

## **Ageing as a risk factor for ALS/FTD**

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### **Abstract**

Like many other neurodegenerative diseases, age is a major risk factor in the development of ALS/FTD. But why is this the case? Recent genetic advances have highlighted some of pathways involved in the development of disease, and, strikingly, they appear to substantially overlap with those known to directly modulate the ageing process. Many ALS/FTD linked genes play a direct role in autophagy/lysosomal degradation, one of most important pathways linked to ageing. However, systemic processes such as inflammation, as well as cellular maintenance pathways including RNA splicing and nuclear-cytoplasmic transport have been increasingly linked both to disease and ageing. We highlight some of the shared mechanisms between the ageing process itself and emerging pathogenic mechanisms in ALS/FTD.

### **Introduction**

Frontotemporal dementia (FTD) comprises a diverse array of disorders broadly characterized by the progressive degeneration of the frontal and temporal lobes [1]. FTD is the second most common cause of early onset dementia after Alzheimer's disease [2, 3] and

is strongly heritable, with 30%-50% of patients displaying a strong family history [4]. FTD can be clinically categorized either by behavioural symptoms (behavioural variant FTD, bvFTD, the most heritable form) or by language dysfunction (primary progressive aphasia, PPA) [5, 6] At the pathological level FTD is characterized by an accumulation of proteinaceous inclusions in the brain, with each pathological subtype defined as frontotemporal lobar degeneration (FTLD) followed by the specific inclusion identified. Inclusions in the majority of FTD patient brains contain either tau protein (FTLD-Tau) or TDP-43 (FTLD-TDP). However, about 10% of FTD patients present with FUS inclusions (FTLD-FUS) and some have poly-ubiquitinated inclusions with none of these proteins (FTD-UPS), or no inclusions at all (FTD-ni) [7]. The clinical symptoms of FTD appear to be determined by the pattern of brain atrophy rather than by the molecular identity of the inclusions [8].

Although clinically distinct in their pure forms, FTD is genetically and pathologically related to amyotrophic lateral sclerosis (ALS), a motor neuron disease that causes upper and lower motor neuron degeneration, eventually leading to paralysis and death by respiratory failure. The link between FTD and ALS has been long known [9, 10], yet only recently was it discovered that several mutations can cause either of these diseases [11] and in about 15% of cases (both familial and sporadic) patients develop both diseases [12, 13]. FTD and ALS also overlap pathologically, as nearly all sporadic forms of ALS (sALS) and nearly 90% of familial ALS (fALS) are associated with TDP-43 inclusions, with the exception of fALS caused by SOD1 and FUS mutations, which are characterized by SOD1- or FUS-containing inclusions respectively [14-16].

The similarities between FTD and ALS suggest that these are two forms of the same disease spectrum. However, unlike FTD, ALS is mostly a sporadic disease [17]. It is a complex polygenic trait with approximately 10-20% common SNP-based heritability [18, 19], which is significantly lower than, for instance, Alzheimer's disease [20]. Low-frequency

genetic variants play a major role in heritability of ALS, and many of them are not yet identified [18].

Ageing is the main risk factor for both FTD and ALS (Fig 1) [21, 22]. The incidence of ALS increases dramatically with age [23] [21] and, of the 5% of patients who develop ALS under the age of 30 [23], most carry specific mutations such as FUS and SOD1 [23]. Similarly, the age of onset of FTD is usually above 35, with incidence increasing considerably with age [22, 24]. In this review, we explore the links between the ageing process and the development of FTD/ALS. We discuss how the pathogenic mechanisms of ALS and FTD are closely related to pathways affecting the ageing process itself. We exemplify this with some key molecular mechanisms underlying ALS and FTD, uncovered by the expanding list of genes associated with these diseases, and discuss the roles of these pathways in the ageing process. The overlap between the molecular mechanisms leading to both ageing and FTD/ALS may well explain why advancing age has such an important function in disease development.

### **Overlapping mechanisms in ageing and FTD/ALS**

The ageing process was once thought to result from random accumulation of insults to molecules, cells, tissues and the systemic environment due to the passage of time, and therefore intractable for both experimental analysis and medical intervention. However, in the last 30 years, a number of conserved mechanisms have been shown to modulate ageing, with single genetic mutations and dietary or pharmacological interventions able to extend the lifespan across a variety of species [25]. We discuss four key processes which become dysregulated during ageing and have also been implicated in the aetiology of FTD/ALS by genetic studies: autophagy, inflammation, nuclear-cytoplasmic transport and splicing of RNA (Table 1).

## Autophagy

Autophagy plays an important role in the ageing process [26]. Mitotic cells can dilute out defective proteins and organelles by cell division and biosynthesis. However, as neurons are mostly post-mitotic cells, efficient mechanisms for clearing proteins and organelles are critical to maintain neuronal homeostasis [27]. Protein homeostasis is maintained by the ubiquitin (Ub)-proteasome system (UPS) and autophagy, both of which clear defective cytoplasmic components. The UPS targets mis-folded proteins tagged with ubiquitin to the proteasome, while autophagy delivers cytoplasmic components to lysosomes. There are three types of autophagy: macro, micro and chaperone-mediated autophagy.

Macroautophagy (hereafter referred to as autophagy), is the process by which autophagosomes engulf proteins or organelles and eventually fuse with lysosomes, leading to degradation of their cargoes [27] (Fig 2). Specific adaptors, such as sequestosome-1 (p62/SQSTM-1), sequester poly-ubiquitinated aggregates into autophagosomes. Over the past decade, growing evidence has revealed an important relationship between autophagy and lifespan. Advancing age causes a progressive impairment of the UPS and autophagy, particularly in neurons [27]. These age-related defects may be due to impaired activity of key components of these pathways, because experimentally restored activity of these can lead to improved cellular homeostasis and organ function [28]. Moreover, lifespan-extending interventions often induce and require autophagy [26], and over-expression of autophagy pathway components, such as Atg8 [29], in *Drosophila* brains, or Atg5 in mice [30], is sufficient to extend lifespan. Autophagy is therefore a conserved pathway which modulates the ageing process. It is also a highly relevant pathway in the development of a number of neurodegenerative diseases, including FTD/ALS [31].

Several mutations associated with ALS and FTD are in genes involved in autophagy, including Ubiquilin 2 (UBQLN2), p62/SQSTM1, optineurin (OPTN) and valosin-containing protein (VCP) (see Fig 2). p62/SQSTM1, OPTN and UBQLN2 are adaptor proteins that target poly-ubiquitinated substrates for degradation by delivering them to the

autophagosomal membrane protein LC3 [32]. ALS/FTD causing mutations occur throughout the coding regions of p62/SQSTM1 [33, 34] and reduce p62/SQSTM1 binding to LC3 [35]. Risk mutations in UBQLN2 [36, 37] most commonly alter a conserved proline residue, affecting its co-localisation with OPTN on endosomal vesicles [38] and impair both autophagic and proteasomal mediated degradation of mis-folded and aggregated proteins [36, 39, 40]. An OPTN E478G mutation disrupts the delivery of damaged substrates, such as mitochondria, to autophagosomes [41]. Further cementing the link between this pathway and FTD/ALS was the discovery of mutations in Tank Binding Kinase 1 (TBK1) [42]. TBK1 directly phosphorylates and binds to p62 and OPTN [42-44], and loss of these interactions also impairs delivery of damaged mitochondria to autophagosomes [44, 45]. Moreover, most TBK1 mutations associated to ALS and FTD are missense [46] or abolish binding to OPTN [42][47], indicating these are loss of function mutations that would impair this pathway. Intriguingly, disease-linked mutations in VCP, an AAA(+)-ATPase chaperone-like protein can affect both autophagosome maturation [48, 49] and induce mitochondrial defects [50, 51].

Interestingly, genes that are solely associated to FTD, rather than to both FTD and ALS appear to affect lysosomal function directly. FTD-linked mutations in Charged Multivesicular Body Protein 2B (CHMP2B) and progranulin (GRN), a secretory lysosomal protein that regulates lysosomal function and biogenesis [52], cause defects in lysosomal storage [53, 54]. Moreover, two FTD risk loci, Transmembrane Protein 106B (TMEM106B) and cathepsin D, are also involved in modulating lysosomal function [54][55]. Thus, while genes associated with both ALS and FTD seem to be involved in the early steps of autophagy, during poly-ubiquitinated protein delivery to the autophagosome, those genes linked exclusively to FTD appear to function at later steps in the autophagy process, during lysosomal maturation and/or function [56].

Therefore several lines of evidence link both aging and FTD/ALS to autophagy and lysosomal degradation. One inference from this is that interventions which promote

autophagy and extend lifespan may also be beneficial for FTD/ALS. Notably, increasing autophagy can indeed alleviate symptoms in ALS/FTD models. For instance, feeding rapamycin, an autophagy enhancer which also extends lifespan in flies and mice [57, 58], to a TDP-43 mouse or fly model ameliorated symptoms and reduced TDP-43 aggregation [59, 60].

## **Inflammation**

A major feature of advancing age is a gradual, chronic increase in pro-inflammatory status, a phenomenon named “inflamm-aging” [61]. How and why this increase happens is still a matter of debate [62]. In the brain, age-related inflammation is mostly driven by an increase in inflammatory microglia, the resident immune cells for the brain [63]. Reducing IKK $\beta$ , a key mediator of the immunity pathway, in hypothalamic microglia in mice can improve health and extend lifespan [64], suggesting that brain inflammation is a key driver of the ageing process. An almost ubiquitous feature of neurodegenerative diseases is neuroinflammation: in response to damage in neurons, microglia are activated to clear cellular debris and help neuronal repair, but prolonged activation can also contribute to neuronal damage [65].

Several genes associated with ALS/FTD are directly linked to inflammatory pathways, suggesting that neuroinflammation is not merely a defensive physiological response in neurons already damaged by disease, but rather that inflammation can also directly contribute to pathogenesis. Mice carrying mutations in SOD1, the first gene to be associated with ALS, show astrogliosis and microglial activation [66]. Moreover, mutant SOD1 expression in astrocytes and microglia accelerate disease development [67, 68].

Conversely, pharmacological or genetic reduction of inflammation in SOD1 mutant animals ameliorates pathology [69, 70]. Mice expressing mutant CHMP2B or deficient for GRN have pro-inflammatory phenotypes accompanied by microglial proliferation [71-73] and FTD patients carrying GRN mutations display a distinctive pro-inflammatory CSF profile [74].

Interestingly, a recent GWAS study investigating the genetic basis for the rate of aging in the cerebral cortex, identified FTD related alleles of GRN and TMEM106B as responsible for higher rates of age-related changes in transcription [75]. In particular, the TMEM106B FTD risk allele is associated with an increased age-related, microglia-specific, inflammatory profile, even in a healthy brain [75]. Another autophagy-related gene, TBK1, is activated by several immune effectors, such as Toll-like receptors, thereby inducing the release of type I interferon (IFN) and proinflammatory cytokines [47]. Moreover, TBK1 alleles linked to FTD/ALS can display reduced IFN induction [47]. However, whether they affect immune function in neurodegenerative disease context remains to be seen. That these autophagy/lysosomal degradation genes are also implicated in microglial function raises the possibility that microglial-mediated protein or aggregate degradation plays a role in disease pathogenesis.

An innate immune receptor recently implicated in FTD/ALS, TREM2, is expressed by microglia and plays a key role in inflammation and phagocytosis. TREM2 mutations have been linked to a number of neurodegenerative diseases, including FTD and ALS. TREM2 missense mutations linked to FTD reduce protein shedding causing a reduction in soluble TREM2, (sTREM2) inflammatory CSF profiles and impaired phagocytosis [76]. However, a decrease in sTREM2 is also found in FTD patients who do not carry this mutation, suggesting that TREM2 may play a broader role in FTD [76]. Overall therefore, inflammation is part of disease progression in ALS and FTD. A number of causal genes are involved in inflammatory response and, in the case of GRN and TMEM106B, also in ageing related inflammatory increase, suggesting again a link between the ageing process and disease development.

### **Nuclear-cytoplasmic transport**

Proteins and RNA transcripts shuttle between the nucleus and the cytoplasm via the nuclear pore complex (NPC). Transport across this large, multi-protein channel is achieved by

nuclear transport receptors (NTR) powered by a RanGTP gradient [77]. The NPC is a highly stable structure, with very low turnover of scaffold proteins [78] [79]. NPC proteins are therefore extremely vulnerable to age-related damage, particularly in post-mitotic cells such as neurons. Moreover, the expression of some essential NPC components, such as Nup93 [80], decreases during ageing, resulting in leakage of cytoplasmic contents into the nucleus [78]. Notably, in yeast modulation of NPC proteins or NTRs can increase lifespan, suggesting that the NPC plays a direct role in ageing [81, 82].

Recent evidence suggests that nuclear transport defects may promote FTD/ALS development [83]. C9orf72 hexanucleotide expansion (C9) is the most common genetic cause of ALS and FTD, accounting for 30-40% and 10% of familial and sporadic disease, respectively [84]. ALS/FTD patients can carry thousands of copies of this GGGGCC stretch in the first intron of C9orf72, whereas healthy individuals carry fewer than 30 copies [85, 86]. C9 is transcribed into a repetitive and stable RNA structure that produces highly toxic dipeptide-repeat proteins [87]. Four independent studies using C9orf72 hexanucleotide expansion (C9) models demonstrated that nucleocytoplasmic defects were key mediators of the pathology [88-91]. Furthermore, in yeast and *Drosophila*, modulating the expression levels of NPC or export components rescues C9 toxicity [88-91], highlighting the importance of impaired nuclear-cytoplasmic transport as a toxic mechanism. Defects in nuclear-cytoplasmic transport can lead to TDP-43 mis-localisation from the nucleus to the cytoplasm [92], a typical feature of C9 patients but also of ALS/FTD more generally, since the accumulation of insoluble cytoplasmic TDP-43 or FUS aggregates is concomitant with nuclear depletion of these proteins. TDP-43 and FUS are predominantly nuclear RNA-binding proteins involved in transcription, translation and splicing. Mutations in the nuclear localization signal (NLS) of FUS cause the most aggressive phenotypes and a mutation totally truncating the NLS of FUS leads to juvenile disease onset [93], indicating that mis-localization is critical for disease development. Mutations in the NLS of TDP-43 have not been identified. However, nuclear depletion of this protein is observed in FTD/ALS patients,



suggesting an impairment in nuclear-cytoplasmic transport. Impairments in nuclear-cytoplasmic transport due to imbalance in levels of importins are also seen in FTD-TDP-43, ALS-SOD1 and sporadic ALS patients [92] [94]. TDP-43 nuclear depletion in patient cells likely causes down-regulation of TDP-43 target mRNAs [95, 96].

Similarly to TDP-43 in FTD/ALS, several proteins specifically associated with ALS, such as EWS [97, 98], TAF15 [97] hnRNPA2B1 and hnRNPA1 [99], are predominantly nuclear RNA-binding proteins and components of stress granules that are depleted from the nucleus in patient cells. Moreover, mutations in GLE1, a direct regulator of nuclear-cytoplasmic transport that is also implicated in stress granule formation, can cause ALS [100].

Interestingly, these disease causing mutations also seem to lead to cytoplasmic localisation [101], suggesting a general mechanism of toxicity whereby proteins with mostly nuclear functions are relocalised to the cytoplasm, possibly altering stress granule formation and mRNA metabolism. Therefore altered nucleocytoplasmic transport may contribute towards the mis-localisation of nuclear proteins observed in FTD/ALS and this could be exacerbated by age-related decline in NPC function.

## **Splicing**

Correct splicing of RNA is impaired during normal ageing. An increase in the expression of genes involved in RNA processing increases alternative splicing in ageing mice [102]. In human brains, the expression levels of several splicing regulators change with age, and an age-dependent increase in splicing has been associated with augmented activity of Polypyrimidine tract-binding protein 1 (PTBP1) [103], these aberrant splicing events could lead to the production of non-functional proteins, and are associated with disease-linked genes or genes involved in DNA repair. Recent reports also suggest that splicing plays an active role in ageing. For instance, a study on mice with accelerated ageing due to progeria mutations showed that the number of alternatively spliced genes increases with age [102]. In *C. elegans*, splicing factor 1 (SPA1) is required for lifespan extension by several

interventions [104] and, more importantly, SPA1 up-regulation was sufficient to extend lifespan.

A direct consequence of the relocation of nuclear factors to the cytoplasm is loss of nuclear function. Depletion of TDP-43 causes splicing changes, including increased cryptic exon incorporation into transcripts, which are also detected in brain tissue from ALS/FTD patients [95] [105, 106]. Other genes implicated in ALS also appear to cause mis-splicing, for instance, depletion of FUS in mice causes splicing defects [96, 107], which is consistent with the RNA-binding function of FUS near repressed exons during splicing. Similarly, ALS-linked hnRNPA2B1 deletions have been associated with splicing defects in patient cells [108]. Therefore increasing evidence indicates that splicing is a modulator of ageing and is directly associated to ALS and FTD development. These findings further support the tight relationship between the ageing process and ALS/FTD disease progression.

## **Conclusions**

A number of FTD/ALS genes are implicated in ageing pathways (Table 1). This substantial overlap could explain why ageing is the main risk factor for these diseases. Recent models propose that ALS is a multi-step process [109] and ageing may facilitate some aspects of the development of this disease. For instance, sub-threshold defects in these pathways may be pushed into overt dysfunction during aging. As familial forms of the disease develop 10 years earlier than sporadic forms [110], it is plausible that genetic mutations further lower the threshold by which the ALS pathogenic process can be driven by ageing. This opens the possibility of re-purposing drugs known to affect lifespan as possible therapeutic avenues.

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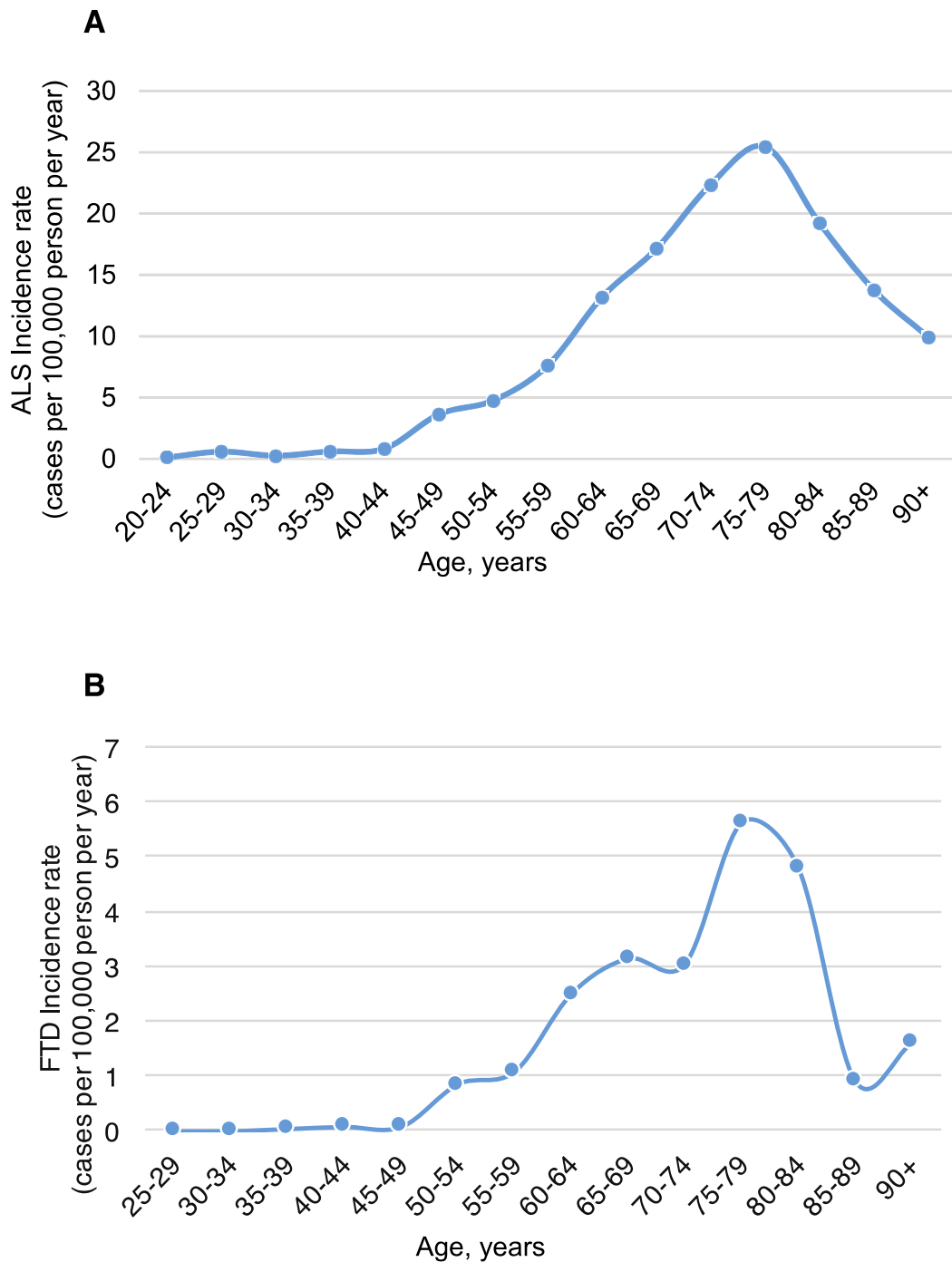
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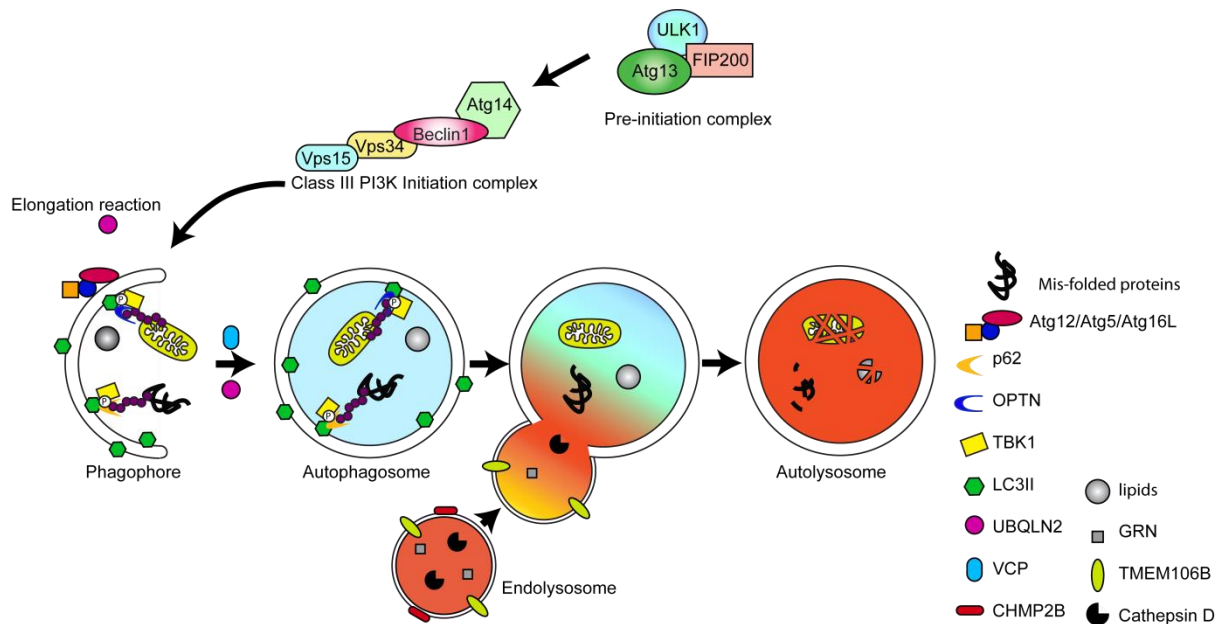
Gene Symbol	Name	Pathway	ALS or FTD
OPTN	Optineurin	Autophagy	ALS/FTD
VCP	Valosin Containing Protein	Autophagy/Mitochondrial function	ALS/FTD
UBQLN2	Ubiquilin 2	Autophagy/Proteasome	ALS/FTD
SQSTM1	Sequestosome 1	Autophagy	ALS/FTD
TBK1	TANK Binding Kinase 1	Autophagy/Inflammation	ALS
GRN	Progranulin	Lysosomal degradation /inflammation	FTD
CHMP2B	Charged Multivesicular Body Protein 2B	Lysosomal degradation/inflammation	FTD
SOD1	Superoxide dismutase	Inflammation	ALS
TREM2	Triggering Receptor Expressed On Myeloid Cells 2	Inflammation	FTD
FUS	FUS RNA binding protein	Nucleocytoplasmic transport/splicing	ALS
TARDBP	TAR DNA Binding Protein	Nucleocytoplasmic transport/splicing	ALS
TAF15	TATA-Box Binding Protein Associated Factor 15	Nucleocytoplasmic transport/RNA metabolism	ALS
C9orf72	C9orf72 hexanucleotide repeat expansion	Nucleocytoplasmic transport/splicing	ALS/FTD
HNRNPA2B1	Heterogeneous Nuclear Ribonucleoprotein A2/B1	Nucleocytoplasmic transport/splicing	ALS/FTD
HNRNPA1	Heterogeneous Nuclear Ribonucleoprotein A1	Nucleocytoplasmic transport/splicing	ALS/FTD
GLE1	GLE1, RNA Export Mediator	Nucleocytoplasmic transport	ALS
TMEM106B	Transmembrane Protein 106B	Autophagy/Inflammation	FTD

**Table 1. Genetic causes and risk factors for ALS/FTD implicated in ageing pathways**

List of genes discussed in the main text implicated in the development of ALS/FTD and associated ageing pathways they appear to be involved in.



**Figure1. Incidence of FTD and ALS increase with age. A.** Incidence of ALS in the UK, according to the 1990-2005 in the General Practice Research Database (Data kindly supplied by Alvaro Alonso) [21]. **B.** Incidence of FTD in Sweden according to the Swedish Dementia Registry [22].



**Figure 2. The autophagy pathway and ALS/FTD genes.** The autophagy process is initiated by the phosphorylation of ULK1, this activates the pre-initiation complex which in turn phosphorylates the PI3K CII complex allowing it to catalyse the first steps required to generate an elongating double membrane. A number of components participate in the elongation reaction, leading to the binding of Atg12/Atg5/Atg16L complex and LC3 II to the membrane, which leads to the membrane enclosing a portion of the cytosol. As the membrane is closing misfolded proteins and damaged organelles are targeted to the autophagosome, which then fuses with a late endosome or lysosome generating an autolysosome where the organelles are digested. Autophagic receptors (p62, OPTN) and adaptor proteins confer selectivity by tethering specific cargoes, such as poly-ubiquitinated proteins or mitochondria to LC3 in forming phagophores, thus targeting them for degradation. Several FTD/ALS linked genes are implicated at different stages of this pathway.