



Recent Updates on the Genetics of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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Received: 5 May 2022 / Accepted: 16 June 2022 / Published online: 30 June 2022
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Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) primarily affect the motor and frontotemporal areas of the brain, respectively. These disorders share clinical, genetic, and pathological similarities, and approximately 10–15% of ALS-FTD cases are considered to be multisystemic. ALS-FTD overlaps have been linked to families carrying an expansion in the intron of *C9orf72* along with inclusions of TDP-43 in the brain. Other overlapping genes (*VCP*, *FUS*, *SQSTM1*, *TBK1*, *CHCHD10*) are also involved in similar functions that include RNA processing, autophagy, proteasome response, protein aggregation, and intracellular trafficking. Recent advances in genome sequencing have identified new genes that are involved in these disorders (*TBK1*, *CCNF*, *GLT8D1*, *KIF5A*, *NEK1*, *C21orf2*, *TBP*, *CTSF*, *MFSD8*, *DNAJC7*). Additional risk factors and modifiers have been also identified in genome-wide association studies and array-based studies. However, the newly identified genes show higher disease frequencies in combination with known genes that are implicated in pathogenesis, thus indicating probable digenic/polygenic inheritance models, along with epistatic interactions. Studies suggest that these genes play a pleiotropic effect on ALS-FTD and other diseases such as Alzheimer's disease, Ataxia, and Parkinsonism. Besides, there have been numerous improvements in the genotype–phenotype correlations as well as clinical trials on stem cell and gene-based therapies. This review discusses the possible genetic models of ALS and FTD, the latest therapeutics, and signaling pathways involved in ALS-FTD.

Keywords Amyotrophic Lateral Sclerosis · Frontotemporal Dementia · Oligogenic Inheritance · Mechanistic Pathways · Novel Therapeutics

Abbreviations

fALS	Familial amyotrophic lateral sclerosis	<i>VCP</i>	Valosin-containing protein
fFTD	Familial frontotemporal dementia	<i>PFN1</i>	Profilin1
sALS	Sporadic amyotrophic lateral sclerosis	<i>TBK1</i>	TANK-binding kinase
sFTD	Sporadic frontotemporal dementia	<i>CCNF</i>	Cyclin <i>F</i>
<i>TARDBP</i>	TAR DNA-binding protein-43	<i>KIF5A</i>	Kinesin family member 5A
<i>TDP-43</i>	TAR DNA-binding protein 43	<i>GLT8D1</i>	Glycosyltransferase 8 domain containing 1
HIV-1	Human immunodeficiency virus	<i>NEK1</i>	NIMA-related kinase 1
<i>c9orf72</i>	Chromosome 9 open reading frame 72	<i>CHMP2B</i>	Charged multivesicular body protein 2B
<i>FUS</i>	Fused in sarcoma	<i>CHCHD10</i>	Coiled-coil-helix-coiled-coil-helix domain containing 10
<i>SQSTM1</i>	Sequestrome-1	WGS	Whole-genome sequencing
<i>SOD1</i>	Superoxide dismutase 1	WES	Whole-exome sequencing
<i>GRN</i>	Granulin	GWAS	Genome-wide association studies
<i>MAPT</i>	Microtubule-associated protein tau	RAN	Repeat-associated non-AUG
		DPR	Dipeptide repeat
		<i>OPTN</i>	Optineurin
		<i>C21orf2</i>	Chromosome 21 open reading frame 2
		<i>DNAJC7</i>	DnaJ heat shock protein family (Hsp40) member C7
		TBP	TATA-box binding protein

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CTSF	Cathepsin F
MFSD8	Major facilitator superfamily domain 8
PGRN	Glycoprotein called progranulin
TDP-43	TAR DNA-binding protein-43
hnRNP	Heterogeneous nuclear ribonucleoprotein
DPRs	Dipeptide repeat proteins
TBK1	TANK-binding kinase 1
UMN	Upper motor neuron
LMN	Lower motor neuron
FTLD	Frontotemporal lobar degeneration
FTDP-17T	Frontotemporal dementia with parkinsonism-17 T
PSP	Progressive supranuclear palsy
CBD	Corticobasal degeneration
NFTs	Neurofibrillary tangles
IHC	Immunohistochemistry
AD	Alzheimer's disease
PD	Parkinson's disease
CJD	Creutzfeldt-Jakob disease
UPS	Ubiquitin–proteasome system
RRM2	Ribonucleoside-diphosphate reductase subunit M2
VCP	Valosin-containing protein
VAPB	VAMP-associated protein B And C
HNRNPA1	Heterogeneous nuclear ribonucleoprotein A1
AMPA	α -Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
GABAA	γ -Aminobutyric acid type A receptors
LLPS	Liquid–liquid phase separation
LCD	Low complexity domain
TUBA4A	Tubulin Alpha 4a
ALS2	Alsin
LAMP-2	Lysosomal associated membrane protein-2
CTSD	Cathepsin D
CSF	Cerebrospinal fluid
ASOs	Antisense oligonucleotides
CuATSM	Diacetylbis(N(4)-methylthiosemicarbazonato) copper II
iPSCs	Induced pluripotent stem cells
CSF	Cerebrospinal fluid

Introduction

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are debilitating, progressive adult-onset brain disorders [1]. Clinically, ALS and FTD are considered as movement and cognitive disorders [2]. Most commonly, ALS affects the upper motor neurons (UMNs) and lower motor neurons (LMNs) as well as the brain stem and the corticospinal tracts of the brain, while FTD causes a gradual degeneration of both the temporal and frontal cortex [3]. ALS and FTD are clinically heterogeneous entities,

although some phenotypes of ALS, such as cognitive impairment, overlap with that of FTD [4]. An estimated 50% of ALS patients demonstrate subtle impairments in behavior, cognition, and dementia-like features, while up to 15% of ALS patients also suffer from FTD; these individuals are called ALS-FTD or FTD-ALS patients [4]. Most of these ALS-FTD patients do not have a family history and are considered sporadic (sALS/sFTD). Nevertheless, ~10% of ALS cases are inherited in an autosomal dominant manner (fALSs) [5], while ~10–30% of FTD cases also show autosomal dominant inheritance or familial FTDs (fFTDs), which increases to 40% if a history of neurodegenerative disease is considered [6]. Moreover, both sALS and sFTD lack a family history that could be attributed to alternative modes of inheritance, such as oligogenic/polygenic inheritance or, most likely, reduced penetrance [7]. Additionally, pleiotropic mechanisms have been hypothesized at the genetic and environmental levels, possibly explaining individual differences due to the involvement of distinct disease pathways [8]. Clinically, most fALS cases are indistinguishable from sALS and vice versa. For example, TAR DNA-binding protein-43 (*TARDBP*) mutations are rare (~1%) in both ALS and FTD patients [1]. However, neuropathological studies have shown the presence of TDP-43 aggregates in ~97% of ALS cases and up to 50% of FTD cases [1, 9]. These studies suggest there is a definitive pathological link between familial and sporadic ALS and FTD. Nevertheless, several well-known genes have been identified in a larger population of ALS/FTD patients [4]. Such examples include those of chromosome 9 open reading frame 72 (*C9orf72*), *TARDBP*, fused in sarcoma (*FUS*), sequestrome-1 (*SQSTM1*), etc. [10]. With the advancement of sequencing technologies and their ease of use, scientists have been able to produce larger datasets for international projects and consortia such as Project MinE (<https://www.projectmine.com/>) and GENFI3 (<https://www.genfi.org/>) which have further identified many novel genes and risk factors, along with genetic modifiers of ALS and FTD, respectively [11]. ALS-FTD is related to over 30 genetic loci, > 100 genes, and numerous mutations, and new genes are continually being discovered [12, 13]. A number of GWASs have revealed the role of several modifier genes in ALS/FTD pathogenesis [14, 15]. Nevertheless, these low penetrating variants, which appear to contribute substantially to disease pathology, must be validated across different populations. There is still uncertainty about whether these genes play a role in disease penetrance or whether environmental factors trigger the disease. It is well established that ALS and FTD are not two separate diseases, but instead, constitute a syndrome or a disease spectrum [16]. These diseases illustrate the presence of oligogenic or polygenic effects, or even pleiotropy, where more than one gene or numerous mutations are present in a variety of genes, resulting in a wide variety of phenotypes

[3, 4, 17]. Besides, phenotypic variability might be triggered by other genetic phenomena such as epistatic interactions. For example, multiple genes involved in ALS may interact epistatically, explaining the substantial differences in phenotypic behavior observed between individuals who carry the same mutation(s); thus, this may also explain the incomplete penetrance of the disease within some families [18]. Therefore, this leads to newer challenges for appropriate diagnostics and prognostics of ALS and FTD. New genetic testing, patient education and counseling, and gene-based clinical trials are equally important. Interestingly, gene-specific therapies such as superoxide dismutase 1 (*SOD1*) and granulin (*GRN*)/*C9orf72* have shown promise in treating ALS and FTD [19–21]. Hence, this review discusses the latest genetic findings related to ALS and FTD in addition to hotspot/modifier genes like *SOD1*, *GRN*, microtubule-associated protein tau (*MAPT*), *TARDBP*, and *C9orf72*. These genes are not only congregated in corresponding pathways, but they also function in DNA repair, axonal transport, RNA metabolism, and formation of stress granules [22]. These insights also spurred mechanistic studies that uncovered a common pathway between ALS and FTD [4]. Despite these discoveries, understanding why mutations in these genes cause ALS, FTD, or both remains obscure.

Novel Genetic Landscape of ALS and FTD

ALS and FTD share many clinical, genetic, and pathological features as evidenced in Table 2. Numerous known and novel genes have also been detected in each group (Tables 1 and 2 and Fig. 1). Mutations in genes known to cause ALS (*SOD1*, *C9orf72*, *TARDBP*, *VCP*, *FUS*, *PFN1*, etc.) and FTD (*PGRN*, *MAPT*, *C9orf72*, *CHMP2B*, *TBP*, *CHCHD10*, etc.) have explained only ~60–70% of fALS/fFTD and ~10% of sALS/sFTD cases [23]. Furthermore, the hexanucleotide expansion mutations in *C9orf72* have been a major causal factor for both ALS and FTD [24, 25]. Despite the identification of several known causal factors, there are still many genetic forms of the disease that are yet to be discovered. Recent advances in sequencing capabilities, including whole-genome sequencing (WGS), and whole-exome sequencing (WES), have made identification of causal alleles and additional genes easier. The WGS focuses to cover all regions in the genome, while WES targets mostly the coding region of the genome. In comparison to WGS, WES is much cheaper and cost-effective and takes lesser time to analyze raw data. With the advent of next-generation sequencing technology, greater in-depth discoveries have been made possible in the genomics of ALS-FTD. Genome-wide association studies (GWAS) is another powerful tool that can be used to discover novel genetic loci involved in ALS-FTD pathogenesis. GWAS involves rapid scanning of

markers scattered throughout the genome or examining complete DNA sets from many individuals to trace the genetic variation(s) associated with a particular trait or disease. GWAS generally identifies common variants, while rare variants conferring disease risk remain undetected. Despite this, identifying novel genes or newer defects involved in disease pathogenesis is extremely crucial, and thus, scientists are sequencing more samples to identify rare variants and genes that significantly contribute to both ALS and FTD. Recently, several genes that carry these rare genetic variants have been identified [10]. This includes two new FTD loci, six ALS genes, and two ALS-FTD genes discovered in the last 7 years (Table 1, Fig. 1, and Fig. 2). There is a higher penetrance for these genes and co-occurrence of multiple mutations in combination with *C9orf72* which are based upon familial, case-control, and candidate-based studies [4]. Among them are *TBK1*, *CCNF*, *KIF5A*, *GLT8D1*, *TIA1*, *NEK1*, *C21orf2*, *DNAJC7*, *TBP*, *CTSF*, and *MFSD8* (see Table 1, Fig. 1, and Fig. 2). We have described each of these genes in detail, and this includes gene descriptions, along with their pathological mechanisms.

Hotspot Genes Known in ALS and FTD: a Brief Overview

Superoxide Dismutase 1 (*SOD1*)

SOD1 was first linked to ALS through genetic linkage analysis in 1993 [26]. Later, the first transgenic mouse model was developed using the Gly93Ala mutation in *SOD1* [27]. The most prevalent mutations in *SOD1* are Asp90Ala (aspartic acid to alanine) and Ala4Val (alanine to valine). It has been observed that Asp90Ala substitutions may be inherited both as dominant and recessive forms of the disorder; however, the majority of the cases are recessive [28]. To date, more than 200 genetic mutations (insertions, deletions, point mutations, and truncation mutations) have been documented in the *SOD1* (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=SOD1> and Supplementary information). Different mutations of *SOD1* lead to destabilization and reduced protein affinity, as well as the formation of protein inclusion and aggregation [29]. Therefore, a variety of mutations in *SOD1* can either increase or decrease its function or lead to complete loss of function (LoF) [30]. Genetically and clinically, *SOD1* mutations are extremely heterogeneous. Symptoms are often very similar to sALS and fALS. *SOD1* has been linked to intra-familial variations in clinical and genetic severity as well as in progression of the disease [31]. Even though the exact pathological process is unknown, it might be that the LoF of proteins, or aggregation of misfolded proteins, or prion formation may create the molecular basis of disease pathogenesis [32]. *SOD1* encodes CuZn superoxide

Table 1 List of known genes identified in ALS-FTD, ALS, and FTD in the last 7 years

Loci number	Chromosomal locus	Gene	Onset	Mode of inheritance	Methodology	ALS-FTD overlay	TDP-43 pathology	Level of evidence	Probable functional importance	References
FTDALS4	12q14	<i>TBK1</i>	Adult	AD	WES	ALS, ALS/FTD	+	Established	Autophagy, inflammation	Cirulli et al., 2015
FTDALS5	16p13.3	<i>CCNF</i>	Adult	AD	GWAS	ALS, ALS/FTD	+	Established	Autophagy, axonal defects, protein aggregation	Williams et al., 2016
ALS25	12q13.3	<i>KIF5A</i>	Adult	AD	GWAS/rare variant analysis	ALS	+	To be validated	Intracellular trafficking, axonal defects	Nicolos et al., 2018
ALS*	3p21.1	<i>GLT8D1</i>	Adult	AD	WES	ALS	n.d	To be validated	Ganglioside synthesis	Cooper-Knock et al., 2019
ALS*	2p13.3	<i>TIA1</i>	Adult	AD	WES	ALS, ALS/FTD	+	To be validated	RNA metabolism	Mackenzie et al., 2017
ALS24	4q33	<i>NEK1</i>	Adult	AD	WES	ALS	n.d	To be validated	Intracellular trafficking, cytoskeleton organization, and DNA damage response	Brenner et al., 2016
ALS*	21q22.3	<i>C21orf2</i>	Adult	AD	GWAS/WGS	ALS	n.d	To be validated	Cytoskeleton organization and DNA damage response	Rheenen et al., 2016
ALS*	17q21.2	<i>DNAJC7</i>	Adult	AD/AR	Case-control study, WES	ALS	n.d	To be validated		Farhan et al., 2019
FTD*	6q27	<i>TBP</i>	Adult	AD	SCA17 testing	FTD	n.d	To be validated	RNA processing	Olszewska et al., 2019
FTD*	11q13.2	<i>CTSF</i>	Adult	AD/AR	WES, targeted resequencing	FTD	n.d	To be validated	Lysosomal pathway	van der Zee et al., 2016
FTD*	4q28.2	<i>MFSD8</i>	Adult	AD	Case-control study/rare variant analysis	FTD	+	To be validated	Lysosomal pathway	Geier et al., 2019

n.d., not determined; +, presence; *, locus not defined.

Table 2 Clinical, genetic, and neuropathological features of the ALS-FTD, ALS, and FTD spectrum

Disorder/disease	ALS-FTD	ALS	FTD
Clinical characteristics	Spasticity Dysarthria Dysphagia Muscle atrophy Social cognition Behavior change Psychiatric symptoms Language dysfunction Cognitive dysfunction executive dysfunction	UMN and LMN signs Muscle weakness Spasticity Respiratory failure Dysarthria Dysphagia Hyperreflexia Fasciculation Babinski’s sign cognition and behavior issues	Apathy, disinhibition Obsessive–compulsive behaviors Loss of insight Change in personality Language abnormalities Unusual verbal, anomia Physical and sexual behavior Loss of semantic knowledge Apraxia of speech Non-fluent aphasia, hallucinations
Genetic mutations	<i>C9orf72, TARDBP, FUS, VCP, SQSTM1, UBQLN2, CHCHD10, OPTN, MATR3 hnRNPA1/A2B1, CHMP2B, TBK1, CCNF, ANG, HTT</i> repeat expansions (Dewan et al., 2021)	<i>SOD1, C9orf72, TARDBP, FUS, OPTN, PFN1, MATR3, TUBA4A, TBK1, GLT8D1, FIG4, ATXN2, VCP, UBQLN2, SIGMAR1, CHMP2B, PFN1, ERBB4, Alsin, hnRNPA1, NFH ANXA11, GLE1, NEK1, KIF5A, SETX, SPG11, FUS, VAPB, ANG, PPARGC1A, Peripherin, EWSR1, TAF15, DAO, TIA1, C21orf2, DCTN1, hnRNPA2B1</i>	<i>PGRN, MAPT, C9orf72, CHMP2B, TBP, CHCHD10, SQSTM1, TBK1, CCNF, DCTN1, hnRNPA2B1, hnRNPA1, VCP, MATR3, TBP, CTCF, MFS2D8</i>
Neuropathology	TDP-43 inclusions FUS inclusions Ubiquitin inclusions huntingtin inclusions (Dewan et al., 2021)	TDP-43 inclusions FUS inclusions Ubiquitin inclusions	FTD-TDP FTD-Tau FTD-FUS

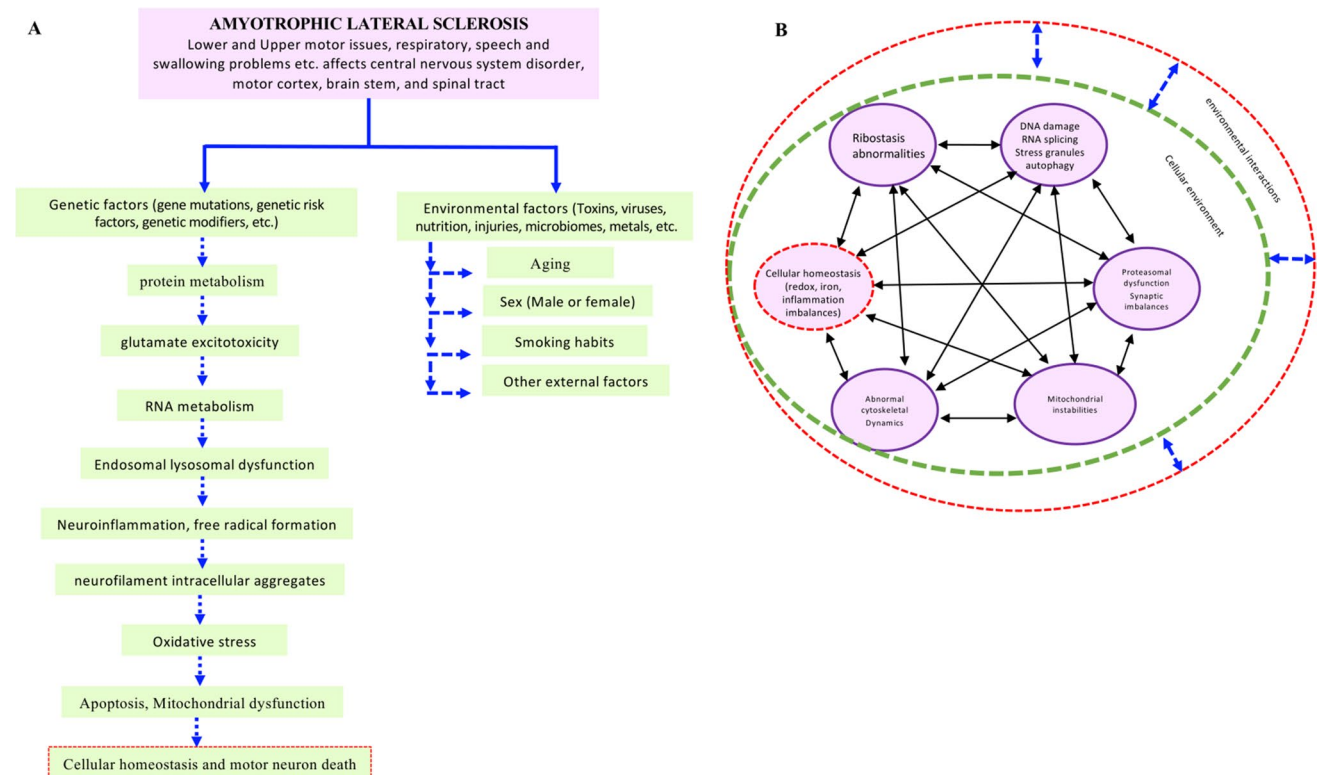


Fig. 1 (A) Flowchart indicating numerous factors that trigger the initiation and progression of ALS. (B) Shows inter-relatedness among different pathways involved in ALS pathogenesis, followed by subsequent cellular stress triggered by cellular microenvironment as well as external factors

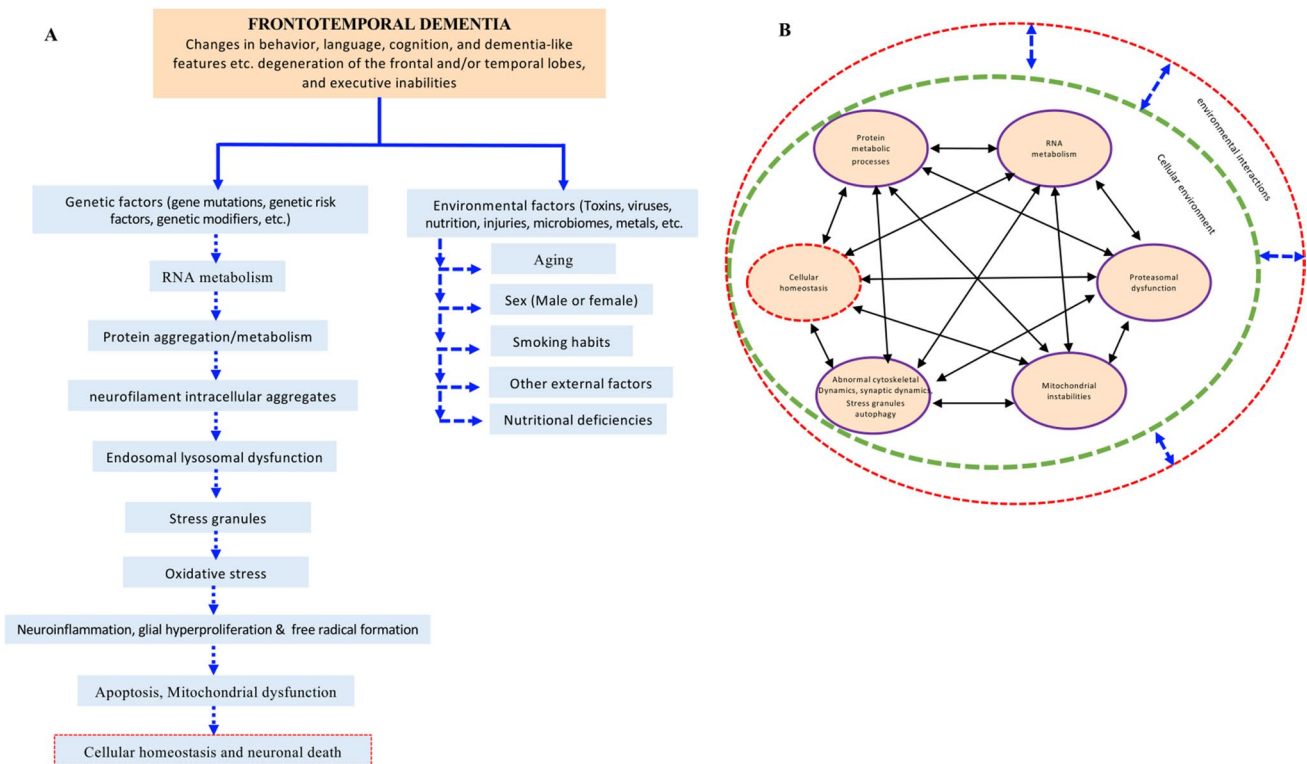


Fig. 2 (A) Flowchart indicating numerous factors that trigger the initiation of complex phenotypes observed in FTD along with the disease progression. (B) Depiction of different pathways involved in

FTD pathogenesis, that can be affected by the cellular stress and, cellular microenvironment as well as external factors

dismutase (32 kDa), which is ubiquitously expressed in the brain [33]. The main function of *SOD1* is to remove the free radicals such as the toxic superoxide anion O_2^- to O_2 and H_2O_2 , thus reducing the oxidative stress within the cell [34]. During, normal oxygen metabolism, oxygen radicals such as superoxide and hydrogen peroxide are produced, and these are involved in normal signaling within the cell. However, their excess amounts increase cellular stress and harm a wide range of biological processes [35]. Consequently, these superoxide and hydrogen peroxide molecules in the cytoplasm must be converted to H_2O by catalase, glutathione peroxidases, or peroxiredoxins [36]. *SOD1* has been reported to protect cells against such molecules in the intermembrane space of the cell as well as in the cytoplasm [37–40]. Furthermore, in the case of *SOD1* mutation or altered *SOD1* functionality, the scavenging systems might not be efficient enough to maintain the homeostasis of normal reactive oxygen species (ROS). Consequently, this further increases both cellular stress and the elevated levels of H_2O_2 that might ultimately lead to mitochondrial damage [41]. Furthermore, *SOD1* is localized in distinct places within the cell, which includes the cytoplasm, nucleus, mitochondria, and lysosomes [27, 33]. Transgenic mice were created harboring these mutations and were seen to generate motor neuron syndrome [42]. In order to develop gene therapy approaches

against mutant *SOD1*, one needs to understand the detailed molecular pathogenesis of each and every mutation identified so far [43].

SOD1 Pathogenesis

Mutations in the *SOD1* cause exclusively ALS and most likely a toxic gain-of-function protein [30]. So far, *SOD1* mutations have caused protein misfolding, nuclear and cytoplasmic aggregation, and cytotoxicity, among others. ALS is a very heterogeneous disease involving genetic, environmental, and other interrelated factors including smoking, aging, etc. (Fig. 3). ALS research was revolutionized by Charcot's description of the disease as well as the discovery of the *SOD1* gene [44]. Despite extensive research, the actual and realistic functions of the *SOD1* remains obscure; however, both toxic gain and LoF are implicated. Regarding the pathogenesis of the *SOD1*, several hypotheses have been proposed, including protein aggregation and protein cytotoxicity [30]. Mutations in the *SOD1* create toxic protein aggregation and RNA toxicity, leading to pathogenesis in multiple parts of the brain, which has been demonstrated by PET studies [45]. ALS autopsy samples and transgenic mice models have demonstrated ubiquitinated *SOD1* protein and intracellular inclusions in both neuronal and astrocyte cells

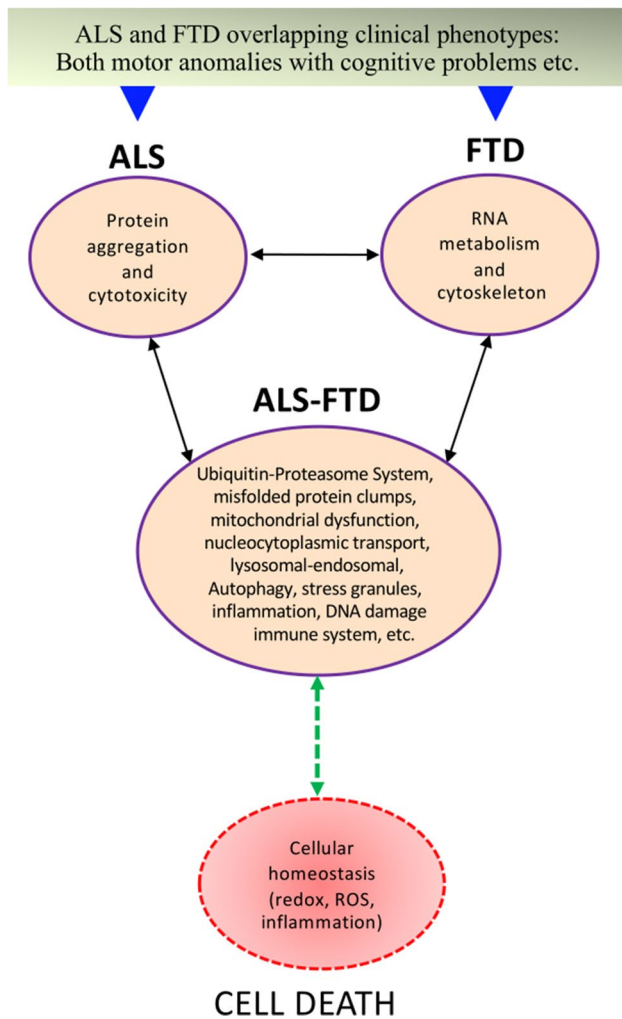


Fig. 3 Flowchart indicating various pathways that trigger the initiation of combined phenotypes observed in ALS-FTD and FTD-ALS disease progression (the steps provide involvement of major pathway-sin cell death which leads to the degeneration and progression of this-multisystemic disease)

[46]. The disorder occurs in both UMN and LMN phenotypes in ALS and in other regions such as the posterior column, thalamus, Clarke's nucleus, and spinocerebellar tracts [47]. There is still uncertainty about the consequences and contributing effects of these inclusion bodies. However, individuals with mutations in the *SOD1* gene are more likely to be vulnerable to stress and cellular injuries in their lifetimes [48]. In this case, the alpha motor neurons (largest post-mitotic neurons) are responsible for intracellular transport, and energy metabolism, and have extensive neurofilament networks [48]. Currently, it is unknown whether a toxic gain of function or a LoF of *SOD1* may be involved in the pathology of motor neuron disease [30].

Protein aggregation may cause misfolding; however, their monomerization and subsequent clump formation may cause cytotoxicity. The *SOD1* protein forms aggregates and

microaggregates of denatured monomers as a result of various genetic mutations. It has been documented that these are common factors driving the formation of numerous microaggregates that disrupt cellular transport, mitochondrial function, proteasomal function, and homeostasis [49]. The latest *SOD1* (G93A) mouse model has shown that morphological and functional changes (dendritic regression and glutamatergic excitation) are related to cortical neuronal hyperexcitability as an early feature of the ALS pathogenesis [49–51]. Motor neuron cells derived from induced pluripotent stem cells (iPSCs) have also displayed similar patterns of neuronal hyperexcitability, and inhibition of this process has been shown to be neuroprotective [52]. Several animal studies support this notion, suggesting that hyperexcitability in the cortex contributes to ALS [53, 54]. Therefore, *SOD1* pathogenesis is integral to ALS, and more research is necessary to understand *SOD1* pathogenesis.

Granulin (GRN)

GRN gene mutations were first identified in families with FTD (5–20%), mainly as autosomal dominant forms associated with chromosome 17 [55]. Likewise, these mutations in *GRN* make up about 5–20% of fFTD and ~1–5% of sFTD in this study [55]. There are more than 240 genetic variations known to date (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GRN> and Supplementary information), and most of the pathogenic mutations result in null alleles or haploinsufficiency [56]. The fact that heterozygous mutations in *GRN* cause FTD (FTD-*GRN*), whereas homozygous mutations cause neuronal ceroid lipofuscinosis, a lysosomal storage disorder, suggests the role of progranulin (PGRN) in lysosomal biogenesis and homeostasis [57]. This gene encodes a PGRN, which is secreted into the extracellular space and absorbed by the cells. Granulin is produced when progranulin is cleaved to form proinflammatory granulin subunits, and the catabolism of progranulin was performed in the lysosomes using cathepsins [58, 59]. Further, PGRN is mainly found in the lysosome where it may have an impact on lysosomal functions such as enzymatic activity and acidification [59]. This gene is strongly expressed in neurons, including microglia, and astrocytes in the central nervous system [60]. FTD affects both the frontal and temporal lobes, leading to behavioral, linguistic, and executive dysfunction. Therefore, variations in clinical presentation among individuals within a family have been observed. Mutations in the *GRN* lead to lipid droplet accumulation in microglia [61], a phenomenon that is also seen with aging. Neurons and microglia derived from patients with heterozygous *GRN* mutations show increased lipofuscinosis and lysosomal storage materials, supporting the notion that FTD-*GRN* may be caused by lysosomal dysfunction [62]. The other molecular pathologies are deficient autophagy, inflammation, and nuclear depletion

of TDP-43 or accumulation of pathogenic forms of TDP-43 [60, 63] (Fig. 4). FTD-GRN patients have been found to have increased reactive microglia, proinflammatory cytokines, and microglial dystrophy [64]. Complete loss of PGRN in Grn^{-/-} mice is known to increase complementary pathways and induce GABAergic synaptic pruning, leading to hyperexcitability in the thalamus [61]. Mice models exhibiting PGRN deficiency show increased NF- κ B-TNF α signaling, leading to hyperexcitability in the striatum [65]. The pathogenesis of FTD-related neurodegeneration associated with PGRN deficiency remains a focus of intense investigation [61]. FTD also exhibits neuropathological protein aggregation, glial hyperproliferation, inflammation, and lysosome dysfunction [65] (Fig. 4).

Microtubule-Associated Protein Tau (MAPT)

The MAPT gene was identified in 1975 on chromosome 17q21 [66]. MAPT encodes tau protein which is abundantly expressed in neurons along with low expression in glial cells [67]. Abundant MAPT has also been seen in various areas of the brain including the cerebral cortex, subcortical, white matter, and brain stem, as well as the spinal cord, which are vulnerable to tau deposition [68]. In 1998, the first mutations were discovered in exons 9, 10, and 13, as well as in

intron 10 [69–71]. Mutations in MAPT occur primarily in the repeats and result in tau proteins that have less affinity to microtubules [72]. The MAPT gene variant is inherited in an autosomal dominant manner, and more than 100 mutations have been reported in MAPT (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=MAPT> and Supplementary information). MAPT mutations are associated with tau-positive neuropathology in familial frontotemporal lobar degeneration (FTLD), and their frequencies are variable across populations, ranging from 5 to 50% [73]. MAPT alleles exhibit complete linkage disequilibrium with several polymorphisms, resulting in two distinct haplotypes H1 and H2 [74]. According to most studies, the predominant haplotype, H1, is associated with sporadic tauopathies and a weaker association with FTLD [74]. MAPT mutations are associated with an autosomal dominant form of FTD and parkinsonism (FTDP-17 T), affecting approximately 10% of people with familial FTD (<http://www.molgen.ua.ac.be/FTDMutations/>). The pathology is characterized by hyperphosphorylated tau inclusions in cortical and subcortical gray and white matter. It shares similarities with sporadic tauopathies in terms of anatomical distribution, inclusion morphology, and biochemistry. It is likely that genetic mutations have some correlation with clinical and pathological features among families [68]. The clinical features linked to MAPT mutations

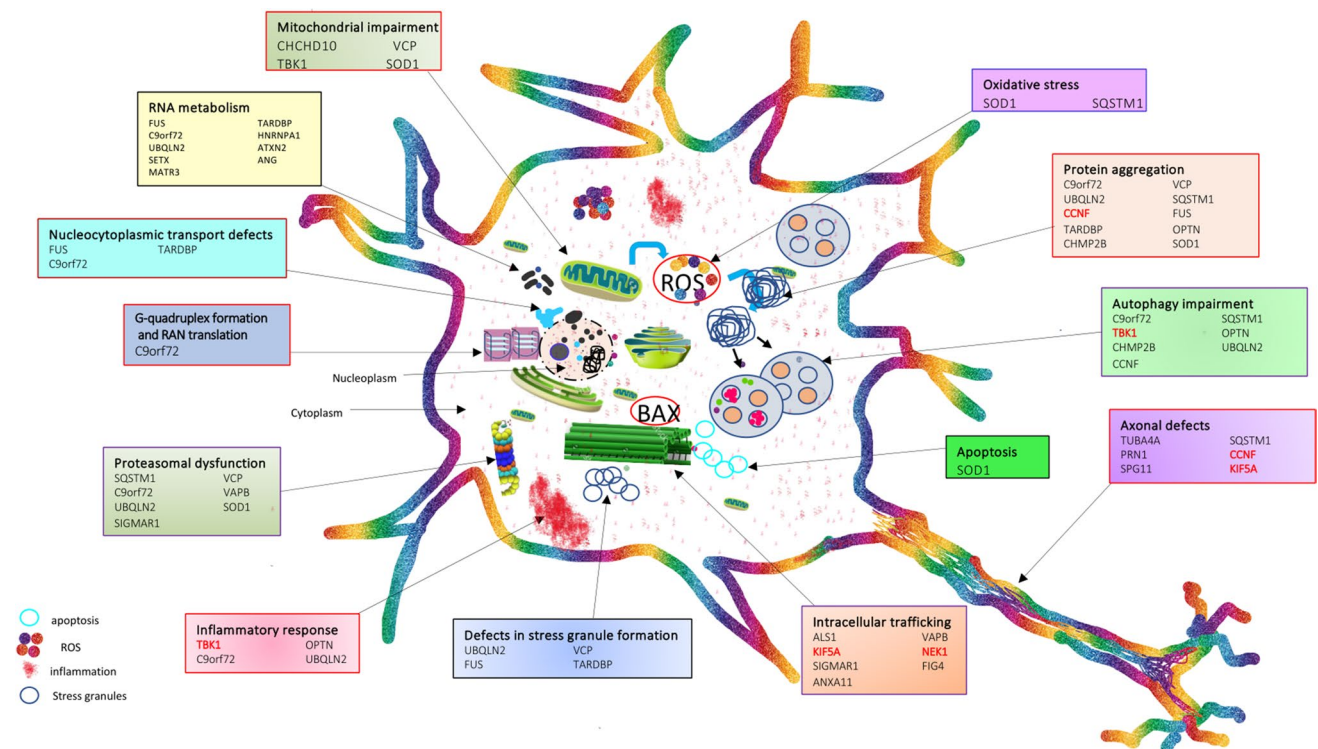


Fig. 4 Depiction of different pathways involved in the pathogenesis of ALS and FTD, including novel genes that have been identified recently in ALS-FTD, ALS, and FTD

are behavior, language, motor, and memory function. Also, the clinical phenotypes often overlap with other symptoms including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick disease, and primary progressive aphasia [75]. Tau plays an important role in microtubule assembly, which is crucial for axoplasmic transport and neuronal integrity [76]. The abnormal intracellular accumulation of hyperphosphorylated tau is thought to contribute to a number of neurodegenerative disorders (tauopathies), including FTD (FTLD-tau) [76]. Based on neuropathological findings, FTLT is characterized by hyperproliferation of glial cells and abnormal protein inclusions in the cytoplasm and nuclei of neurons [77]. It has been shown that FTLT-tau and TDP-43 protein aggregates (~45% of FTLT-tau and ~50% of FTLT-TDP) have been observed in the brains of FTLT patients [78]. There are heterogeneous genetic features in FTLT, reflecting its complex clinical and pathological nature. Despite enormous advances in FTLT genetics over the past 20 years, it's clear that molecular mechanisms remain the major obstacle in unraveling FTLT pathogenesis to date [79].

Chromosome 9 Open Reading Frame 72 (C9orf72)

The massive GGGGCC repeat expansion (~700–1600 copies) in the first intron of *C9orf72* has been identified in 2011 with familial and sporadic forms of both FTD and ALS [24, 80]. Since then, it has become a hallmark not only of ALS and FTD but also of AD, PD, PSP, ataxia, CJD, and Huntington's disease (HD) [24, 25]. A total of 29 genetic variants have been linked to *C9orf72* (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=C9orf72> and Supplementary information), including missense, splice site, and repeat variations. *C9orf72* is responsible for up to 80% of familial ALS-FTD, 20–50% of familial ALS, 5–20% of sporadic ALS, and 10–30% of FTD cases [81]. Critical clinical phenotypes include behavioral variant of FTD, primary progressive aphasia, movement issues, memory problems, and psychosis [82]. Patients with the *C9orf72* repeat expansion have been shown to have higher rates of bulbar onset ALS, cognitive impairment with an earlier onset of disease, and accelerated disease progression [83]. The actual function of *C9orf72* is yet to be defined, but accumulating evidence suggests that it functions (directly or indirectly) in coordinating autophagic flux or endosomal trafficking [84]. The genetic, clinical, and neurological heterogeneity of *C9orf72* is also evident in families with *GRN* mutations. Different neuropathological phenotypes also demonstrate overlapping inclusions of abnormal proteins, including FTLT-TDP and typical ALS-TDP-43 inclusions in LMN of different patients [77, 82, 85]. Brain pathologies of patients have also shown overlapping phenotypic categories [77, 82]. Apart from TDP-43 pathology, ubiquitin–proteasome system (UPS) dysfunction,

repeat-associated non-AUG (RAN) translation, dipeptide repeat (DPR) protein synthesis, and intracellular RNA accumulation can also be detected as a resultant of *C9orf72* mutations [24, 84]. In order to determine the role of *C9orf72* in cellular physiology, studies are being aimed at targeted reduction of mutant *C9orf72* expression, to deplete the formation of toxic nuclear foci. Further, lysosome–autophagosome connections and proteasomal activities may also be associated with *C9orf72*-mediated pathways [1].

TAR DNA-Binding Protein 43 (TDP-43)

TDP-43 was initially cloned as a repressor protein involved in HIV-1 transcription [86]. It binds to a trans-active response element within viral DNA sequences and is essential for the regulation of viral gene expression [86]. The TDP-43 (1p36.22) encodes 414 amino acids and functions as an hnRNP. TDP-43 has been implicated in both ALS and FTD [87]. TDP-43 is ubiquitously expressed in almost all tissues, including the brain [87]. It contains two RNA recognition motifs (RRM1 and RRM2) and a glycine-rich C-terminal sequence, which is a “hot spot” for mutations in TDP43 [87]. A total of 70 different genetic variants have been reported so far in *TARDBP* (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=TARDBP> and Supplementary information). One of the major pathways perturbed in TDP-43 pathogenesis might be dysregulation of RNA splicing, which could result in functional defects in vital proteins. However, further research is needed to elucidate the role of TDP-43 in normal cellular function, as well as in other mechanistic processes affected by mutations in *TARDBP*. The most important domain of TDBP-43 is its glycine-rich domain, which has been implicated in exon skipping, splicing inhibition, and biogenesis of mRNA [88]. Recently, it has been demonstrated that TDP-43 regulates spermatogenesis and acts as a scaffold for nuclear bodies called Gemini of coiled bodies (GEMs) and interacts with the survival motor neuron protein [89, 90]. Although its biological functions are not fully understood, TDP-43 has been shown to function by binding to single-stranded DNA, RNA, and/or proteins [88, 91]. Likewise, the anatomical distribution of DPR pathology does not correlate with the patterns of neurodegeneration and pathology related to TDP-43 [92]. Currently, it is debated whether TDP-43 or DPR pathology modulates the pathogenesis caused by *C9orf72* mutations [92].

Novel Genes Identified in ALS and FTD

TANK-Binding Kinase (TBK1)

In 2015, mutations in the TBK1 gene were reported to be associated with ALS [93, 94], FTD [95], and ALS-FTD

[17]. Similarly, a large-scale GWAS study identified *TBK1*, which is located on chromosome 12q14.2, as a risk locus in ALS [96]. There are many LoF mutation in *TBK1* resulting because of frameshifts, nonsense mutations, splice site alterations, and possibly pathogenic read-through mutations [97]. Many of these missense mutations in *TBK1* are clustered in the kinase and ubiquitin-like domains [98]. Missense mutations in the functional domains as well as those that impair *TBK1* phosphorylation and binding of target proteins to *TBK1* may result in disease pathogenesis [98]. This was supported by the difference in the odd ratio between cases and controls observed in this study (11.78 and 1.62, respectively) [99]. Furthermore, patients with ALS, FTD, and ALS-FTD are estimated to have a mutation frequency between 0.4 and 1.7% in *TBK1* [95, 100]. A recent meta-analysis found that the two mutation combinations (LoF mutations at 1% and missense mutations at 1.8%) are more prevalent in European populations than in Asian populations suffering from ALS and/or FTD [99]. Probably, this was because the numbers of Caucasian cohorts studied were more than that of Asian cohorts [1]. *TBK1* mutations were also found to be the second most common cause of ALS-FTD pathogenesis, after *C9orf72* mutations [101]. Mutations in *TBK1* are related to bulbar onset in ~15% of ALS patients and progressive behavioral changes in FTD patients [94]. It has been shown that both ALS and FTD patients exhibit increased inclusions of TDP43 and p62 in their affected brain regions [97]. The knockout of *TBK1* mutations in rodent models led to similar symptoms of cognitive impairment and motor dysfunction as those seen in ALS/FTD patients [102]. Further, a germline *TBK1* deletion has been associated with embryonic lethality, suggesting that it plays an important role in development. Moreover, T2K-deficient mice showed embryonic lethality and apoptotic liver degeneration, along with altered NF- κ B gene expression [103].

TBK1 belongs to the I κ B kinase gene family, and it is essential for binding and phosphorylating several proteins involved in autophagy [104], mitophagy [105], and innate immunity [106]. *TBK1* is highly expressed in neurons of the hippocampal formation, the cerebral cortex, and the lateral ventricles [107]. *TBK1* interacts with optineurin (OPTN) and SQSTM1 to form an autophagic adaptor complex [108]. Mutations in these two genes as well as *TBK1* have been detected in patients with ALS-FTD [17, 101, 109]. Furthermore, *TBK1* mutations have been found along with *C9orf72* expansion [95, 100], *TARDBP* [94, 98], *FUS* [109], or *FUS* and *DCTN1* [110]. Mutations harboring *TBK1* with *TARDBP* [98] or *TBK1* with *FUS* [94] have a more rapid onset of disease pathogenesis than those harboring *TBK1* alone [94, 111]. Mutations in *TBK1* and repeat expansion in *C9orf72* have also been associated with alterations in disease onset and penetrance [95]. The clinical phenotypes of patients with *TBK1* mutations showed variable onsets, progressions,

and survival rates [95, 98, 100, 111]. *TBK1* mutations have also been detected in other cohorts, including patients with motor neuron disease alone or with FTD [17, 93–95]. *TBK1* mutations have been linked to a variety of overlapping diseases, including behavioral FTD, prominent parkinsonism, and semantic paraphasias [95, 97]. Future studies should investigate clinical, phenotypic, and clinicopathological correlations to confirm or disprove the distinct genetic identification and treatment associated with *TBK1*.

Cyclin F (CCNF)

Genome-wide linkage analysis led to the identification of *CCNF* in 2016 in an Australian family with British ancestry afflicted with ALS-FTD [112]. The *CCNF* mutation frequency ranged from 0.6 to 3.3% among Australian, American, European, and Asian populations with fALS-FTD [112, 113]. *CCNF* encodes the cyclin F protein (part of the E3 ubiquitin–protein ligase complex), also known as the Skp1-Cul1-F-box E3 ubiquitin ligase complex [114]. *CCNF* catalyzes and transfers ubiquitin molecules to the specified proteins, which are then degraded by the UPS [115]. The mutation Ser621Gly in *CCNF* inhibits this degradation by disrupting ubiquitination, resulting in the accumulation of ubiquitinated proteins, such as TDP-43 and ribonucleoside-diphosphate reductase subunit M2 [112]. Interestingly, *CCNF* also acts on SQSTM1 like *TBK1* and triggers ubiquitinated protein degradation by autophagous receptor binding [116]. *CCNF* is expressed in neuronal cells, and mutations in *CCNF* are associated with defects in ubiquitination processing and autophagosome–lysosome fusion [112, 116]. Recently, a zebrafish model of the p.Ser621Gly mutation has been used to demonstrate its effects on axonal growth [116, 117]. *CCNF* has been shown to interact with *VCP* and increase its ATPase activity, leading to the aggregation of TDP-43 [118]. The genetic and functional findings obtained in cellular as well as model organisms indicate that mutant *CCNF* leads to impaired UPS/autophagy pathways resulting in impaired axonal growth. Hence, this gene has been implicated in the ALS-FTD spectrum and is also known as locus FTDALS5 (Table 1).

Kinesin Family Member 5A (KIF5A)

For the first time, *KIF5A* was identified using WES followed by rare variant analysis in fALS patients (case = 426, control = 6137) [119]. Splice site mutations were reported to be clustered in the C-terminal region of *KIF5A* [119]. Further, functional analyses of lymphoblast cell lines demonstrated defective splicing and haploinsufficiency, resulting in disease pathogenesis [5, 119]. This study was initiated as there have been previous findings on the involvement of *KIF5A* in other diseases, such as monogenic spastic paraplegia and

Charcot–Marie–Tooth disease type 2 (CMT2) [120]. In 2018, similar findings were reported using two analogous methods: (1) the GWAS in 20, 806 ALS cases, and 59,804 controls and (2) the rare variant burden in 1,138 fALS cases and 19,494 controls [120]. Consequently, a missense heterozygous variant (p.Pro986Leu, rs113247976) and other LoF variants (within amino acids 996–999) were identified, suggesting the need for additional cohort validation [119]. The variant (p.Pro986Leu, rs113247976) was checked in additional cohorts of ALS patients (cases = 4159, controls = 18,650) and confirmed the original GWAS findings [119]. Further validation of this observation was done by meta-analysis and replication studies (cases = 24,965, controls = 78,454) that generated a highly significant p value (7.09×10^{-13}) [120]. An independent study using rare variant burden analysis showed that this variant (rs113247976) was associated with fALS [120]. Three additional carriers with LoF variants in *KIF5A* were also found [120]. In their research, the authors suggested that the variant p.Pro986Leu in *KIF5A* posed a lower penetrance with a relatively common occurrence in fALS [119, 120]. There is also evidence that LoF variants in *KIF5A* are rare and have a higher penetrance and are at higher risk factors for ALS [119, 120].

KIF5A belongs to a family of motor proteins, called kinesins (*KIF-5* major isoform). It plays a role in the transport of organelles within the cells, such as axonal transport [119, 120]. It has also been reported that mutant *KIF5* plays a role in the pathogenesis of motor neuron degeneration [121, 122]. Nevertheless, *KIF5* transports granules in axons and dendrites that interact with RNA and RNA-related molecules. [123]. Most of these granules/cargos are related to other genes associated with ALS, for example, *FUS*, *VAPB*, and *hnRNPA1* [124, 125]. The knockout mice of *KIF5A* demonstrated abnormal neurofilament transport [126] and pathological accumulation of these neurofilaments in ALS [127]. Similarly, *KIF5A*^{-/-} mice also show defects in axonal transport and survival [128]. ALS patients also have impaired axonal transport and mitochondrial activity [124, 129]. In addition to the *KIF5* family members, other receptors including the α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and γ -Aminobutyric acid type A receptors (GABA_A) types are also affected [130, 131]. Furthermore, other ALS genes (*NEK1* and *PFN1*) modulate *KIF5A* expression [132, 133], and this impacts the formation of neurite-like membrane protrusions [125]. In contrast, the majority of the LoF variants have been identified in the C-terminal domain of *KIF5A*, and haploinsufficiency has been observed which may disrupt the binding affinity of *KIF5A* with other cargo proteins [119, 120].

Furthermore, the zebrafish models with a truncated C-terminus of *KIF5A* led to mitochondrial translocation disruption [134]. It has been suggested that lack of *KIF5A* expression can lead to accumulations of downstream proteins, such

as phosphorylated neurofilaments and amyloid precursor proteins, which are associated with neurodegeneration in patients with multiple sclerosis (MS) [135]. Recently, *KIF5A* has emerged as a promising and predictive biomarker in MS [135]. *KIF5A* mutations show genetic heterogeneity that can result in a variety of distinct phenotypes depending on their location within the gene [119, 135]. For example, *KIF5A* mutations can lead to classical ALS phenotypes, myoclonus in infancy, CMT2, and hereditary spastic paralysis, etc., suggesting a pleiotropic role of this gene in various neurological conditions [119, 135].

Glycosyltransferase 8 Domain Containing 1 (GLT8D1)

GLT8D1 was discovered by WES in a family with autosomal dominant ALS that harbored variant p.Arg92Cys within exon 4 [136]. Among the affected individuals, the heterozygous p.Arg92Cys mutation in *GLT8D1* co-segregated in an autosomal dominant manner [136]. The findings were confirmed by Sanger sequencing [136]. Within the same exon, additional rare deleterious mutations within *GLT8D1* have been linked to ALS [136]. The mutations p.Arg92Cys and p.Gly78Trp are located at the substrate-binding site and alter the enzyme activity of *GLT8D1* [136]. Further, in vitro cytotoxicity analysis using zebrafish revealed p.Arg92Cys and p.Gly78Trp variants in *GLT8D1* cause insufficient motor activity resembling ALS, suggesting that the glycosyltransferase activity is lost in these mutants [136]. The possible roles of *GLT8D1* are related to synthesizing signaling molecules, such as gangliosides, which are important in motor neuron functions [137]. A mice model of *Ugt8a* (the orthologue of *UGT8*) has shown the involvement of different brain-gangliosides in dysfunction of motor coordination [138, 139]. It is interesting to note that *GLT8D1* deficiency has been linked to a number of other neurodegenerative conditions, including AD, PD, HD, and schizophrenia [140, 141].

TIA1 Cytotoxic Granule-Associated RNA-Binding Protein (TIA1)

The *TIA1* gene was first discovered by WES [142] in a European family with ALS-FTD. Heterozygous missense mutation (p.Pro362Leu) in *TIA1* segregated in the affected family members [142]. Five additional mutations in six different patients were identified in the low complexity sequence domain (LCD) [142]. *TIA1* encodes an RNA-binding protein with a C-terminal LCD similar to that of TDP-43 or *FUS* [142]. *TIA1* is also found in membrane-less organelles like stress granules and can modify liquid–liquid phase separation (LLPS) using LCD [142]. Due to the *TIA1* mutation, the LLPS undergoes changes

in their biophysical properties, which lead to changes in the formation of stress granules [142]. A genetic mutation occurring in this domain causes Welander distal myopathy and is also associated with TDP-43 and p62 aggregation [143–145]. Mutations in *TIA1* affect stress granule dynamics and result in TDP-43 accumulation [142]. In a case–control study (cases = 1039, controls = 3036), additional six nonsynonymous variants were present in the LCD domain of *TIA1* in affected members [146]. A significant value with ~2% with fALS and <0.5% of sALS patients were observed [142]. Further, neuropathological examination of autopsied brains and spinal cords of *TIA1* carriers revealed TDP-43 pathology [147]. Additionally, inclusions of hyaline-like cytoplasmic Lewy bodies were also observed in LMNs [142, 147]. There may be a link between the inclusions present in the LMNs and the *TIA1* mutation, which is characteristic of ALS patients [148].

NIMA-Related Kinase 1 (NEK1) and Chromosome 21 Open Reading Frame 2 (C21orf2)

NEK1 was first identified as a hit in WES study of >2,000 ALS patients [4, 93, 149]. The rare variants in *NEK1* were significantly enriched in ALS patients compared to that of controls (cases = 2303, controls = 1059) [150]. Approximately 3–4% of ALS patients of European descent had the presence of rare variants in *NEK1*, including heterozygous LoF variants in 1% of patients [4, 93, 149, 150]. Mutations in this gene were also reported in another WES study that examined 827 controls and 265 index ALS patients [150].

NEK1 is a member of the conserved NIMA-related serine/threonine kinases family, and it plays an important role in cell cycle, DNA damage repair, mitochondrial membrane regulation, and ciliogenesis [151–153]. A heterozygous mutation (p.Arg812Xaa) in *NEK1* has been demonstrated in patient-derived neuronal cells with an increased DNA repair response to irradiation [152]. *NEK1* is involved in the maintenance of the cytoskeleton system in neurons [154] and interacts with other ALS genes like tubulin alpha 4a (*TUBA4A*) [155] and *PFN1* [133]. Along with other ALS proteins, such as VAPB and ALS2 (alsin), *NEK1* binds to *C21orf2* in response to DNA damage [93, 156].

C21orf2 has recently been identified as a novel ALS gene containing nonsynonymous and LoF variants [96]. Additionally, in vitro cell-based assays have shown that knocking down *NEK1* expression results in cellular death, resulting in the LoF mechanism [157]. The function of *C21orf2* is unknown, but it is believed that it interacts with *NEK1* and participates in primary cilia formation [158–160]. Mutations in *C21orf2* and *NEK1*, like those in *TBK1* and *GLT8D1*, are associated with other diseases, including axial spondylopathies and retinal dystrophies [159].

DnaJ Heat Shock Protein Family (Hsp40) Member C7 (DNAJC7)

DNAJC7 has been recently identified in a large WES-based case–control study (cases = 3864 and controls = 7839) [161]. Eight individuals were found to have six protein-truncating variants (PTVs) (cases = 5095, controls = 28,911). A higher rate of significant PTVs has been observed in cases with constrained genes. Gene-based analyses have shown the presence of PTVs in the well-known ALS genes like *SOD1*, *FUS*, and *NEK1*. In GWAS, *DNAJC7* showed a greater occurrence of PTVs, such as variant p.Arg156Ter [162]. Western blot analysis of patient-derived fibroblasts revealed a depletion of *DNAJC7* protein (p.Arg156Ter) [162]. Thus, it was concluded that *DNAJC7* loss was responsible for neurodegeneration, since it encodes a chaperone and contributes to protein folding and clearance of mature proteins, along with protein homeostasis. The study was limited to a single population, and therefore, further research is needed both in ALS and FTD cohorts from other populations. *DNAJC7* encodes mainly a heat shock protein (HSP40), which facilitates the homeostasis of HSP70 by modulating folding, misfolding, and clearance of other proteins and peptides [162].

TATA-Box Binding Protein (TBP)

Recently, TBP has been identified in an Irish family that contributed to partial frontal dysfunction and cerebellar atrophy [163]. The proband had a 43 repeat expansion in *TBP* that co-segregated with other family members [163]. *TBP* encodes a transcription initiation factor that may have a role in RNA metabolism [164]. The mutations in *TBP* have been associated with spinocerebellar ataxia 17, suggesting that dementia and ataxia share overlapping mechanisms [163]. Future studies in *TBP* warrant better clinical profiling and genetic testing.

Cathepsin F (CTSF) and Major Facilitator Superfamily Domain 8 (MFSD8)

CTSF and *MFSD8* have recently been identified in FTD [165, 166]. Two unrelated FTD patients in a Belgian cohort carried the heterozygous p.Arg245His mutation in *CTSF* [165]. Nevertheless, case–control, genetic association, and rare burden analyses showed a higher rate of risk variants in *MFSD8*, which has been linked to FTD [166]. It is interesting to note that these two genes are involved in the lysosomal–autosomal pathway that leads to ALS/FTD. The *CTSF* encodes cathepsin F, which is an enzyme involved in lysosomal cysteine protease activity [167, 168]. Recently, another missense variant (p.Leu465Trp) was identified in *CTSF* of an individual affected with FTD [169]. The *MFSD8* encodes a ubiquitous integral membrane protein that is found

in lysosomes [170]. According to this study, mutations in *MFSD8* cause FTD by increasing the concentration of other proteins such as LAMP2 and CTSD and, concurrently, by decreasing the rate of protein degradation [166]. The presence of homozygous LoF in these two genes can result in neuronal ceroid lipofuscinoses [171, 172], suggesting that lysosomal dysfunction may exacerbate the disease. Further studies are needed to confirm the role of these genes in FTD pathogenesis.

Involvement of Common Interlinked Pathways in ALS-FTD Pathogenesis

Numerous genes are known to play a vital role in different pathways linked to ALS and FTD [4]. Some genes are exclusively associated with ALS/FTD. These genes include *SOD1*, *MAPT*, and *GRN* [80]. In *SOD1*, the disease has been classified as a pure case of ALS, while in *MAPT* and *GRN*, it has been classified as a pure case of FTD. The development of the disease is also influenced by related pathways, for example, genes that regulate autophagy and proteasome damage (*C9orf72*, *OPTN*, *VCP*, *UBQLN2*, *SQSTM1*, *CCNF*, *FUS*, *TARDBP*, *TBK1*, *CHMP2B*), RNA metabolism (*C9orf72*, *UBQLN2*, *SETX*, *ANG*, *ATXN2*, *hnRNPA1*, *MATR3*, *FUS*, *TARDBP*),

mitochondrial dysfunction (*TBK1*, *CHCHD10*, *VCP*), and the cytoskeleton dynamics (*TUBA4A*, *SQSTM1*, *CCNF*, *SPG11*, *KIF5A*, *PFN1*) [4] (Fig. 2). However, other pathways such as lysosomal–endosomal involvement (*NEK1*, *FIG1*, *ALS2*), unfolded protein response (*VAPB*, *SIGMAR1*), stress granule formation (*TAF15*, *FUS*, *ATXN2*, *TIA1*, *EWSR1*, *hnRNPA1*), excitotoxicity, oxidative stress, neuronal survival, neurite outgrowth, and neuroinflammation are other important emerging mechanisms [4, 163] (Fig. 1). A systemic pathway that plays a role in ALS, FTD, and ALS-FTD pathogenesis is illustrated in Figs. 3, 4, and 5, respectively. ALS, FTD, and ALS-FTD appear to be characterized by a complex interaction between genetic and environmental factors, leading to dysfunction of critical molecular pathways and neurodegeneration and neuronal cell death (Figs. 3, 4, and 5). It still remains unclear as to how these steps or factors work. A combination of genetic, environmental, and epigenetic factors appears to contribute to the disease pathogenesis (Fig. 3, 4, and 5). Neurophysiological tests have shown that the hyperexcitability of the cortex may play an important role in ALS and FTD [3]. It is shown that both ALS and FTD are associated with similar pathogenic mechanisms that involve RNA and protein imbalances, as well as disturbed cellular homeostasis that promotes disease progression (Fig. 3, 4, and 5).

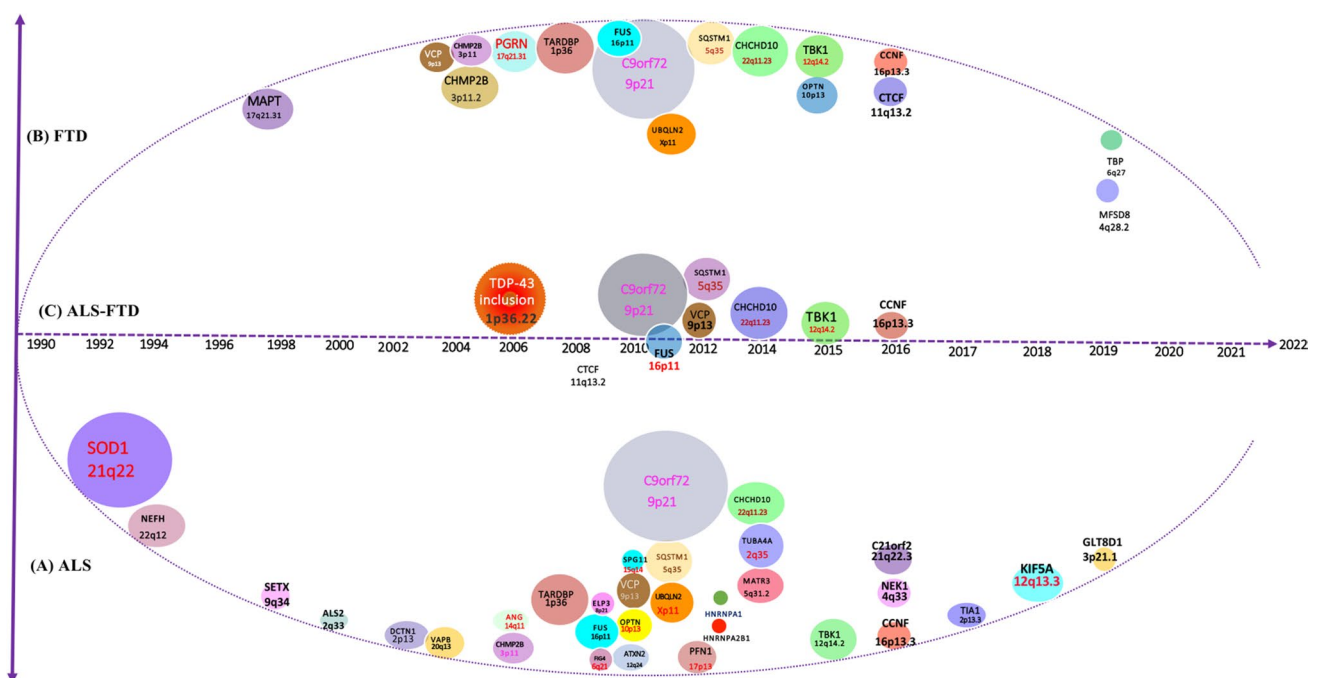


Fig. 5 Genetic spectrum of ALS, FTD, and ALS-FTD. The timelines and coordinates of the genes discovered in ALS are shown in (A), those discovered in FTD are shown in (B), and overlapping genes

implied in both ALS as well as FTD patients are shown in (C). Additionally, TDP-43 inclusions were detected in both ALS-FTD patients. The diameter of each gene indicates its relative frequency

New Genetic Risk Loci Identified in ALS and FTD

ALS-FTD, ALS, and FTD genes can be classified into three major pathways, namely, autophagy/proteasome impairment (*C9orf72*, *SQSTM1*, *TBK1*, *OPTN*, *VCP*, *CHMP2B*, *UBQLN2*, *CCNF*, *FUS*, *TARDBP*), RNA processing (*C9orf72*, *FUS*, *TARDBP*, *UBQLN2*, *SPG11*, *KIF5A*, *MATR3*, *SETX*, *hnRNPA*, *PFN1*), and cytoskeleton dysfunction (*CHCHD10*, *TBK1*, *ALS2*, *FIG1*, *NEK1*, *VCP*, *TUBA4A*, *CCNF*, *SQSTM1*) [13, 173] (Fig. 3). Risk factors or modifier genes are equally important for understanding the molecular basis of the disease, along with the onset of disease, as well as subtle modulations in the disease phenotype [5]. Recent GWAS studies have revealed numerous novel genes related to ALS and FTD [174]. For example, p.A152T in *MAPT* increases the risk for FTD, while loss of *EPHA4* variants is associated with a higher survival rate in patients with ALS [3, 175]. GWAS analysis identified *UNC13A* on chromosome 19p13.3, which has been shown to play a role in susceptibility to ALS [6, 176]. Recently, *UNC13A* was found to be a risk factor in FTD patients along with deposition of TDP-43 [6, 176]. Studies have previously linked *C21orf2* (explained above) with *SCFD1*, *MOBP*, and *TNIP1* to ALS [96, 177]. Currently, gene expression analysis and patient stratification are being conducted in ALS, and this could lead to the development of personalized therapy [178]. GWAS and DNA methylation studies have recently identified a number of genes (*DLG1*, *METTL7A*, *KIAA1147*, *PCNX*, *UBTD2*, *WDR35*, *ELP2/SLC39A6*), which harbor mutations and perhaps have connections to differential DNA methylation or epigenetic changes leading to the involvement of common pathways [174]. Therefore, these genes indirectly contribute to neurodegeneration in ALS, FTD, and ALS-FTD [174]. Recently, another study has shown that known genetic risk loci for AD/FTD have a nominal causal effect on immune-related traits [115]. It was found that a higher rate of fold change in immune-related genes in FTD was seen when compared with other diseases such as rheumatoid arthritis, ulcerative colitis, and celiac disease [115]. Moreover, a number of other genes comprising of *ATXN2*, *TMEM106B*, *UNC13A/KCNN1*, and *ZNF512B* have also been identified as modifiers or risks for ALS/FTD with distinctive stages of signs [13, 173]. Thus, these genes/variants with low penetrance have been found in a subgroup of ALS/FTD patients, suggesting that many genetic elements contribute to the ALS/FTD spectrum. Although these risk factors and modifiers are not directly linked to ALS/FTD, they increase the likelihood of developing the disease [13, 115]. Further, these observations indicate that environmental triggers may be also involved,

thus leading to oligogenic/polygenic models of ALS/FTD, which have been described in details below. Several recent studies have suggested that ALS/FTD patients may carry more than one genetic variant, which may have additive effect on the disease pathogenesis [3, 17]. However, more studies are needed to identify risk, modifier, and protective factors in ALS/FTD biology to cover the spectrum of these diseases [4, 17].

Oligogenic/Polygenic or Pleiotropy Models in ALS and FTD

As discussed above, ALS is closely linked to FTD at various stages. There can be more than one gene or variant(s) that causes both ALS and FTD; for example, mutations in *TARDBP*, *C9orf72*, or *TBK1* may occur even within the same family [23, 179]. However, phenotypic pleiotropy is speculated among a multitude of disorders beyond ALS or FTD [180]. In fact, most *C9orf72* mutations have also been reported in AD, Alzheimer's dementia, and PD [85, 181]. Additionally, recently identified *TBK1*, which has been observed with LoF leading to haploinsufficiency, also could be a cause for cerebellar ataxia and progressive supranuclear palsy [182]. Intriguingly, *KIF5A* has also been associated with a variety of other neurodegenerative disorders, including hereditary spastic paraplegia and hereditary neuropathy (CMT2A) and neurodevelopmental disorder NEIMY (see above under *KIF5A* section). Thus, continuous high-throughput sequencing of patients will reveal new genes which will help in dissection of phenotypic nuances.

Oligogenic Architecture of ALS/FTD

Several years ago, it was assumed that most genetic causes of ALS and FTD could be explained by pathogenic mutations that do not co-segregate in carriers or unaffected family members, such as *SOD1* in ALS [26]. A similar phenomenon has also been observed in FTD patients [24, 25]. Together with other studies, these observations have addressed genetic penetrance, expressivity, epigenetics, and environmental influences [183, 184]. Moreover, new discoveries in this era of ALS/FTD genetics point at the oligogenic/polygenic or reduced penetrance models for these diseases [4]. Past and ongoing studies indicate a significantly higher number of patients with two or more mutations, which is more than expected, suggesting an additive or synergistic impact of oligogenic diseases on disease penetrance and progression [3, 4, 7, 15, 17]. There is a similar pattern of oligogenic disease onset, penetrance, and progression associated with *C9orf72* repeat expansion in ALS [185]. This may be explained by the higher prevalence, incomplete penetrance,

and the co-occurrence of numerous other mutations with the *C9orf72* repeat expansion in carriers with both ALS-FTD and ALS [184–186]. Further, the loss and gain of *C9orf72* function in ALS may also allow identification of a common therapeutic pathway in the near future [24, 187]. A recent study has shown that activating the autophagy pathway can ameliorate TDP-43 proteinopathies, in mice models, suggesting the possibility of a potential treatment for neurodegenerative disorders involving TDP-43 inclusions [188]. New therapeutic approaches, including stereopure oligonucleotides, may have some striking correlations with future genetic and model-based research [189]. Numerous other known and novel genes, as well as their inheritance patterns, have resulted in a wide spectrum of ALS-FTD disease presentations [22]. The discovery of ALS and FTD gene mutations has created new ways to diagnose/treat as well as identify disease penetrance. In recent months, advances in sequencing techniques have made it possible to analyze gene panels and to document multiple gene mutations simultaneously in ALS and FTD [179, 190]. An analysis of one such study found that cases with more than one mutation tend to be more penetrant than those with single-gene mutations [179]. According to another study, patients with mutations in more than one gene had a lower survival rate than those with mutations in only one gene. Thus, mutations in multiple genes within one individual lead to a more severe and progressive disease onset (imitating oligogenic and polygenic disease models) [2, 109].

Advances in Novel Gene-Based Therapies

In 1995, riluzole, an antiglutamatergic agent, was identified as the only effective treatment for ALS with a minimum survival time of 3 months [191]. Edaravone (Radicava, a neuroprotective agent) has been approved by the US Food and Drug Administration for the treatment of ALS [192], but no treatment has yet been approved for FTD (<https://clinicaltrials.gov/ct2/show/NCT04220021>). Nevertheless, various treatment strategies are being used in different drug classes, such as antipsychotics, antidepressants, cholinesterase inhibitors, memantine, riluzole, and serotonin inhibitors, depending on the phenotype [85]. For example, specific serotonin inhibitors are prescribed to treat behavioral problems, and riluzole is prescribed to treat conditions related to motor function or parkinsonism [193]. Despite this, these treatments are effective for up to 6 or 8 months after they are administered to patients with a milder form of the disease [85, 193].

ALS and FTD, however, do not have any other beneficial and effective treatments that can extend life expectancy significantly; hence, it is crucial to continuously develop better therapies, treatments, and patient care [85].

Until now, advances in genetics and molecular understanding of these diseases have led to numerous novel gene identifications and subsequently newer therapeutic approaches [85]. Antisense oligonucleotides (ASOs) and stereopure oligonucleotides, for instance, target majority of the ALS genes [189]. In ongoing clinical trials, it has been shown that ASOs function directly against *SOD1* mutations in the CSF of patients without causing any adverse effects [194]. Different phases of clinical trials are currently being conducted with the latest generation of ASOs (NCT02623699). Further, iPSCs generated from fALS patients carrying *SOD1* mutations with ASOs have shown decreased apoptotic markers, which indicates improved survival rates [195]. The p.Gly93Ala mutation in *SOD1* transgenic mice was shown to delay the disease onset and improved survival when combined with a microRNA linked to miR-155 (miR-155) [196, 197]. Interestingly, copper-based therapeutic diacetylbis(N(4)-methylthiosemicarbazonato) copper II (CuATSM) pet analysis rendered controlled activity in mice with p.Gly93Ala mutation in *SOD1* [198]. CuATSM is delivered into the CNS with a metal cofactor (copper), and without this copper, these proteins become misfolded and toxic, potentially leading to motor neuron degeneration [198]. In addition, ASO inhibited the formation of RNA foci linked to *C9orf72* repeat expansion and thus prevented dipeptide repeat pathogenesis [19, 199]. In a mouse model, stereotactic ASO injection reduced RNA foci formation by 60–70% in the brain and spinal cord [200]. ASO has been used for ALS and FTD modifiers as well as targeting causal genes. Moreover, *ATXN2* has been demonstrated to be associated with ALS pathogenesis and acts primarily as a modifier of TDP-43 toxicity in cellular and animal models [201]. ASO has been used to silence *ATXN2*, and this has also been validated in knockout mice, demonstrating that the reduced pathology associated with TDP-43 is due to silenced *ATXN2* [201].

Other tools, including CRISPR/Cas9 technology and adeno-associated viral vectors, have been used to develop mutant and wild-type alleles for personalized and precision therapy [194, 200]. Systematic review and meta-analysis of human transcriptomics also revealed neuroinflammation [20]. Each technology has its limitations, but an ongoing effort to develop and decipher efficient therapeutics is the basis of any study. The study of epigenetic changes in these genes, such as hypermethylation, is an emerging field that poses new challenges and requires new approaches [174]. In both ALS and FTD research, CRISPR/Cas9 technology is being used to create new animal models for testing genes and their penetrance in patients. This will, in turn, open up new therapeutic options such as personalized, permissive, and precise therapies [187].

Conclusions

Genetic research on ALS and FTD continues to reveal genotype–phenotype correlations based on monogenic/oligogenic gene(s), genetic risk factor(s), and disease modifier(s). Further studies are needed to examine numerous patients and control samples, and this can help in better understanding of the data and increases the statistical power to make new discoveries and validate findings. Our predictions are that new gene discovery will continue, and within a few years, this may lead to more effective treatment options for overlapping conditions. However, progress is being made in modeling oligogenic risks and conquering non-coding regions of the human genome [2, 3]. Genetic findings have shed light on individualized medicine and gene-specific treatments over the past 10–20 years of study [85]. This serves as a proof-of-principle for the treatment of patients using novel techniques such as ASO-based splice modifiers in young patients with spinal muscular atrophy. Patients with *SOD1* mutations/*C9ORF72* mutations are in clinical trials [19–21]. ALS and FTD have similar pathological mechanisms, such as protein aggregation, RNA metabolism, autophagy–lysosomal dysfunction, cytoskeleton and mitochondrial dysfunction, and stress granules, suggesting a causal relationship between the two disorders [4, 19, 177]. The genetic basis of *SOD1* in ALS, *MAPT*, and *GRN* in FTD is still debated as distinct pathologies, so it is argued that pure ALS and pure FTD cases should be treated separately [57]. It has been suggested that diagnosis and prognosis biomarkers should be developed based on their distinct neuropathological findings. ALS/FTD genetics has been studied using a variety of advanced sequencing tools (e.g., WES, WGS, and targeted sequencing) to discover novel and rare genetic variants. This adds not only to the genetics of ALS/FTD, but also to the genetics of other diseases [143, 169]. Further, by including interaction between genes/epistasis, other aspects of genetics have been dissected, such as reduced penetrance, variable expression, and oligogenic/polygenic/pleiotropic inheritance models [180]. Numerous studies have shown the potential for personalized medicine and future therapies for ALS/FTD in the near future [85, 181].

Summary

Even after years of research in the field of ALS-FTD, it is still not clear as to what extent the two diseases overlap. Several new genes have been identified in ALS-FTD, ALS, and FTD over the past few years (Table 1). There

are also phenotypic characteristics common to the ALS and FTD phenotype, such as language and behavioral difficulties (Table 2). The overlap between ALS and FTD is also incomplete; for example, *SOD1* is included in ALS cases, while *GRN* and *MAPT* are included in FTD cases. It is still unclear what causes their distinct pathologies. Intriguingly, much of the pathophysiology in ALS/FTD shows a massive overlap, which is still a matter of debate among scientists. However, clinical and genetic heterogeneity provides clues beyond these overlays, for example, the *C9orf72* repeat expansion, which includes intra- and inter-family variations in disease onset, incidence, penetrance, and progression, as well as cognitive and motor impairments. [24].

It is due to a combination of genes and environmental factors that the disease develops and progresses. Environmental factors can include toxic compounds, heavy metals, and electromagnetic frequencies, and many of these factors have been associated with neurological disorders in humans [202]. A person's habits and lifestyle are equally important, and studies indicate that metabolic changes such as eating habits, weight loss, insulin resistance, and body cholesterol levels may have an effect on neurodegenerative diseases including ALS and FTD [174] (Fig. 3, 4, and 5). A study conducted with > 700 phenotypic traits and ALS GWAS data (cases = 20,806; controls = 59,804) revealed a shared polygenic risk for this disease [203]. These include smoking, educational attainment, physical activity, anxiety/agitation, and an elevated level of low-density lipoprotein, suggesting more controlled trials are needed to prove causality [203]. Environmental factors do interact with many gene sets and subsets, and this can be related to genes with dissimilar functions. Recent studies on the gene *TET2* (which promotes demethylation and is considered an environmental interacting gene) have confirmed the presence of coding and non-coding variants in individuals with neurodegenerative diseases including ALS and FTD patients [204]. *TET2* is essential for methylation conversion to 5-hydroxymethylation, a process essential for aging, learning, and memory [204]. Therefore, a combined approach to studying non-coding parts of the genome is also important. In the future, it is crucial that we focus on genetic epidemiology studies, cohort studies based on population data, and clinical phenotyping, which considers epigenetic features, genetics, lifestyle, and environmental factors.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12035-022-02934-z>.

Author Contribution L. K. and M. M. generated the theme for this article, and L. K. executed the literature search, tabulations, figures, data collection, and analysis. The final draft was edited and modified by L. K., A. M., and M. M.

Funding LK is supported by Malaviya Postdoctoral Fellowship by Institute of Eminence (IoE), Banaras Hindu University (BHU) from Ministry of Education (MoE), Government of India (GOI). Funding from IoE, BHU to MM and AM is duly acknowledged. MM is supported by SERB-Power Fellowship by Science and Engineering Research Board, GOI.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication All authors have given their consent to publish this manuscript in Molecular Neurobiology.

Conflict of Interest The authors declare no competing interests.

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