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Molecular mechanisms of amyotrophic lateral sclerosis

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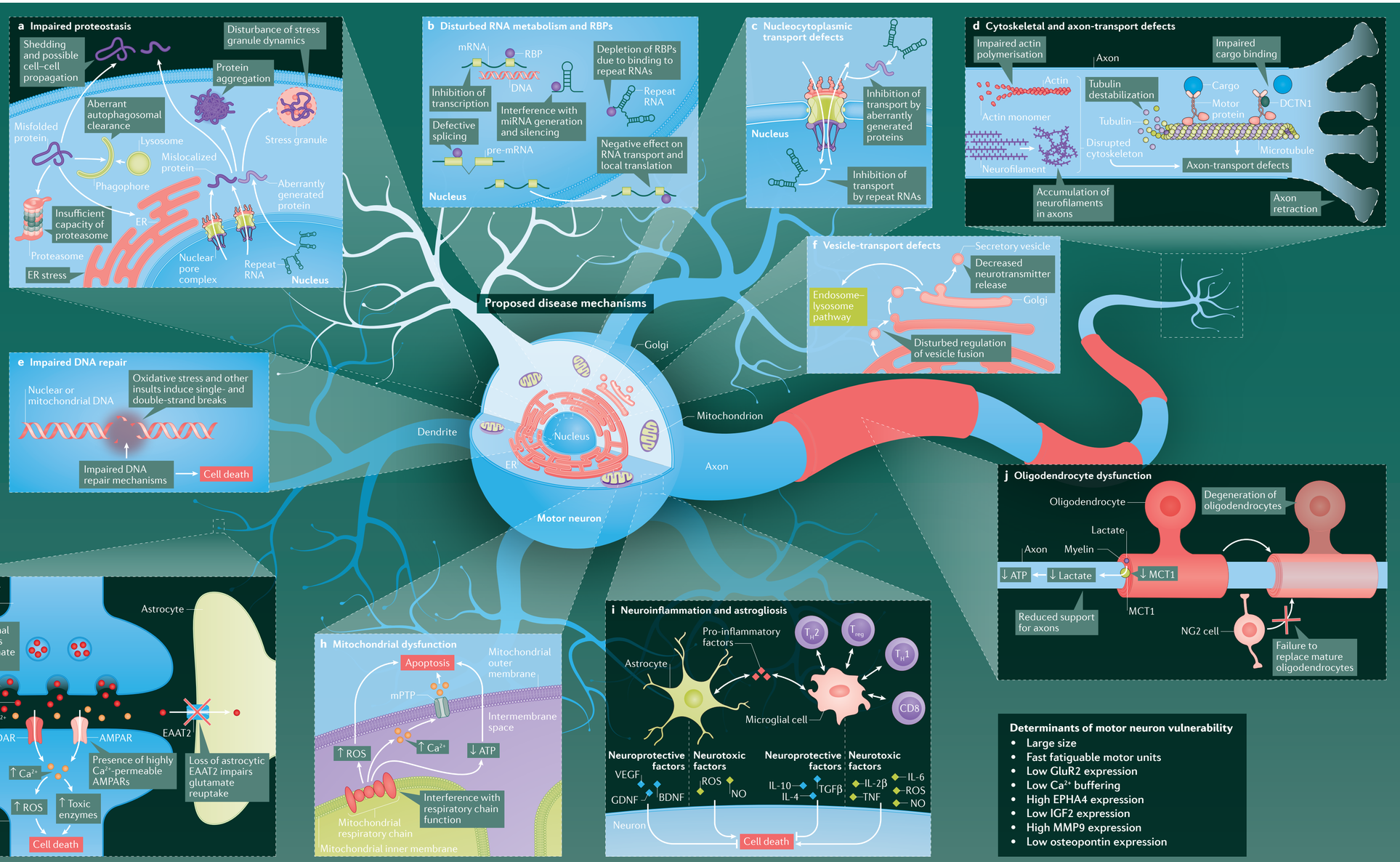
Amyotrophic lateral sclerosis (ALS) is a fatal, neurodegenerative disorder that primarily affects the motor system, resulting in progressive muscle weakness and paralysis. In almost 90% of patients, the cause of ALS remains enigmatic, and most of our current understanding of ALS is based on its genetics and neuropathology. The disease-causing gene mutation has been identified in the majority of patients with familial ALS, as well as in 5–10% of patients with sporadic ALS. The affected genes are involved in various cellular functions, pointing to a large variety of possible disease mechanisms that could lead to selective motor neuron degeneration. In this Poster, we provide an overview of the genetic causes of ALS and risk factors, and link these to the specific characteristics of motor neurons and to the most important pathogenic mechanisms.

ALS usually has a focal onset and spreads throughout the motor system, which explains the relentless progressive character of the disease and is suggestive of an underlying 'prion-like' spreading mechanism. In some patients, degeneration extends to the frontal and anterior temporal lobes, giving rise to executive dysfunction, language impairments, behavioural changes and/or frontotemporal dementia. Despite being uniformly fatal, ALS is associated with considerable variation in the age at onset, rate of disease progression, relative upper versus lower motor neuron involvement and the degree of frontotemporal involvement. ALS is also linked with considerable genetic heterogeneity: more than 20 genes have been linked to ALS to date (table 1). Even in families with a monogenetic cause of ALS, the disease presentation is highly variable, suggestive of the existence of disease-modifying factors.

The ALS disease process is characterized by axonal retraction and subsequent loss of the cell bodies of upper and lower motor neurons. In most individuals with this disease, the degenerating neurons are characterized by cytoplasmic, ubiquitin-containing inclusions in which TDP43 is present. Moreover, the affected motor neurons are surrounded by reactive astrocytes and microglia, and oligodendroglial function is compromised. These cells clearly contribute to the disease process, and ALS is thus considered a non-cell-autonomous disease.

As illustrated (main figure), many different mechanisms have been proposed to drive ALS pathogenesis. For at least some of these, it remains to be established whether the disturbances are involved in the disease mechanism or are a secondary consequence of the disease process. Further research is necessary to clarify this issue.

The cornerstone of ALS treatment remains multidisciplinary care, including nutritional and respiratory support and symptom management. The only approved drug for ALS is riluzole, which presumably has an anti-excitotoxic mode of action, but the survival benefit of this drug is limited. Future therapeutic strategies might involve the development of therapies that directly regulate the expression of the mutated genes or modulate the different proposed pathogenic mechanisms (main figure).



Determinants of motor neuron vulnerability

- Large size
- Fast fatiguable motor units
- Low GluR2 expression
- Low Ca^{2+} buffering
- High EPHA4 expression
- Low IGF2 expression
- High MMP9 expression
- Low osteopontin expression

Table 1 | **Genetics of ALS**

Gene	Pathogenic pathways
Frequent	
*C9orf72**	a–c,f,g
*FUS**	a,b,e,g
*SOD1**	a,d,g–j
*TARDBP**‡	a,b,h
Less frequent or in some cases associated with atypical ALS	
*ALS2**, *CHMP2B**, *UNC13A*§ and *VAPB**	f
*ANG**, *ATXN2*, *SETX**, *ELP3*§ *HNRNPA1/A2/B1* and *MATR3*	b
C21ORF2 and *NEK1*	e
CCNF, *FIG4*, *OPTN**, *SIGMAR1*, *SQSTM1*, *UBQLN2**, *TBK1** and *VCP**	a
CHCHD10	h
DAO	g
DCTN1, *NEFH*, *PRPH*, *TUBA4A*, *SPG11** and *PFN1**	d
GLE1	c

*Segregation of mutation with the disease in several families. ‡Encodes TDP43. §SNP association.

Abbreviations

ALS2, alsin Rho guanine nucleotide exchange factor; AMPAR, AMPA receptor; *ANG*, angiogenin; *ATXN2*, ataxin 2; BDNF, brain-derived neurotrophic factor; *C9orf72*, chromosome 9 open reading frame 72; *CCNF*, cyclin F; *CHCHD10*, coiled-coil-helix-coiled-coil-helix domain containing 10; *CHMP2B*, charged multivesicular body protein 2B; *DAO*, D-amino acid oxidase; DCTN1, dynactin subunit 1; EAAT2, excitatory amino acid transporter 2; *ELP3*, elongator acetyltransferase complex subunit 3; EPHA4, ephrin type A receptor 4; ER, endoplasmic reticulum; *FIG4*, FIG4 phosphoinositide 5-phosphatase; GDNF, glial cell line-derived neurotrophic factor; *GLE1*, GLE1 RNA export mediator; *HNRNPA1*, heterogeneous nuclear ribonucleoprotein A1; IGF2, insulin-like growth factor 2; IL, interleukin; *MATR3*, matrin 3; MCT1, monocarboxylate transporter 1; miRNA, microRNA; MMP9, matrix metalloproteinase 9; mPTP, mitochondrial permeability transition pore; *NEFH*, neurofilament heavy polypeptide; *NEK1*, NIMA-related kinase 1; NMDAR, NMDA receptor; NO, nitric oxide; *OPTN*, optineurin; *PFN1*, profilin 1; *PRPH*, peripherin; RBP, RNA-binding protein; ROS, reactive oxygen species; *SETX*, senataxin; *SIGMAR1*, sigma non-opioid intracellular receptor 1; SNP, single-nucleotide polymorphism; *SOD1*, superoxide dismutase 1; *SPG11*, spastic paraplegia 11; *SQSTM1*, sequestosome 1; *TARDBP*, TAR DNA-binding protein; *TBK1*, TANK-binding kinase 1; TDP43, TAR DNA-binding protein 43; TGFβ, transforming growth factor-β; T_H1, T helper 1 cell; TNF, tumour necrosis factor; T_{reg}, regulatory T cell; *TUBA4A*, tubulin alpha 4A; *UBQLN2*, ubiquilin 2; *UNC13A*, unc-13 homologue A; *VAPB*, VAMP-associated protein B and C; *VCP*, valosin-containing protein; VEGF, vascular endothelial growth factor.

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