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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).

Proposed disease mechanisms

a Impaired proteostasis — Shedding and possible cell–cell propagation; Disturbance of stress granule dynamics; Protein aggregation; Aberrant autophagosomal clearance; Misfolded protein; Lysosome; Mislocalized protein; Phagophore; Stress granule; Insufficient capacity of proteasome; ER; Aberrantly generated protein; Proteasome; ER stress; Nuclear pore complex; Repeat RNA; Nucleus

b Disturbed RNA metabolism and RBPs — mRNA; RBP; DNA; Depletion of RBPs due to binding to repeat RNAs; Repeat RNA; Inhibition of transcription; Interference with miRNA generation and silencing; Defective splicing; pre-mRNA; Negative effect on RNA transport and local translation; Nucleus

c Nucleocytoplasmic transport defects — Inhibition of transport by aberrantly generated proteins; Nucleus; Inhibition of transport by repeat RNAs

d Cytoskeletal and axon-transport defects — Impaired actin polymerisation; Axon; Impaired cargo binding; Actin; Tubulin destabilization; Cargo; DCTN1; Actin monomer; Tubulin; Motor protein; Neurofilament; Disrupted cytoskeleton; Microtubule; Axon-transport defects; Accumulation of neurofilaments in axons; Axon retraction

e Impaired DNA repair — Nuclear or mitochondrial DNA; Oxidative stress and other insults induce single- and double-strand breaks; Impaired DNA repair mechanisms; Cell death

f Vesicle-transport defects — Secretory vesicle; Decreased neurotransmitter release; Endosome–lysosome pathway; Golgi; Disturbed regulation of vesicle fusion

g Excitotoxicity — Presynaptic neuron; Astrocyte; Increased neuronal excitability drives increased glutamate release; Glutamate; Ca^{2+}; NMDAR; AMPAR; EAAT2; Presence of highly Ca^{2+}-permeable AMPARs; Loss of astrocytic EAAT2 impairs glutamate reuptake; $\uparrow Ca^{2+}$; $\uparrow ROS$; $\uparrow$ Toxic enzymes; Motor neuron; Cell death

h Mitochondrial dysfunction — Apoptosis; Mitochondrial outer membrane; mPTP; Intermembrane space; $\uparrow ROS$; $\uparrow Ca^{2+}$; $\downarrow ATP$; Interference with respiratory chain function; Mitochondrial respiratory chain; Mitochondrial inner membrane

i Neuroinflammation and astrogliosis — Pro-inflammatory factors; T_H2; T_{reg}; T_H1; Astrocyte; Microglial cell; CD8; Neuroprotective factors: VEGF, GDNF, BDNF; Neurotoxic factors: $\downarrow ROS$, NO; Neuroprotective factors: IL-10, IL-4, $\uparrow TGF\beta$; Neurotoxic factors: $\downarrow$ IL-2β, IL-6, ROS, TNF, NO; Neuron; Cell death

j Oligodendrocyte dysfunction — Oligodendrocyte; Degeneration of oligodendrocytes; Lactate; Axon; Myelin; $\downarrow ATP$; $\downarrow$ Lactate; $\downarrow MCT1$; MCT1; Reduced support for axons; NG2 cell; Failure to replace mature oligodendrocytes

Motor neuron; Golgi; Dendrite; Nucleus; ER; Mitochondrion; Axon

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.

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

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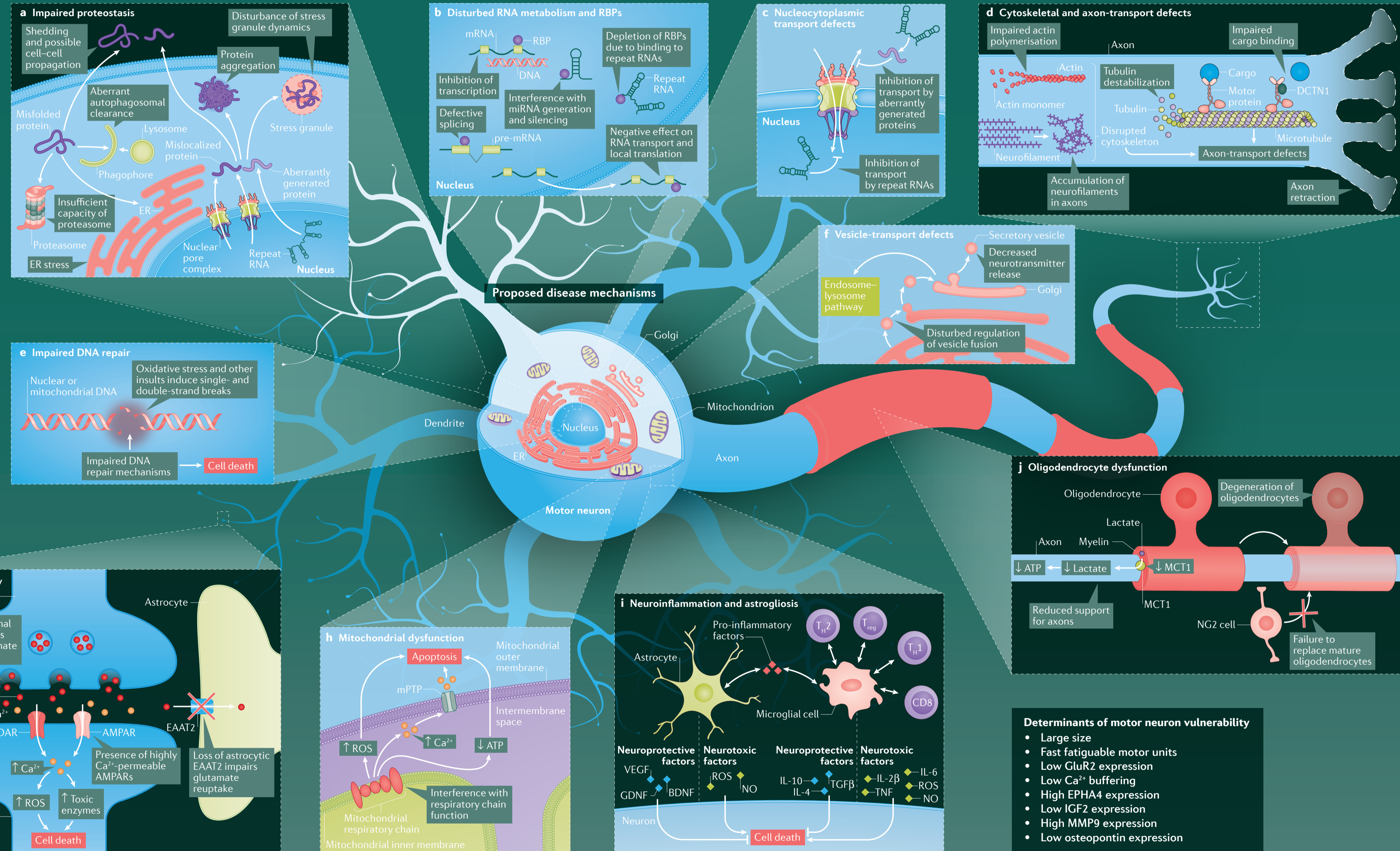6. Boeynaems, S. et al. Inside out: the role of nucleocytoplasmic transport in ALS and FTLD. Acta Neuropathol. 132, 159–173 (2016).