'S DISEASE

AD is a multifactorial and complex neurodegenerative disorder and the leading cause of dementia among elderly people. Genetically, AD can be subdivided into a rare familial form, accounting for 2-3% of all patients presenting with autosomal dominant inheritance, and a multifactorial sporadic form in which specific environmental exposures in combination with genetic susceptibility contribute to the

exacerbation of the disease [1]. Genetically inherited AD usually develops before 65 years of age early onset AD (EOAD), whereas the sporadic type of disease often occurs later in life in individuals older than 65 years and is referred as LOAD [13].

Three genes, discovered thanks to linkage analysis, are responsible for familial AD: Presenilin 1 (*PSEN1*), Presenilin 2 (*PSEN2*), and Amyloid precursor protein (*APP*). They map on three different chromosomes, but share a common biological pathway related to amyloid processing [14]. A number of variants in these genes have been described, the majority of which play a causal role in the pathogenesis of the disease (see [15] for details).

The proportion of cases of autosomal dominant AD explained by mutations in these genes is high but vary widely from 12% to 77% [16, 17], suggesting that there are additional genetic factors involved in the pathogenesis of EOAD. Recently, thanks to the NGS approach, some new genetic variants were found in small families with unexplained EOAD. Guerreiro et al. [18] identified a missense mutation in *NOTCH3* (R1231C), that is a gene previously linked to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Nevertheless, complete screening of *NOTCH3* in a cohort of 95 EOAD cases and 95 controls did not reveal any additional pathogenic mutations [18].

Another study [19] identified mutations in the Sortilin related receptor 1 (*SORL1*) gene in EOAD. This gene encodes a neuronal sorting protein able to bind APP, driving it toward the endosome-recycling pathways [19]. Other studies involving EOAD found association between the Triggering Receptor Expressed on Myeloid cells 2 (*TREM2*) gene and the risk of develop the disease. *TREM2* is an immune phagocytic receptor expressed in brain microglia, able to modulate microglial phagocytosis and inflammatory pathway [20].

By using a NGS WES based approach, an association between *TREM2* variants in exon 2 and EOAD in Caucasian subjects of French origin was identified. In particular, an association between rs75932628T allele (R47H) and the risk of developing the disease was described [21]. The same variant was further confirmed to be a risk factor for EOAD in a recent study [22], which showed that individuals with the R47H variant had significantly earlier symptom onset than individuals without *TREM2* variants [22]. *TREM2* genetic variability has been investigated also with regard of LOAD susceptibility by different groups. Jonsson et al. [23] found that the rs7593628T in

TREM2 confers a significant threefold increased risk for AD in a cohort of Icelanders. The same variant was further tested by Guerreiro et al. [24] by WES and was found to cause a five-fold increased risk to develop AD. Furthermore, six additional *TREM2* variants were found in AD but not in controls, highlighting their possible consistent contribution to increase AD risk [25]. In this study, the protective rs728224905 in *PLCG2* and the risk variant rs616338 in *ABI3* gene were also associated with AD, suggesting an implication of microglial-mediated innate immunity in the pathogenesis of the disease [25].

A recent study [26] identified, by GWAS, a novel missense mutation in phospholipase D family member 3 gene (*PLD3*) in an EOAD autopsy-confirmed patient. However, further confirmatory analysis in larger populations of European EOAD did not lead to significant evidence for an enrichment of rare *PLD3* variants [26]; therefore the genetic role of *PLD3* in AD remains to be demonstrated. The use of NGS with a target panel able to analyze 10 genes involved in dementia led instead to the identification of novel coding variants in *PSEN1*, predicted to be pathogenic [27].

Recent GWAS studies [28, 29] confirmed that *APOE* $\epsilon 4$ remains the single most important genetic risk factor for AD (see [30] for review), although about additional ten risk factors emerged recently as strongly associated with LOAD [29, 30]. Notably, the majority of such AD susceptibility loci (*CLU*, *BIN1*, *CR1*, *ABCA7*, *CD33*, *EPHA1*) have putative functions in lipid metabolism and immune system [30] (Table 1).

Table 1
Causal genes and genetic risk factors for AD

Causal genes	Chromosome	Function
<i>APP</i>	21	Amyloid precursor protein
<i>PSEN1</i>	14	APP cleavage
<i>PSEN2</i>	1	APP cleavage
Risk factors	Chromosome	Function
<i>APOE</i>	19	Lipid metabolism
<i>TREM2</i>	6	Innate immunity; expressed by microglia
<i>BIN1</i>	2	Nucleocytoplasmic adaptor protein
<i>CLU</i>	8	Lipid metabolism
<i>ABCA7</i>	19	Lipid homeostasis in cells of the immune system
<i>CR1</i>	1	Immune response
<i>PICALM</i>	11	Membrane metabolism
<i>MS4A6A</i>	11	Transmembrane protein
<i>CD33</i>	19	Membrane antigen
<i>MS4A4E</i>	11	Transmembrane protein
<i>CD2AP</i>	6	Cytoskeleton dynamics

A rare variant is the Nicastrin gene, recently identified by NGS as risk factor for LOAD in a Greek population [31].

Lastly, Kohli and colleagues, using WES on 11 affected individuals in a large kindred with apparent autosomal dominant LOAD, found damaging missense mutations in the Tetratricopeptide repeat domain 3 gene (*TTC*) in all affected individuals [32].

GENETICS OF FRONTOTEMPORAL DEMENTIA: MAJOR CAUSAL GENES

The majority of FTD cases are sporadic and likely caused by the interaction between genetic and environmental factors. A number of cases, however, present familial aggregation and are inherited in an autosomal dominant fashion, suggesting a genetic cause [32–34]. Up to 40% of patients have a positive family history, with a diagnosis of dementia in at least one extra family member [33, 35]. At present, three major causal genes have been identified: Microtubule Associated Protein Tau (*MAPT*), Progranulin (*GRN*), and Chromosome 9 Open Reading Frame 72 (*C9ORF72*). In addition, some rare causal genes have been identified (Table 2).

MAPT

The first evidence of a genetic cause for familial FTD came from the demonstration of a linkage with chromosome 17q21.2 in autosomal dominantly inherited form of FTD with parkinsonism [36], named FTDP-17. The gene responsible for such association, *MAPT*, was discovered few years later [37].

MAPT encodes the protein tau, which is involved in microtubule stabilization, assembly, and cytoskeletal dynamics [38]. It is composed of 15 exons and transcribed, by alternative splicing, in 6 different isoforms, all of which play a role in the maintenance of microtubular structure. Any excess of tau protein can be bundled into protein aggregates that fill the cells and induce neurotoxicity. Tau has four repeat domains in the C-terminus, which mediate the interaction with microtubules. These domains are encoded by exons 9–12, in which the majority of pathogenic mutations have been found. In addition, alternative splicing of exon 10 leads to two different isoforms that contain either three (3R) or four (4R) 31-amino acids repeats [39].

The pathology of all *MAPT* mutations is characterized by the deposition of insoluble aggregated tau proteins within neurons and glial cells in the cerebral cortex and in other brain regions.

To date, more than 40 pathogenic *MAPT* mutations have been described and classified according to their position in the gene [40], their effects on *MAPT* transcription, and the type of tauopathy. The frequency of *MAPT* mutations is highly variable, but in general *MAPT* mutations are very rare in sporadic patients, whereas in most familial cases the frequency ranges between 5% and 20% depending on the geographic distribution [41].

The pathogenic mechanism of each different mutation depends on the type and location of the genetic defect, and affects 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

Table 2
Causal genes and genetic risk factors for FTD

Causal genes	Chromosome	Function
<i>MAPT</i>	17	Microtubule stabilization, assembly and cytoskeletal dynamics
<i>GRN</i>	17	Inflammation
<i>C9ORF72</i>	9	Nucleocytoplasmic transport, autophagy, intercellular trafficking
<i>CHMP2B</i>	3	Autophagy, protein trafficking and degradation
<i>VCP-1</i>	9	Autophagy, protein trafficking and degradation
<i>SQSTM1</i>	5	Encodes for p62, autophagy, protein degradation
<i>CHCHD10</i>	22	Mitochondrial protein
<i>TBK1</i>	12	Autophagy, protein trafficking and degradation
<i>TARDBP</i>	1	Encodes for TDP-43, transcription factor
<i>FUS</i>	16	Encodes for FUS, transcription factor
<i>UBQLN2</i>	X	Autophagy, protein trafficking and degradation
<i>TUBA4A</i>	2	Cytoskeletal dynamics
Risk Factors		
<i>TMEM106B</i>	11	Transmembrane protein
<i>GRN</i>	17	Inflammation
<i>RAB8/CTSC</i>	11	Lysosomal biology and protein trafficking
<i>HLA</i>	6	Immune system

tau aggregation, while others lead to an aberrant phosphorylation of tau protein, which damages microtubule stabilization [41]. Regarding mutations localized in the donor splicing site following exon 10, it was shown that these intronic mutations increase the inclusion of *MAPT* exon 10 by destabilizing the stem-loop structure that spans the splice site of exon 10, resulting in an increased production of 4R tau. Mutations in the acceptor splicing site following exon 10 lead to an enhanced inclusion of this exon [42].

Alternatively, other mutations affect the alternative splicing, thus producing altered ratios of the different isoforms (3R/4R tau). Most of missense mutations, such as the p.P301L mutation, reduce the ability of tau to bind microtubules leading to a decreased tau capacity to promote microtubules assembly [43]. Moreover, it was observed in *in vitro* studies that several coding mutations accelerate the aggregation of tau [44]. In 2009, Rovelet-Lecrux and coworkers identified a heterozygous 17.3 Kb deletion responsible for the removal of exons 6–9 of *MAPT* in one FTD patient [45]. This deletion caused the loss of the first microtubule binding domain and a decrease in the binding abilities of tau to the microtubules. The same group reported a 439 Kb duplication in the region encompassing *CRHR1*, *MAPT*, and saithoin (*STH*) in one patient affected by behavioral and amnesic disorders [46].

The clinical presentation in *MAPT* mutation carriers is heterogeneous, but behavioral changes, semantic impairment, episodic memory decline, and parkinsonism have been proposed as key clinical features. From the pathological point of view, patients present atrophy of the frontotemporal lobes and basal ganglia and variable presences of tau-positive inclusions, typical of FTLD-tau [47].

GRN

After the discovery of *MAPT* as causal gene for FTDP-17, there were still numerous autosomal dominant FTD cases genetically linked to the same chromosomal region of *MAPT* (chr17q21), without any mutation in *MAPT*, in spite of an extensive fine mapping of the gene. A small region rich in 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. The first identified mutation in *GRN*, identified in 2006, consisted of a 4-bp insertion of CTGC between coding nucleotides 90 and 91, causing a frameshift and premature termination in progranulin

(C31LfsX34) [48]. In a parallel study, Cruts and coworkers found at the same time another mutation of five base pairs into the intron following the first non-coding exon of *GRN* (IVS1+5G>C) [49]. This mutation causes the splicing out of the intron 0, leading the retention of mRNA within the nucleus and its degradation.

GRN mutations were subsequently found to account for 5–20% of FTD patients with positive family history and 1–5% of apparently sporadic patients [50].

GRN encodes for the growth regulation factor named progranulin. Progranulin is an 88 kDa secreted glycoprotein, which in brain is expressed by neurons and microglia [51]. Its expression is low in early development and increases with age. The protein is composed by seven and one half cysteine-rich granulin domains and can be cleaved by several proteases into 6 kDa units called granulins. It belongs to a family of proteins involved in multiple biological functions, including development, wound repair, and inflammation, by activating signaling cascades that control cell cycle progression and cell motility [51].

Since the original identification of null-mutations in FTLD, more than 70 different mutations have been described so far. Most of the known pathogenic *GRN* mutations, particularly 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 [52]. Also rare partial deletions and a complete deletion of the gene have been described [53].

At neuropathological examination, *GRN*-mutated FTD cases displayed ubiquitin-positive, tau-negative inclusions (FTLD-U) similar to the microvacuolar-type still observed in a large proportion of apparently sporadic FTD, that were different from the tau-positive inclusions typical of *MAPT* mutated cases. 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 FTD and of a proportion of cases of amyotrophic lateral sclerosis (ALS) [54]. According to the novel neuropathological classification of FTLD-TDP pathology in FTD [55], TDP-43 neuropathological subtype A is consistently found in association with *GRN*-mutated cases.

A collaborative study [53] analyzing *GRN* mutations in 434 patients estimates a frequency of 6.9% of all included FTD-spectrum cases. About 56% of such

cases was represented by FTD subjects with ubiquitinated inclusions at the neuropathology (FTD-U) with a positive family history of FTD.

From the clinical point of view, mutations in GRN are associated with extremely heterogeneous phenotypes, but the main clinical diagnosis is FTD following by diagnosis of primary progressive aphasia [56]. Language impairment seems to be more relevant as the disease progresses. About 40% of patients have parkinsonism, and episodic memory impairment is frequently observed, leading to a clinical diagnosis of AD in some cases [57]. Although rarely, an overlap between psychiatric disorders and genetically determined FTD can occur, as shown by Rainero et al. [58], who described a patient with heterosexual pedophilia who was a carrier of a GRN mutation and developed FTD over time, and by Cerami et al. [59], who reported two clinically different, apparently sporadic FTD cases sharing the Thr272fs GRN mutation, who had a premorbid bipolar disorder history.

The penetrance for GRN mutations is age dependent with only 50% of GRN mutation carriers affected at the age of 60 and 90% of mutation carriers affected at 70 years of age. Age at disease onset is extremely wide, even in the same family, ranging from 47 to 79 years [60]. In a large Calabrian family harboring a heterozygous c.1145insA mutation, the age at onset ranged from 35 to 87 years whereas the age of death was from 56 to 87 years [61]. In that family, the clinical presentation was homogenous; all of affected members had clinical diagnosis of FTD with subsequent language impairment.

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 [62, 63].

Regarding the function of progranulin, Pickford et al. [64] demonstrated, in an *in vitro* model, that it has chemotactic properties toward cultured mouse neurons. In addition, progranulin-treated primary neurons secrete a number of cytokines and chemokines, particularly those involved in proliferation (i.e., IL-4), and, importantly, induce microglia to switch from a pro-inflammatory to an anti-inflammatory phenotype [64]. Another recent observation is that progranulin binds the Tumor Necrosis Factor Receptor (TNFR)2, that is expressed specifically in neuronal subtypes and glial cells in the brain, leading to an anti-inflammatory cascade [65].

Abnormalities of several cytokines and chemokines has been observed in cerebrospinal fluid (CSF) of GRN carriers compared with controls [66], suggesting an imbalance of specific inflammatory factors possibly related to GRN haploinsufficiency.

C9ORF72

One of the most intriguing discoveries in the genetics of FTD has been the investigation of FTD/motor neuron disease (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 autosomal dominant FTD-MND [67]. Additional data confirmed the linkage to chr9q21-22 in FTD-MND families [68], until, in 2011, two international groups identified the gene responsible for the disease in this locus, C9ORF72 [69, 70]. The mutation consists of a large hexanucleotide (GGGGCC) repeat expansion in the first intron of the gene.

In healthy subjects, most individuals carry between 2 and 20 repeats, but FTD and ALS patients had from 100 to also 1000 s of copies of repeats. The minimum repeat length to confer risk of disease is unknown, probably due to the presence of somatic mosaicism. In fact, the length of repeats is different between tissues even in the same individual and this phenomenon complicates genotype-phenotype correlation studies [71].

C9ORF72 repeat expansion is the most common cause of FTD (with or without ALS) worldwide. There is a particular high frequency in a Finland population, probably due to a common founder. Studies in Asian cohorts have reported instead much lower frequencies [72].

Clinical phenotypes are very variable [73] as well as the age at onset and disease duration; in fact, age at onset can range between 27 and 83 years and disease duration from 1 to 22 years. The most common clinical presentation is FTD, ALS, or both. As mentioned above, in families where FTD-ALS is the clinical phenotype, the C9ORF72 repeat expansion is very common, explaining the disease in more than 50% of families [74]. FTD patients present behavioral disturbances, whereas language impairment is less commonly observed [75]. In addition to classical behavioral presentations, such as apathy, disinhibition, socially inappropriate conduct, and loss of empathy, C9ORF72 expansion carriers present a high frequency of hallucinations, psychosis, and delusions [76], which lead to a primary diagnosis of schizophrenia and bipolar disorders [77, 78]. Sometimes patients

have episodic memory problems at the beginning of the disease course, receiving a primary diagnosis of AD [76, 79]. Less than 1% of clinically diagnosed AD patients carry a *C9ORF72* expansion with TDP43 pathology [79]. Other studies [80] found no *C9ORF72* expansions in AD patients, suggesting the total frequency of *C9ORF72* positive cases in AD is very rare (<1%). Most likely, there is no association between AD and *C9ORF72*. Likely, some AD cases have been misdiagnosed or some expansions are not big enough to be causal. Early-parkinsonism has also been reported in *C9ORF72* expansion carriers, although very rarely in *MAPT* and *GRN* mutation carriers [76].

From a neuropathological point of view, post-mortem examination showed that *C9ORF72* expansion carriers present TDP-43 positive inclusions in different brain areas. Most patients present with FTL-D-TDP type A or B [55]. In addition, they have neuronal inclusions in the cerebellar granule cell layer, hippocampal pyramidal neurons, and other anatomic sites that are positive for ubiquitin and p62 proteins. These inclusions are composed by dipeptide repeat proteins (DPRs), translated from the GGGGCC repeat through unconventional repeat-associated non-ATG translation. Poly-GP, Poly-GA, and Poly-GR are generated from sense strand and detected in hippocampus and cerebellum of expansion carriers [81]. Normal *C9ORF72* functions were reported to be involved in the nucleocytoplasmic transport, autophagy, intercellular trafficking, and TDP-43 aggregation (see [82] for review).

Reddy et al. [83] demonstrated that the r(GGGGCC)_n RNA forms extremely stable G-quadruplex structures, which theoretically may affect promoter activity, genetic instability, RNA splicing, translation and neurite mRNA localization.

Moreover, several studies, conducted in derived cells and tissue of patients, demonstrated that these foci are able to sequester RNA binding protein, including hnRNP h, hnRNP A1, and SC35, affecting the mRNA nuclear transport system [84]. However, the clear mechanism linking RNA foci and sequestered proteins to neurodegeneration has not been fully understood. Together with the formation of RNA foci and DPR, another suggested pathological mechanism of the *C9ORF72* expansion is gene downregulation due to *C9ORF72* methylation [85].

In cultured cells and primary neurons, Poly-GA overexpression led to the generation of p62-positive inclusions and neurotoxicity attributed to impaired

ubiquitin proteasome function [86]. On the other hand, arginine-rich dipeptide (poly-GR and poly-PR) led to the formation of nucleolar inclusions in fly models [87]. Since the clinical utility as well as the significance and the temporal course of DPRs in the pathogenesis of the disease is still unclear, Lehmer et al. [88] established a poly-GP immunoassay from CSF in order to identify and characterize *C9ORF72* patients. Intriguingly, they observed Poly-GP CSF levels were already detectable in *C9ORF72* asymptomatic carriers compared to healthy subjects and these levels are similar in symptomatic expansion carriers, demonstrating a possible use as a diagnostic biomarker in addition to genetic screening [88].

GENETICS OF FRONTOTEMPORAL DEMENTIA: RARE CAUSAL GENES

CHMP2B

Few FTL-D families display mutations in the charged multivesicular body protein 2B gene (*CHMP2B*), which encodes a component of the heteromeric ESCRT III complex, involved in the endosomal trafficking and degradation [89]. *CHMP2B* is involved in sorting and trafficking surface receptors or proteins into intraluminal vesicles for lysosomal degradation and binding the Vps4 protein responsible for the dissociation of ESCRT components [90]. The first mutation in *CHMP2B* was identified in one large kindred from Denmark [91]. Behavioral and cognitive impairment associated with extrapyramidal and pyramidal signs are the main clinical manifestations in *CHMP2B*.

All mutations described (missense and truncation mutations) show a common mechanism of action: the deletion of the C-terminus of the protein with the loss of the Vsp-4 binding domain [90]. This causes the accumulation of mutated *CHMP2B* on the endosomal membrane and prevent the recruitment of other proteins necessary for endosomal fusion with lysosomal. This phenomenon leads to the impairment of the late endosomal trafficking and contributes to neurodegenerative processes in FTD [91]. This can be observed as enlarged and abnormal endosomal structures in postmortem brain tissue from patients [92]. From a histological point of view, patients with *CHMP2B* mutations present FTL-D-U with ubiquitin- and p62-positive but TDP-43-negative neuronal cytoplasmic inclusions [93].

VCP-1 and SQSTM1

Mutations in the Valosin Containing Protein gene (*VCP*) were firstly described as cause of hereditary inclusion body myopathy with Paget's disease of the bone (PDB) and FTD [94]. Myopathy is the most frequent clinical symptom, present in about 90% of affected subjects, whereas FTD is seen in about 33%, usually many years after the onset of muscle symptoms. From a histological point of view, brain tissues of patients carrying *VCP* mutations are characterized by FTLD-TDP type D pathology with TDP43 and p62 positive inclusions within neuronal nuclei [95].

VCP-1 encodes a monomeric protein composed of 806 aminoacids. It is known as a regulator of many cellular processes, such as ubiquitin-dependent protein quality control, labeling proteins for degradation, and coordination of the removal of protein aggregates via multivesicular body formation [96].

Another gene involved in the mechanism of protein degradation as well as in FTLD pathogenesis is Sequestosome 1 gene (*SQSTM1*). This gene encodes for p62 protein, a connector between ubiquitinated proteins and autophagy receptor or proteasome degradation pathways [97]. Mutations in *SQSTM1* were first described in PDB and are responsible for around 30% of familial PDB cases (see [98] for review). In 2014, Van der Zee et al. published a large-scale resequencing study in an FTLD cohort of patients and identified a number of mutations in the C-terminal of the gene that is involved in the binding with ubiquitinated proteins [99].

CHCHD10

A coiled-coil-helix-coiled-coil-helix domain containing 10 (*CHCHD10*) gene encodes a mitochondrial protein that is enriched at cristae junctions in the intermembrane space. By exome sequencing, it was possible to identify the first pathogenic mutation, p.S59L, in an atypical family with late onset MND, FTD, cerebellar ataxia, and mitochondrial myopathy [100]. Subsequent genetic studies identified additional potential pathogenic mutation in FTD and ALS patients with 1–3% frequency [101]. Very recently, Perrone et al. identified a novel nonsense mutation (p.Gln108*) in a patient with atypical clinical FTD and pathology-confirmed Parkinson's disease (1/459, 0.22%) leading to loss of transcript. They further observed three previously described missense variants (p.Pro34Ser, p.Pro80Leu, and p.Pro96Thr) that were also present in the matched control series [102].

TBK1

In 2015, a large exome sequencing case-control study identified mutations in the TANK binding kinase 1 gene (*TBK1*) in sporadic ALS cohort of patients [103]. Subsequent studies showed *TBK1* loss of function mutations in families with FTD-ALS but also in clinical FTD and pathologically confirmed FTLD-TDP even in the absence of motor neuron disease [104]. The majority of mutations identified are loss-of-function mutations leading to a decrease 50% of *TBK1* expression. Missense mutations instead impair the binding of *TBK1* to optineurin (*OPTN*). As *VCP* or p62, *TBK1* is also involved in protein degradation and autophagy mechanisms. In fact, it phosphorylates p62 and *OPTN*, another member of the autophagy pathway. In 2015, Potteir et al. discovered, in a pathologically confirmed cohort of patients, one heterozygous mutation and one deletion in *OPTN* as well as a nonsense mutation in *TBK1* suggesting that both genes contribute to FTLD-TDP etiology [104].

TARDBP

TARDBP encodes for TDP-43 protein, which is localized in the nucleus of the cell, where it is able to form heterogeneous nuclear ribonucleoprotein (hnRNP) complexes with several functions, such as RNA regulation, mRNA stability and transport, and splicing control. A link between FTLD and ALS and TDP-43 was supported by the evidence that TDP-43 regulate axon growth *in vivo* and *in vitro* suggesting that the capacity of motor neuron to produce and maintain axons is compromised by TDP-43 dysregulation [105].

FUS

Similar to TDP-43, Fused in sarcoma (*FUS*) is highly conserved and ubiquitously expressed gene. *FUS* is a component of the hnRNP complex and involved in RNA transport in and out of the nucleus, RNA splicing, and DNA/RNA metabolism [106]. In 2009, *FUS* mutations were discovered to be the cause of 3% of familial ALS. They are mostly located in the C-terminal of the protein, particularly in the nuclear localization sequence, resulting in an impairment of transportin (TRN1)-mediated nuclear import of *FUS* [106]. Neuropathologically, ALS patients with *FUS* mutations display abnormal cytoplasmic neuronal and glial inclusions positive for *FUS*. However, in

some FTL-D-FUS patients, no FUS mutations have been identified.

UBQLN2

UBQLN2 is involved in a rare form of chromosome X-linked familial ALS and FTL-D-ALS [107]. Mutations are located in proline residues in the highly conserved PXXP repeat domain involved in the degradation of misfolded proteins via ubiquitin proteasome system and autophagy.

TUBA4A

TUBA4A encodes 1 of 8 human α -tubulins, which polymerize with β -tubulins to form the microtubule cytoskeleton. *TUBA4A* mutations have primarily been associated with ALS, although some patients also had cognitive involvement ranging from mild cognitive impairment to FTD. In *TUBA4A*, 10 missense, 1 nonsense, and 1 splice donor site mutation have been identified in both sporadic and familial ALS patients, with some also presenting with FTD [102].

GENETICS OF FRONTOTEMPORAL DEMENTIA: GENETIC MODIFIERS

In addition to genes mentioned above and generally involved in familial autosomal dominant transmission, several genetic risk factors have been studied. The most important and replicated is the transmembrane protein 106b gene (*TMEM106B*). In 2010, Van Deerlin and coworkers published the first GWAs on 515 FTD patients with TDP-43 pathology; they identified a possible susceptibility locus, which encompasses *TMEM106B* gene on chromosome 7p21 [108]. In particular, the study identified three associated single nucleotide polymorphisms (SNPs), rs102004, rs6966915 and rs1990622, which are correlated with an increase of *TMEM106B* expression level [108]. Several subsequent studies showed that the highest association with *TMEM106B* locus was found in patients with *GRN* mutations with TDP-43 pathology [109, 110]. In *GRN* mutation carriers, the presence of protective C allele of SNP rs1990622, protects these patients from developing FTD [110]. The protective effects of *TMEM106B* are not confined to carriers of *GRN* mutations but also extend to *C9ORF72* carriers [111, 112]. *TMEM106b* is a glycosylated type 2-membrane protein that localized to late endosomes and lysosomes where it seems

to have an important function. Over-expression of *TMEM106b* in cell cultures showed an aberrant vacuole formation and an impairment of endolysosomal pathway [113].

Common SNPs in the major causal genes have been studied to determine their association as FTD risk factors. For example, rs5848, located in 3'UTR of the *GRN* gene in a putative miRNA binding site, has been investigated. Unfortunately, its role remains unclear with significant association in initial series of FTD-TDP43 patients but not in subsequent series of clinical patients [114]. More recently, a two-stage GWAS identified the HLA locus at chromosome 6p21.3 and a locus at chromosome 11q14 encompassing *RAB38* and cathepsin C (*CTSC*) [115]. These two gene are especially associated with FTD and an association was observed between the top SNP at *RAB8/CTSC* locus and a 50% reduction of *RAB8* levels in the blood of patients suggesting that a loss of *RAB8* function may play a role in the development of FTD. *RAB8* is a protein involved in the regulation of lysosomal biology and protein trafficking. The HLA locus, instead, suggests a link between FTD and immune system [115].

EPIGENETICS

Epigenetics is focused on the investigation of mechanisms able to influence the expression of genes without altering the DNA sequence. DNA methylation, chromatin remodeling, and non-coding RNAs (ncRNAs) are the three most investigated epigenetic modifications [116]. Epigenetic processes are able to regulate DNA replication and repair, RNA transcription, and chromatin conformation, that influence in turn transcriptional regulation and protein translation.

Methylation

DNA methylation is the best characterized epigenetic modification that involves the addition of a methyl group to the carbon-5 of a cytosine residue in DNA and is carried out by one of the several DNA methyltransferase (DNMT) enzymes. DNMT1 is the enzyme responsible for the maintenance of DNA methylation patterns during DNA replication. It localizes to the DNA replication fork, where it methylates nascent DNA strands at the same locations as in the template strand [117]. DNMT3a and DNMT3b are involved in the *de novo* methylation of unmethylated and hemimethylated sites in nuclear and mitochondrial DNA, respectively [117, 118].

In mammals, DNA methylation occurs predominantly at CpG sites-locations, where a cytosine nucleotide is followed by a guanine nucleotide. CpG sites can occur in concentrations of up to several hundred dinucleotide repeats, called CpG islands, which are frequently found in gene promoters. The methylation or hypermethylation of CpG islands usually prevents the expression of the downstream gene [119]. DNA methylation is currently the best understood epigenetic mechanisms, and is known to have a crucial role in normal development, cell proliferation, and genome stability [120]. In addition, non-CpG methylation may happen in stem cells and neurons [121].

Early epigenetic investigations related to AD focused on DNA methylation, finding non AD specific hypomethylation of the *APP* gene promoter region in one patient [122].

More recent studies support an overall reduction in DNA methylation in AD patients thus highlighting the importance of DNA methylation in AD [123]. Interestingly A β has also been implicated as a trigger of epigenetic changes as it was found that A β induces global DNA hypomethylation [124]. Moreover, a DNA methylome paper found genes with altered methylation in AD brains [125].

Tau gene expression is also subject to complex epigenetic regulation, involving differentially methylated binding sites for transcription factors [126].

Recently, Bollati and colleagues investigated the methylation status of repetitive elements in blood, including *Arthrobacter luteus* elements (Alu) blood, long interspersed element 1 (LINE-1), and satellite- α (SAT- α), that comprise a wide portion of the human genome and are known to contain large numbers of CpG sites. They found that LINE-1 methylation was increased in AD patients and that enhanced LINE-1 methylation was associated with a better cognitive performance in AD patients [127].

Regarding FTD, two studies analyzed the *GRN* promoter methylation in relation to its ability to regulate progranulin expression. They found that increased methylation in FTD subjects negatively correlates with *GRN* mRNA levels [128, 129].

A recent GWAS on DNA methylation pattern in peripheral blood of patients with FTD and progressive supranuclear palsy compared to healthy subjects found a specific methylation signature associated pathologically with tauopathy, suggesting this signature as a risk factor for neurodegeneration [130].

Regarding the *C9ORF72* expansion, it was suggested that the length of the repeat might influence the

level of DNA methylation at the *C9ORF72* promoter. This process was found in a family from Canada with the father carrying an intermediate length allele, about 70 repeats, with an unmethylated *C9ORF72* promoter, that expanded to about 1750 repeats in his children. The expanded allele carried by the four children was characterized by *C9ORF72* promoter hypermethylation and associated with reduced *C9ORF72* expression [131]. Recent findings demonstrated that DNA hypermethylation was found in the 5' CpG region (~36% ALS cases), as well as the *C9ORF72* repeat itself in both ALS and FTD patients (~100%) [132, 133].

ncRNAs

It was widely believed in the past that most of the human genome consisted in “non-functional” DNA. It was later discovered that almost the whole genome is transcribed, but that just about 2% is translated into proteins [134].

It is now instead ascertained that most of this “junk” is functional and composed by ncRNA, whose signaling and editing is able to play a crucial role in chromatin and nuclear structure. In particular, ncRNAs are involved in epigenetic regulation by recruiting chromatin-modifying complexes. ncRNAs operate through repressive control but have also the potential to act as gene activators [134].

ncRNAs comprise small RNAs (sRNAs) of less than 200 nucleotides and long non coding RNA (lncRNAs) of more than 200 nucleotides. sRNAs are further subdivided as micro (mi)RNAs, short interfering (si)RNAs, and PIWI-associated (pi)RNAs, whereas lncRNA are categorized according to their direction and position of their transcription in: anti-sense, intergenic, exonic, intronic, overlapping [135].

miRNAs are single stranded, non-coding small RNAs that are abundant in plants and animals, and are conserved across species [136]. The raw transcripts undergo several nuclear and cytoplasmic post-translation processing steps to generate mature, functional miRNAs. In the cytoplasm, mature miRNAs associate with other proteins to form the RNA-Induced Silencing Complex (RISC), enabling the miRNA to imperfectly pair with cognate miRNA transcripts. The target mRNA is then degraded by the RISC, preventing its translation into protein [137, 138]. miRNA-mediated repression of translation is involved in many cellular processes, such as differentiation, proliferation, and apoptosis, as well as other key cellular mechanisms [139, 140].

It is now well established that altered RNA processing could act as a contributing factor to several neurological conditions including aging-related neurodegenerative diseases such as AD, FTD, ALS, and Parkinson's disease [141–143].

In AD, the implication of miRNAs in A β production, via BACE1 modulation, and in tau phosphorylation, that leads to hyperphosphorylated neurofibrillary tangle formation, has been demonstrated [142].

Altered miRNA signatures were also identified in AD and FTD. In particular, several miRNAs have identified differentially expressed in postmortem tissue, blood, and CSF that also differ by disease stage [145, 146].

Regarding lncRNAs, they also have been involved in neurodegenerative diseases [146].

These ncRNAs are involved in different functions; they act as scaffolds for chromatin modifiers and nuclear paraspeckles, as transcriptional co-regulators, and even as decoys for other RNAs [145]. Dysregulations in lncRNAs can influence any one of these processes, thus contributing to neurodegeneration. lncRNAs associated with disease condition can post-transcriptionally increase gene expression, as it happens with the lncRNA BACE1-antisense whose expression is selectively increased in AD brains and competes with miR-545-5p binding to stabilize BACE1 mRNA. This will finally result in increased expression of BACE1 that contribute to the formation of the toxic A β peptides that is a major hallmark for AD [146].

Another lncRNA, BC200, likely plays a role in AD as increased levels were found in specific brain regions mostly affected by AD, such as the Brodmann's area 9 [147]. MALAT1 and NEAT1 are other two lncRNAs very important for splicing and synapse formation [148, 149].

Chromatin remodeling

In mammalian cells, histone proteins interact with DNA to form chromatin, the packaged form of DNA. Histones are octamer consisting of two copies of each of the four histone proteins: H2A, H2B, H3, and H4. Each histone octamer constitutes in 146 bp of the DNA stand wound around it to make up one nucleosome, which is the basic unit of chromatin. Histone proteins can be modified by post translational changes, including: acetylation, methylation, phosphorylation, ubiquitination, and citrullination. These histone modifications induce changes to the structure

of chromatin and thereby affect the accessibility of the DNA strand to transcriptional enzymes, resulting in activation or repression of genes associated with the modified histone [150]. The best-understood histone modification is acetylation, which is mediated by histone acetyltransferases and deacetylases [151]. Acetylation of histones is usually associated with upregulated transcriptional activity of the associated gene, whereas deacetylation of histones to transcriptional silencing [152].

Histone acetylation was found to be largely decreased in the temporal lobe of AD patients compared to controls and in mouse models of AD [153]. Moreover, increased H3 acetylation at the promoter region of the BACE1 gene in AD patients was found [153].

Besides acetylation, different forms of histone methylation exist [154], and may be linked to neurodegenerative diseases.

CONCLUSIONS

Herein, we provided an overview of the current genetic and epigenetic progresses in AD and FTD. We reviewed current knowledge on causative genes and altered mechanisms leading to the two diseases, genetic risk factors and disease modifiers shown to influence the age at onset and clinical course of the diseases, and the role of epigenetics, including methylation, non-coding RNAs, and chromatin remodeling, in influencing gene expression. Data obtained so far suggest a crucial role of microglia and immunity in AD and a role of autophagy and proteasomal degradation in FTD. Future challenges will be a better understanding of the interplay among genetic and epigenetic factors in order to correlate pathogenic mechanisms with clinical phenotypes and pave the way for novel therapeutic approaches such as miRNA mimics or miRNA antagonists (antagomirs), specifically designed to either reverse the downregulation or upregulation of disease-associated miRNAs.

DISCLOSURE STATEMENT

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/17-0702r2>).

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