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Genetics of Frontotemporal Dementia: An Updated Overview

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ABSTRACT: Frontotemporal dementia (FTD) involves a category of disorders characterized by behavioral, linguistic, and mobility abnormalities resulting from neurodegeneration in the frontal and temporal lobes. FTD represents the second most common etiology of early-onset dementia, and is distinguished by a wide range of clinical features. Indeed, three clinical variants are well known: the behavioral variant (bvFTD), which is the most prevalent and predominantly associated with personality and behavioral changes, the semantic variant primary progressive aphasia (svPPA), which is associated with gradual loss of speech integrity and word meaning, and the non-fluent variant primary progressive aphasia (nfvPPA), in which patients have difficulties getting words out, with slurred speech and an abnormal voice. About 15% of FTD patients also have another neurodegenerative motor neuron disease, amyotrophic lateral sclerosis (ALS), and this co-occurrence is called FTD-ALS. About half of FTD cases are familial. The most common observed mode of inheritance for familial FTD is autosomal dominant. So far, at least ten causal genes have been implicated in the etiology of FTD. Three of these genes: the microtubule-associated protein tau (*MAPT*), progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9ORF72*), are the most common and are responsible for more than half of familial FTD. The remaining genes are rarely reported, and the pathological mechanisms of many of them are unclear. The causes of the remainder of the familial FTD proportion, as well as the sporadic FTD, are to be determined. We conclude that despite all the breakthroughs in discovering the etiology of FTD, the majority of work is still to be done. The discovered causal FTD genes give insights toward a better understanding of the clinical and genetic heterogeneity of FTD, and help in its early and correct diagnosis. Despite the current management of FTD relies mainly on supportive treatment several promising clinical trials showed promising results in the correction of the harmful effects caused by the mutant genes.

Keyword: Genetics, FTD, Dementia, Heterogeneity.

Background

Frontotemporal dementia (FTD) represents a group of clinical disorders that results due to loss of neurons, predominantly in the frontal and temporal lobes of the brain. FTD is the third most common type of dementia and the second leading cause of early-onset dementia in patients under the age of 65 years. In most cases, the age at onset varies from 45 to 70 years old. FTD alone accounts for around 5% of all dementias [1]. A wide range of psychological and neurological disorders with symptoms similar to those of FTD may lead to misdiagnosis and underestimate the frequency of FTD due to diagnostic challenges. Epidemiological data estimates that FTD affects 15 to 22 per 100,000 in the population [2, 3]. The incidence is 2.2/100,000 between ages 40-49, 3.3/100,000 between ages 50-59, and peaks to 8.9/100,000 between ages 60-69 [2, 4]. It is noteworthy that most of the published research on FTD has relied heavily on data from countries in North America, Western Europe, and Australia [2]. However, in most developing countries, little research about FTD and dementia in general has been published due to several challenges including the lack of funds and resources, the insufficient knowledge, and the unavailability of specialized centers for neurodegenerative disease research [5-7]. FTD affects both sexes, with a small dominance of males [8].

The FTD has a substantial mortality rate, and the average survival time varies greatly depending on subtype. The typical survival time from diagnosis to death might be as short as three years for bvFTD patients with motor neuron disease, and up to 12 years for those with svPPA [9]. There is a family history of dementia in roughly 40% of cases of frontotemporal dementia (FTD), and autosomal dominant is the most common mode of inheritance [10-12]. Indeed, in 10-25% of cases, FTD shows an autosomal dominant inheritance pattern [13]. After discovering the link between chromosome 17 and hereditary FTD, a mutation in the microtubule-associated protein tau (*MAPT*) gene, which encodes the tau protein, was discovered in 1998. Notably, tau is a protein identified in the neurofibrillary tangles found in Alzheimer's disease patients' brains. However, this was not Alzheimer's disease because no amyloid plaques were found [14, 15]. The frontal and temporal lobes are responsible for personality, behavior, language learning, motivation, abstract thinking, and executive functions. Therefore, behavioral changes and/or language difficulties are the most prominent clinical manifestations of FTD patients, followed by a decline in executive function and cognitive capacities. FTD refers to a group of neurological conditions that primarily affect the brain's frontal and temporal areas. The anatomical localization is linked to the clinical picture characterized by impairments of social cognition, behavioral changes, executive function deficits, linguistic disorders, and, to a lesser extent, memory impairment.

The definition of FTD has been refined over the course of many years. Prior to the twenty-first century, FTD was divided into three subtypes: behavioral difficulties predominance, progressive nonfluent aphasia [16], and semantic dementia [17]. In 2011, additional diagnostic criteria and subtypes were

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amended and added to the list of available options. Because of this, the FTD was divided into two categories: behavioral variation FTD (bvFTD) and primary progressive aphasia (PPA), which was further subdivided into two subtypes: the semantic variant (svPPA) and the nonfluent variant (nfvPPA). (Figure 1) [18].

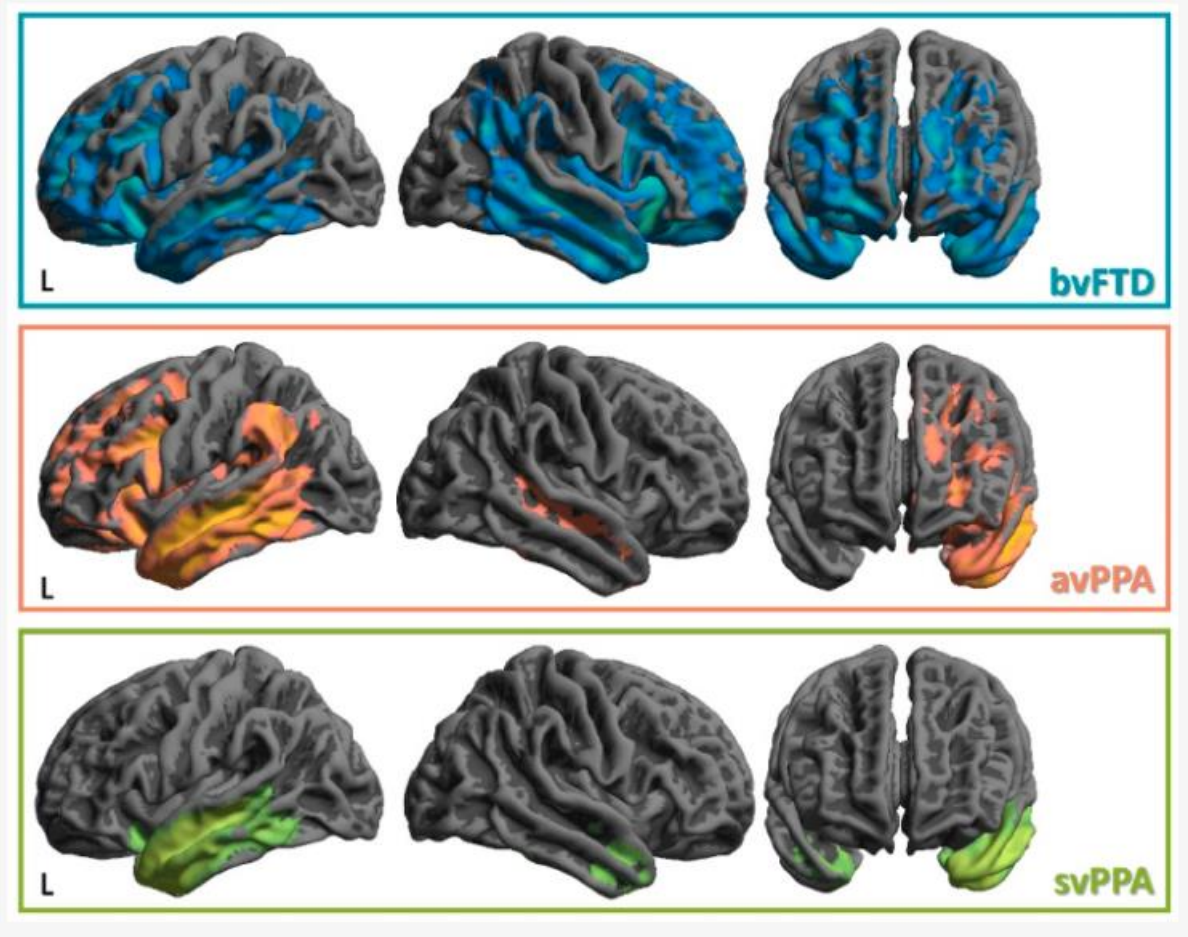

Figure (1): Illustration of patterns of frontal and temporal lobes atrophy in FTD patients by magnetic resonance imaging. The pattern of atrophy is different between these variants but in general they involve the frontal and the temporal lobes. Note: avPPA refers to agrammatic variant of Primary Progressive Aphasia which is the nonfluent variant of primary progressive aphasia that is labeled as nfvPPA in this article [19].

Over the course of several years, a large number of researchers have arrived at the conclusion that FTD may be traced back to its genetic roots. The first locus for FTD was discovered in 1998, and it was demonstrated that mutations in microtubule-associated protein tau (*MAPT*) are responsible for familial FTD with Parkinsonism, which is linked to chromosome 17q21 (FTDP-17) [15]. A number of new mutations have been discovered after the year 2006, including hexanucleotide repeat expansions in the chromosome 9 open reading frame 72 (*C9ORF72*) gene, transactive response DNA-binding protein 43 (*TDP-43*), and the progranulin (*GRN*) gene [20-23]. The mode of inheritance in FTD patients due to mutations in these genes is autosomal dominant.

Three clinical variants of FTD (Figure 2)

bvFTD causes an early and progressive deterioration in social functioning, as well as personality changes. It accounts for almost 50% of all cases of FTD. The hallmark signs of borderline personality disorder are progressive changes in emotional control, behavior, and personality [24, 25]. Patients with bvFTD may present with general lack of self-awareness and lack of empathy and sympathy toward friends or stranger due to lesions in right medial orbitofrontal cortex and anterior part of insula [26, 27], disinhibition due to the involvement of orbitofrontal cortex, repetitive movement suggesting frontosubcortical dysfunction [28], and deficit in executive function due to involvement of dorsolateral prefrontal cortex [29]. Despite the fact that some reports indicate that the right hemisphere is more affected than the left, the behavioral variation is characterized by localized and significant bilateral frontal atrophy [8, 30]. Phenotypic syndromes, in which a patient has mild autism spectrum disorder or personality problems alongside intact social and emotional functions and no atrophy in magnetic resonance imaging (MRI), and decreased daily functional capacity, both of which can be severe in early stages, are additional symptoms that behavior variant patients may have. Patients may also exhibit hyperorality, changes in nutrition, and repetitive or ritualistic behaviors, as well as perseverative or stereotyped tendencies [4]. Typically, diagnostic criteria are used in conjunction with neuroimaging, cognitive testing, and clinical evaluation to confirm a diagnosis of FTD. The International Consensus Criteria (ICC) guides the diagnosis of bvFTD [31]. The hallmarks of bvFTD include neuroimaging evidence of frontal and/or anterior temporal lobe atrophy, progressive behavioral or personality changes, and cognitive impairment affecting multiple domains. Significant cerebrovascular illness and alternative neurological or psychiatric disorders should be excluded before the diagnosis of bvFTD is established. It should be noted that neuropathological examination after death is usually required to confirm the diagnosis of FTD.

svPPA: represents about 20 to 25 percent [32] of patients with a mean age at symptom onset of 60 years old. Compulsions, loss of language skills, and bilateral anterior temporal lobe atrophy are all symptoms that are typical clinical manifestations of this condition [3, 4, 33]. Furthermore, this condition is

associated with dysfunctional emotional processing. There is a correlation between svPPA and semantic information loss, which is described as the loss of object knowledge, impoverished content, semantic and paraphasic mistake. Neuroimaging research shows asymmetrical bilateral atrophy of the anterior temporal lobe, as well as changes in the left inferior frontal gyrus and posterior superior temporal gyrus. Furthermore, MRI indicated asymmetrical anterior hippocampus atrophy, which is associated to language, compulsions, and dysfunctions in emotional processing [34]. Genetically, svPPA is related with mutations in the *GRN* and *MAPT* genes. [35, 36]. However, genotype-phenotype correlations are complex, with variable clinical presentations even among individuals with the same genetic mutation. The diagnostic criteria for svPPA, outlined by the ICC and the International Behavioral Variant FTD Criteria Consortium (FTDC), emphasize progressive language impairment, relatively preserved other cognitive functions and characteristic neuroimaging findings [37].

nfvPPA is characterized by a noticeable and early symptom of language impairment. This impairment is characterized by apraxia of speech, which causes sluggish speech output due to a speech motor planning deficit. Additionally, nfvPPA is associated with a condition known as agrammatism in language production. Neuroimaging studies of nfvPPA typically reveal asymmetric atrophy in the left posterior frontal lobe, particularly affecting Broca's area and the supplementary motor area, along with corresponding white matter changes [38-40]. Genetically, nfvPPA is associated with mutations in the *MAPT* gene, and the *C9ORF72* gene [35, 41, 42]. The diagnostic criteria for nfvPPA, outlined by the ICC and the FTDC, emphasize progressive non-fluent language impairment, relatively preserved other cognitive functions, and characteristic neuroimaging findings.

Several research and centers have found a higher prevalence of bvFTD in males [2, 43]. Males are more likely to have svPPA, while females are more likely to have nfvPPA [44]. The median survival time from diagnosis to death varies from three years for bvFTD patients with motor neuron disease to twelve years for those with svPPA [9].

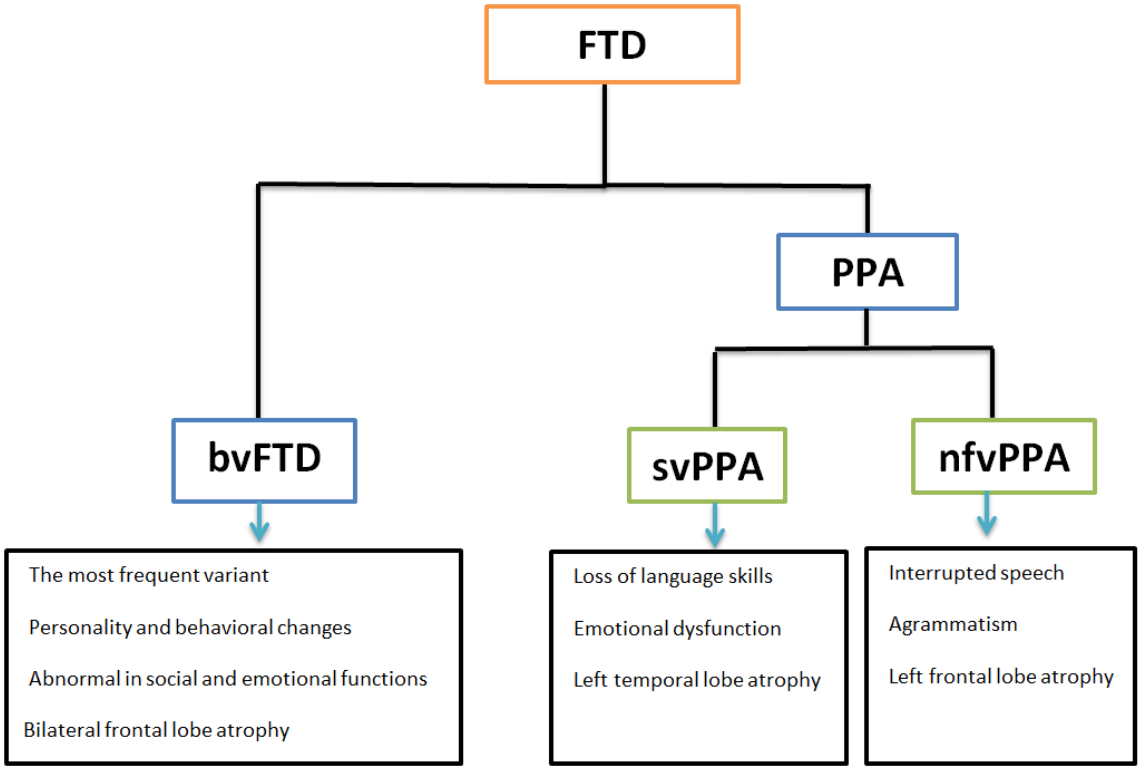

Figure (2): The three clinical variants of FTD with their characteristics and the predominantly affected brain are in each variant.

Association between FTD and ALS

ALS is a fatal type of motor neuron disease caused by irreversible neurodegeneration of nerve cells in the spinal cord and brain. ALS has great overlap with FTD both in terms of clinical manifestations, neuropathological features, and more interestingly the genetic aspects [45]. About 15% of patients with ALS have also FTD, and the same percentage of FTD patients have also ALS. Nevertheless, the explanation of the co-occurrence of both disorders in the same patient is not fully understood. It is believed that ALS and FTD are both ends of the same disorder [46-48].

Genetics of FTD

FTD is a heritable neurodegenerative disease characterized by significant clinical, pathological, and genetic variations. [49], This is supported by the fact that approximately 25-50% of FTD patients reported a positive family history of dementia or related neurodegenerative disorders. Autosomal dominant transmission was the most frequently identified mode of inheritance [11, 50, 51]. Notably, the heredity of FTD varies substantially depending on the clinical phenotype. The bvFTD was shown to be the most frequent heritable variation [52], while svPPA is generally considered the least one to have a genetic etiology [52]. Mutations in at least ten genes (Figure 3) were identified as causal in patients with familial FTD. Three of these genes (*MAPT*, *GRN*, *C9ORF72*) represent the most common genes in cases of FTD. Causal mutations in the remaining genes were rarely reported in some families and represented rare causes of FTD and/ or FTD-ALS. The summary of these ten genes is illustrated in Table 1.

Table (1): Summary of genes implicated in the etiology of FTD with their characteristics.

Gene	Date of mutation discovery	Mutation frequency	Types of mutations	Mechanism of mutations	Mode of inheritance	Phenotype
MAPT	First discovered major gene 1998	5-20% of familial FTD	Missense, silent, deletion and splice site mutations	Gain of toxic function of tau protein	AD	bvFTD with Parkinsonism
GRN	Second discovered major gene 2006	5-20% of familial FTD	Nonsense, splice site and frameshift mutations	Loss of function	AD	bvFTD and nfvPPA with or without parkinsonism
C9ORF72	Third discovered major gene 2011	The most frequent, responsible for one third of familial FTD	Hexanucleotide (G4C2)n repeat expansion	Haploinsufficiency and gain of function	AD	bvFTD and FTD-ALS
TARDBP	2008	Rare	Missense mutations	Unclear but thought gain of function, haploinsufficiency	AD	bvFTD and svPPA, FTD-ALS
CHMP2B	2005 called FTD3 as it is located on chromosome 3	Rare, private mutations in Danish and Belgian families	Splice site and nonsense mutations	Loss of function	AD	bvFTD with personality change as the most commonly presentation
VCP	2004	Rare	Missense mutations	Gain of function, haploinsufficiency	AD	bvFTD and FTD-ALS
TBK1	2015	Rare	Missense, inframe deletions, non-sense, frame shift mutations	Loss of function	AD	bvFTD and FTD-ALS
FUS	2009	Rare	Missense mutations	Unclear but thought gain of function, haploinsufficiency	AD	bvFTD and FTD-ALS
SQSTM1	2012	Rare	Missense mutations	Unclear but thought gain of function, haploinsufficiency	AD	bvFTD and FTD-ALS
UBQLN2	2011	Rare	Missense mutations	Unclear but thought gain of function, haploinsufficiency	XLD	bvFTD and FTD-ALS

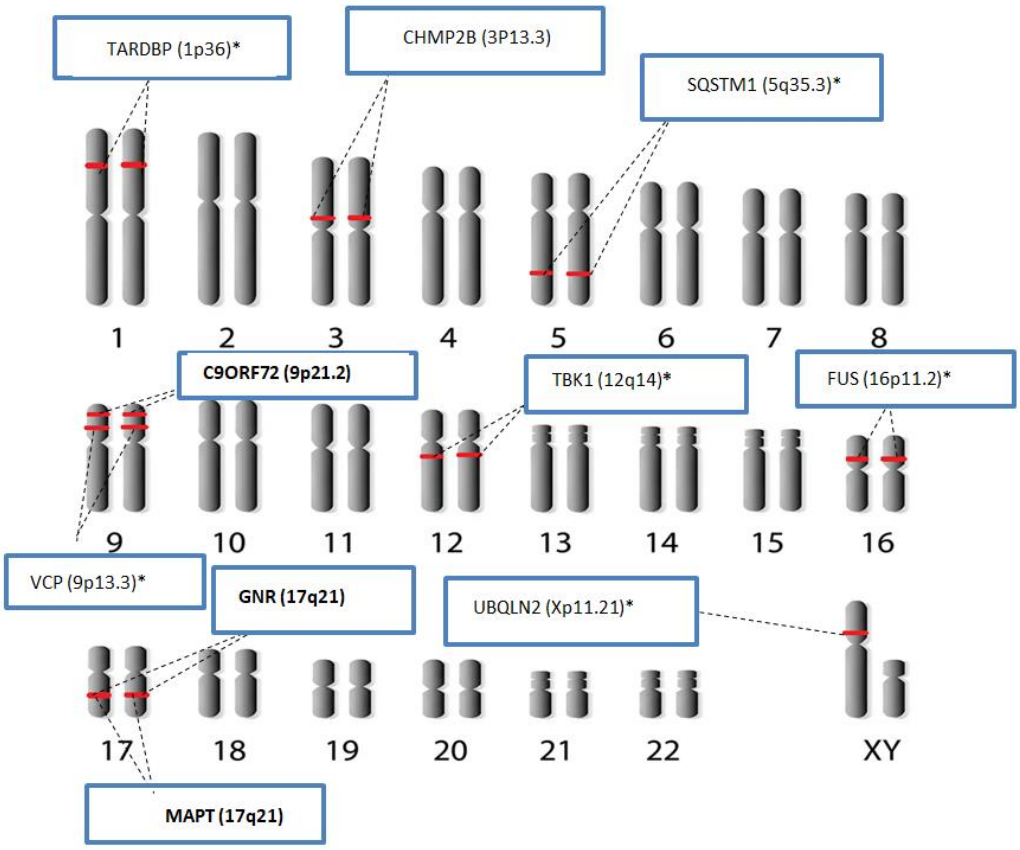

Figure (3): The locations of the ten genes implicated in FTD on human chromosomes. Bolded genes are the common ones in FTD. * Genes which are involved in FTD-ALS.

***MAPT* gene:** The microtubule-associated protein Tau (*MAPT*) gene, which is located on the 17q21 chromosome, contains 16 exons [53]. Its transcripts can undergo alternative mRNA splicing to produce six isomers [54]. These isomers are important to enhance the formation of microtubules, as well as to maintain their stability. These microtubules are vital for the integrity of the cytoskeleton and cytoplasmic transport in human cells, including neuronal cells, because this gene is strongly expressed in the nervous system [55]. More than 50 different *MAPT* pathogenic mutations were identified in patients with FTD, particularly in the bvFTD and, to a lesser extent, in the svPPA and nfvPPA which are often associated with the movement disorder Parkinsonism [56]. They showed autosomal dominant mode of inheritance [57]. These different mutations lead to abnormal structure and subsequently gain of toxic function of tau protein, which leads to its abnormal aggregation and disruption of the formation and stability of microtubules [58]. It is noteworthy that certain *MAPT* mutations are causal in rare familial cases of Alzheimer disease [59, 60].

***GRN* gene:** In 2006, a granulin (*GRN*) gene, located very close to *MAPT* gene on 17q21 chromosome, was discovered as causal for FTD [21]. *GRN* gene product is found in several tissues including the central and peripheral nervous system. It acts as a growth factor that is involved in angiogenesis, brain development and synapse functioning. More specifically, it is involved in the survival, growth, maintenance, and differentiation of both neurons and glia [61]. More than 70 different *GRN* mutations were detected in FTD. All *GRN* mutations cause FTD by haploinsufficiency with incomplete penetrance [62, 63]. Lysosome dysfunction in FTD patients was proposed as the main mechanism of pathology in FTD patients with *GRN* loss of function [64]. Moreover, it was reported that lysosome dysfunction might lead to the activation of microglia and the deposition of myelin debris in the central nervous system as proposed mechanisms of the neurodegeneration [65]. *GRN* mutations were mostly found in the bvFTD and nfvPPA with or without movement disorders. *GRN* mutations are associated with great variability in the clinical presentation in patients with FTD [66].

***C9ORF72* gene:** Hexanucleotide repeat expansions in chromosome 9 open reading frame 72 (*C9ORF72*) gene, located on chromosome 9p21.2, consists of two non-coding exons (1a and 1b) and 10 coding exons (from 2 to 11). Alternative splicing of its transcripts results in the formation of two isoforms: C9-short of 24 kDa and C9-long of 54 kDa [27]. *C9ORF72* transcripts are detectable in most tissues, notably in all brain regions and the spinal cord, and play a role in neuronal axon growth and maintenance of neuronal synapsis integrity [67].

In 2011, a breakthrough in the uncovering of the genetic basis of FTD was achieved by the identification of a hexanucleotide (G4C2)n repeat expansion in the *C9ORF72* gene as the most frequent mutation in familial FTD [68, 69]. As with other genetic disorders caused by nucleotide repeat expansion, age at onset of FTD patients due to *C9ORF72* mutations varied greatly from 20s to 90s [70, 71]. The clinical presentations of patients with *C9ORF72* mutations vary greatly from very rapidly to slow progressive disease [68, 72, 73]. Several genotype-phenotype relationships in bvFTD can result from *C9ORF72* gene mutations. First, larger repeat expansions cause earlier onset and worse clinical progression. *C9ORF72* repeat expansion is connected to disinhibition, apathy, and social cognitive deficits. *C9ORF72* mutations in bvFTD produce neuronal loss, gliosis, and proteinaceous inclusions including *TDP-43* and p62-positive aggregates [68]. It is noteworthy that about one third of patients with *C9ORF72* mutations receive another diagnosis at the onset due to the atypical clinical presentations [74, 75]. It is proposed that the mechanism by which *C9ORF72* gene mutations lead to FTD include haploinsufficiency through the loss of function of the gene, as well as gain of novel toxic functions including RNA and protein toxicity [76]. It is important to note that the toxicity of *C9ORF72* hexanucleotide repeat expansions was suggested to be the result of a variety of mechanisms, such as the accumulation of toxic cytoplasmic proteins and the formation of RNA foci through phase separation. The *C9ORF72* protein's functionality is significantly impaired as a consequence of these abnormal alterations [77, 78].

Rare genes in FTD

***TARDBP* gene:** TARDBP gene, which is located on 1p36 chromosome, codes TAR DNA-binding protein 43 (TDP43) which has a crucial role in RNA metabolism [79, 80]. Rare missense *TARDBP* mutations were identified in patients with FTD and FTD-ALS [81]. These mutations affect predominantly the C-terminal region inducing the aggregation propensity [82-85].

CHMP2B gene: Charged multivesicular body protein 2B (CHMP2B) gene, located on 3p11.2 chromosome, codes for a protein involved in autophagy and Endo-lysosomal trafficking. Rare autosomal dominant splice site and nonsense mutations were described in Danish and Belgian FTD families with great clinical variability among these patients [86-89]. These mutations affected the C-terminus of the protein. It is proposed that CHMP2B mutations cause accumulation of autophagosomes with ubiquitinated proteins resulting in neurodegeneration [90]. Endosomal-lysosomal dysfunction and ubiquitin-SDP-43 neuronal intranuclear inclusions (NIIs) result from CHMP2B mutations [91-95].

VCP gene: Valosin-containing protein (VCP) gene, which is located on 9p13.3 chromosome, is a highly conserved eukaryotic protein [96, 97]. VCP is widely expressed in several organs including the brain. It belongs to the type II AAA family, which encompasses a variety of cellular processes, such as the regulation of the cell cycle, the maturation of the autophagosome and the ubiquitin-proteasome system e [98, 99]. Several missense mutations in VCP were detected in FTD patients. These mutations are suggested to cause neurodegeneration by defects in protein clearance, and autophagy. It is noteworthy that VCP mutations are characterized by phenotypic heterogeneity as different mutations result in different disorders including myopathy, motor neuron disease, Paget, and FTD [100].

TBK1 gene: The TBK1 (TANK binding kinase 1) gene is located on the 12q14 chromosome. It codes for a protein that plays a critical role in several cellular pathways including the selective clearance of mitochondria and regulation of inflammation. Several missense, inframe deletions, non-sense, and frame shift mutations identified in bvFTD and FTD-ALS patients. Behavior, motor and cognitive impairment result from *TDP-43* pathology and TBK1 mutations. TBK1 mutations may contribute to neurodegenerative diseases through defective clearance of damaged mitochondria. Indeed, this process this vital in neuronal survival [92, 101-104].

FUS gene: The fused in sarcoma (FUS) gene, which is located on 16p11.2 chromosome, codes for RNA-binding protein. This protein is involved in alternative RNA splicing, RNA translation and transport [105]. Some missense FUS mutations were reported in FTD patients and FTD-ALS patients [106-108]. The aberrant RNA metabolism especially defective splicing pattern was proposed as the cause of neurodegeneration of FUS mutations [109].

SQSTM1 gene: The sequestosome 1 (SQSTM1) gene, which is located on 5q35.3, codes for p62 adaptor protein. This multifunctional protein is involved in vital cellular processes including cell differentiation, apoptosis, transcriptional regulation, and oxidative stress, and ubiquitin-proteasome degradation pathways [110]. Some missense SQSTM1 mutations were rarely reported in the neurodegenerative disorders FTD, ALS, and FTD-ALS patients [111, 112]. It was suggested that the defects in cellular pathways caused by mutant SQSTM1 product result in neurodegeneration [104, 113].

UBQLN2 gene: Several missense mutations were rarely reported in UBQLN2 gene, which is located on the Xp11. 21 chromosome, in patients with FTD-ALS. Interestingly, these mutations follow X-linked dominant inheritance [114, 115]. At least, some of these mutations altered the structural and functional characteristics of the resulting protein and showed a clear correlation between the increased tendency to aggregate and its ability to induce neurotoxicity [116-118]. Indeed, it was proved that UBQLN2 encodes a protein that functions in protein quality control and regulation of proteasomal degradation [118].

Diagnosis of FTD: The diagnostic criteria for FTD, both for the behavioral bvFTD variant and the two language variants of FTD (svPPA and nfvPPA), were established by international expert consensus.

The clinical diagnosis of bvFTD [37] is established if the patient meets at least three of the following criteria: (I) early disinhibition; (II) apathy or early inertia; (III) early loss of empathy/sympathy; (IV) perseverative, stereotyped, or early compulsive/ritualistic behavior; (V) hyperorality and dietary changes; and (VI) neuropsychological profile with executive dysfunction and relative preservation of episodic memory and visuospatial abilities.

On the other hand, the clinical diagnosis of the language variants of FTD (svPPA and nfvPPA) requires fulfilling three core criteria: (1) the presence of a language impairment that interferes with the usage and/ or comprehension of words; (2) this language impairment should be the most prominent neurobehavioural deficit that restricted the daily activities during the initial stages of disorder; and (3) the language impairment should be progressive in nature as it is caused by neurodegenerative changes. Furthermore, the pattern of deficits must not be explained by another neurological or psychiatric disorder [119].

The definitive FTD diagnosis is established only when histopathological changes are observed on brain biopsy, post-mortem examination, or by genetic testing with identification of the causal mutation [120]. It is important to rule out any metabolic or infectious disease which has clinical manifestations that overlap or looks like those cause by FTD. To this end, hormonal analysis, liver function tests, appropriate blood and urine tests should be performed. In addition to that, causes of reversible cognitive impairment like vitamin B12 and folic acid deficiency should be taken into consideration [120].

Neuroimaging analyses of FTD patients can be used to confirm the clinical diagnosis and to exclude other neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and ALS with overlapping clinical manifestations. Depending on the mechanism of action, these neuroimaging methods are classified into three categories: structural, functional, and molecular imaging. Structural imaging includes computed tomography (CT) and structural magnetic resonance imaging (MRI), which can show gross neuroanatomical changes. Functional imaging includes positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional MRI (fMRI), tests the metabolic activity, regional blood flow, or hemodynamic changes with patient activity. While the molecular imaging measures molecular and, biological, physiological, and cellular events in living neuronal tissues such as testing for specific receptors or protein aggregates. For the diagnosis of FTD, the structural MRI and PET are two of the most commonly used [121].

Structural imaging can be used to test for the abnormalities in the neuroanatomy of the frontotemporal lobes, and to detect any increase in the sulci and fissures. They are also used to check for the presence of any frontotemporal tumors, ventricular dilatation, or cerebrovascular lesions that are associated with symptoms related to FTD [120].

The functional imaging PET can be used to detect areas in the brain that are characterized by hypometabolic activity and a reduction in blood flow [122, 123].

FTD Prognosis, treatment, clinical trials and future perspectives: FTD is a fatal and irreversible condition for which there is no known curative therapy. The median survival age varied greatly according the clinical presentation. It was the poorest if FTD is associated with motor disease (FTD-ALS) with median survival age of only 2.5 years. On the other hand, the mean survival age was the longest (8 years) in patients with svPPA. In the most common variant (bvFTD) as well as in the nfvPPA, the mean survival rate was 8 years after diagnosis of the disorder. Notably, the sex of the patient did not affect the mean survival age [124]. There is no curative treatment to prevent, stop or delay the neurodegeneration in FTD patients until now. Supportive management is offered to patients and is directed to handle the cardinal symptoms and improving the quality of life [125].

Significant research has been done to specify certain biomarkers to help in presymptomatic and early diagnosis. Nevertheless, there is currently no reliable specific biomarker to be tested for FTD [126]. There are ongoing clinical trials with drugs with potential disease-modifying effect. These therapeutic targets are directed towards preventing and clearing tau aggregates, maintaining the normal tau function, restoring progranulin levels; and suppressing the expression of harmful genes [127]. The ongoing promising clinical trials are designed for the three major genetic defects [128]. The use of antisense oligonucleotide (ASO) demonstrated beneficial effects by selective suppression of the toxic *C9ORF72* transcripts containing the expansions but not affecting the normal transcripts of the gene [129]. ASO was also found to be effective to lower the expression and correct the disturbances resulting from *MAPT* mutations in neurodegenerative disorders [130, 131]. On the other and, adeno-associated virus delivery gene therapy is being tested to offer a functional copy of the *GRN* gene in patients having mutations in this gene to correct the normal expression level, and consequently restore the normal functions of the protein [132]. Additional proposed therapeutic options include tau monoclonal antibodies which are beneficial in some *MAPT* mutations [133], and the use of sortilin protein to rescue *GRN* expression level by sortilin-*GRN* interactions [134] .

CONCLUSION

FTD is characterized by wide range of clinical variability and genetic heterogeneity. The etiology is still unknown in the majority of FTD patients. Identifying several causal genes of FTD is of great importance as it points towards a significant genetic component of this disease, as well as multiple disease mechanisms that might share common pathological pathways. The accumulation of these discoveries leads the progress of correct and early diagnosis, and the development of drugs that prevent or delay the neurodegeneration as the main pathological

feature of the disorder. Establishing genotype and phenotype correlations in FTD (when present) is particularly important to provide genetic counseling for FTD patients and families. Further studies should be performed to discover additional genetic and environmental factors that impact in the etiology of familial and sporadic FTD.

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- **Author Contributions:** Each of the authors played a substantial role in this research, including contributions to the conception and study design. Additionally, they were involved in drafting, and revising the article. Furthermore, all authors provided approval for the manuscript's publication, selected the journal for submission, and committed to being accountable for all aspects of this research.
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