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## Nuclear pore complexes — a doorway to neural injury in neurodegeneration

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### Abstract

The genetic underpinnings and end-stage pathological hallmarks of neurodegenerative diseases are increasingly well defined, but the cellular pathophysiology of disease initiation and propagation remains poorly understood, especially in sporadic forms of these diseases. Altered nucleocytoplasmic transport is emerging as a prominent pathomechanism of multiple neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer disease, frontotemporal dementia and Huntington disease. The nuclear pore complex (NPC) and interactions between its individual nucleoporin components and nuclear transport receptors regulate nucleocytoplasmic transport, as well as genome organization and gene expression. Specific nucleoporin abnormalities have been identified in sporadic and familial forms of neurodegenerative disease, and these alterations are thought to contribute to disrupted nucleocytoplasmic transport. The specific nucleoporins and nucleocytoplasmic transport proteins that have been linked to different neurodegenerative diseases are partially distinct, suggesting that NPC injury contributes to the cellular specificity of neurodegenerative disease and could be an early initiator of the patho-physiological cascades that underlie neurodegenerative disease. This concept is consistent with the fact that rare genetic mutations in some nucleoporins cause cell-type-specific neurological disease. In this Review, we discuss nucleoporin and NPC disruptions and consider their impact on cellular function and the pathophysiology of neurodegenerative disease.

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The genetic causes and end-stage pathological hallmarks of neurodegenerative diseases are increasingly well defined. However, the molecular and cellular events that contribute to and initiate disease pathophysiology are still poorly understood. The nuclear pore complex (NPC) — which is made up of many nucleoporin proteins — mediates nucleocytoplasmic transport, genome organization and gene expression<sup>1–3</sup>. Pathological disruptions to individual nucleoporins or the overall integrity of the NPC are, therefore, likely to have detrimental effects on neuronal function and survival. Consistent with this notion, multiple studies indicate that disruptions of the NPC and the nucleocytoplasmic

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Author contributions

Both authors contributed to all aspects of the manuscript.

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transport machinery (for example, nuclear transport receptors (NTRs), RAN GTPase-activating protein 1 (RANGAP1) and RAN GTPase energy gradients) are prominent contributors to the pathogenesis of neurodegenerative disease.

Most of these studies have focused on amyotrophic lateral sclerosis (ALS) but some evidence indicates that similar mechanisms exist in Alzheimer disease (AD), frontotemporal dementia (FTD) and Huntington disease (HD)<sup>4–11</sup>. Genetic interaction studies in flies and yeast suggest that NPC and nucleocytoplasmic transport proteins are potent modifiers of disease phenotypes<sup>12,13</sup>, and evidence suggests that these proteins can influence the aggregation state of several other proteins associated with neurodegeneration, including TAR DNA-binding protein 43 (TDP43), fused in sarcoma (FUS) and tau<sup>6,14–16</sup>. Furthermore, mutations in specific nucleoporins cause cell-type-specific neurological diseases<sup>17–20</sup>, suggesting that defects in the NPC or nucleoporins are sufficient to initiate neurodegeneration.

In this Review, we discuss the latest knowledge about how disruptions in the NPC and nucleocytoplasmic transport contribute to neurodegenerative disease pathophysiology. We also highlight the potential of NPC and nucleocytoplasmic transport dysfunction as a therapeutic target in neurodegenerative disease.

## Structure and function of the NPC

The mammalian NPC is a multi-protein complex of ~120 MDa that is highly organized and has eightfold rotational symmetry<sup>1,21</sup>. All NPCs comprise multiple copies of ~30 nucleoporins, although the exact number and stoichiometry of the nucleoporins varies in yeast and mammalian cells<sup>22–27</sup>. NPCs within a single cell nucleus are not compositionally identical — a heterogeneous distribution of specific nucleoporins has been observed within individual nuclei of neuronal and non-neuronal mammalian cells<sup>5,28</sup>. The composition of nucleoporins within NPCs also varies between cell types<sup>26,27</sup>. Despite slight differences in the composition of specific nucleoporins and subcomplexes within yeast and mammalian NPCs, the overall structure and organization are consistent<sup>21,23</sup>. Nucleoporin nomenclature varies for mammalian and yeast cells; in this Review, we use the mammalian nomenclature.

All NPCs have the same basic structural components that are each made up of various nucleoporins (FIG. 1): the cytoplasmic ring and filaments (NUP88, NUP214 and NUP358), the central channel (NUP54, NUP58, NUP62 and NUP98), the outer ring (ELYS, NUP37, NUP43, NUP85, NUP96, NUP107, NUP133, NUP160, SEC13 and SEH1), the inner ring (NUP35, NUP93, NUP155, NUP188 and NUP205), the transmembrane ring (GP210, NDC1 and POM121), and the nuclear basket (NUP50, NUP153 and TPR). The core NPC scaffold comprises the inner and outer rings, which are anchored within the nuclear envelope via the transmembrane nucleoporins and provide structural support to the cytoplasmic filaments, central channel and nuclear basket. Besides ELYS, which is present only in the nucleoplasmic side of the outer ring subcomplex in mammalian cells, the other nucleoporins are symmetrically localized to the two faces of the NPC<sup>21</sup>. The nucleoporins that make up the cytoplasmic ring and filaments and the nuclear basket are distributed asymmetrically on the cytoplasmic and nucleoplasmic faces of the NPC, respectively. Thus, the nucleoporins

within the scaffold rings on the cytoplasmic and nucleoplasmic faces of the NPC are the same but the nucleoporins that comprise the cytoplasmic filaments and the nuclear basket are distinct (FIG. 1).

The NPC and its nucleoporin constituents collectively regulate nucleocytoplasmic transport of macromolecules, organization of the genome and gene expression. In general, macromolecules of <40–60 kDa can passively diffuse through the NPC. However, the passage of larger molecules relies on active transport facilitated by the binding of the cargo to specific NTRs (karyopherins) via nuclear localization and/or nuclear export sequences<sup>29–33</sup>. Active nucleocytoplasmic transport is maintained by RAN GTPase and a RAN gradient. In the cytoplasm, RANGAP1 hydrolyses RAN–GTP to RAN–GDP and in the nucleus, RCC1 converts RAN–GDP to RAN–GTP. This process increases the levels of RAN–GTP in the nucleus and of RAN–GDP in the cytoplasm, thereby providing an energy source for active transport<sup>34–40</sup>.

Approximately one-third of nucleoporins contain FG repeat domains, which form a selective permeability barrier that regulates the transport of macromolecules. These intrinsically disordered domains transiently bind to and interact with NTRs to facilitate active nucleocytoplasmic transport<sup>41,42</sup>. In the nuclear basket, TPR and NUP153 mediate nuclear mRNA export<sup>43–49</sup> and NUP50 plays a role in the dissociation of NTR–cargo complexes upon nuclear protein import<sup>50–52</sup> and might also have a role in nuclear protein export<sup>53</sup>.

In addition to their role in facilitating nucleocytoplasmic transport, the NPC and specific nucleoporins regulate chromatin organization and gene expression. Nucleoporins, including NUP98, NUP50 and NUP153, can interact with chromatin and tether it to specific nuclear landmarks. Furthermore, these nucleoporins have direct and indirect roles in gene expression. They directly regulate gene transcription by interacting with DNA in an RNA polymerase II-dependent manner<sup>54–59</sup> and they indirectly influence gene expression by aiding RNA transport, ultimately leading to RNA processing events in the cytoplasm. The functions of the NPC and individual nucleoporins have been reviewed in depth elsewhere<sup>1–3,21,41,60–66</sup>.

Although the NPC and its functions are common to all cell types, the pathobiology of this macromolecular complex and its constituents seems to differ between cell types and diseases. Most studies of this pathobiology in neurodegenerative disease have focused on ALS. However, increasing evidence suggests that alterations in the NPC and nucleocytoplasmic transport contribute to several neurodegenerative diseases. Differences in the contributions to different diseases might reflect the cell-type-specific compositions of nucleoporins and nucleocytoplasmic transport proteins, although they could also reflect differences in the model systems used to study neurodegenerative disease pathophysiology.

## **Nucleocytoplasmic transport and the NPC in ALS**

### **Pathogenesis of ALS.**

ALS is characterized by progressive degeneration of upper and lower motor neurons, along with degeneration of local interneurons and regional dysfunction of oligodendrocytes and

astrocytes, and later activation of microglia<sup>67,68</sup>. Up to 50% of patients with ALS have mild dementia and a small subset has concomitant FTD<sup>69,70</sup>.

In up to 10% of affected patients, ALS is inherited, and more than 20 genes can cause familial ALS. The most common causal genetic mutation is a hexanucleotide repeat expansion (HRE) within intron 1 of *C9orf72*, which accounts for ALS in up to 40% of patients with familial ALS. Mutation of *C9orf72* is also the most common cause of familial FTD. Mutations in genes that encode proteins involved in RNA metabolism, including TDP43 and FUS, and cytoskeletal integrity, including profilin 1 (PFN1), cause ALS in a small subset of patients with familial ALS<sup>71–75</sup>. The remaining 90% of patients with ALS have sporadic disease, although *C9orf72* mutations are commonly found among patients with apparent sporadic ALS<sup>71,72</sup>.

Familial and sporadic ALS have similar clinical manifestations and end-stage pathologies<sup>67,76,77</sup>. For example, the RNA-binding protein TDP43 is cleared from the nucleus and accumulates and aggregates in the cytoplasm in 97% of all patients with ALS<sup>78,79</sup>. Whether TDP43 cytoplasmic mislocalization is the result of impaired active and passive nucleocytoplasmic transport or an independent cellular response to neurodegeneration remains unknown, but the fact that the end-stage pathology and clinical manifestations are similar suggests that the cellular and molecular events that initiate the disease are at least partly shared between familial and sporadic ALS.

### **Nucleocytoplasmic transport alterations.**

Two studies published in 2015 were the first to identify defects in nucleocytoplasmic transport as a prominent pathomechanism underlying *C9orf72* ALS–FTD<sup>10,12</sup>. One of these studies, using induced pluripotent stem cell (iPSC)-derived neurons (iPSNs) and *Drosophila* models of *C9orf72* ALS, showed that pathological repeat RNA generated by the *C9orf72* HRE disrupts nucleocytoplasmic transport by sequestering RANGAP1, thereby disrupting the RAN GTPase gradient<sup>7</sup>. Use of a fluorescent nucleocytoplasmic transport reporter and fluorescence recovery after photobleaching (FRAP) demonstrated that nuclear protein import is impaired in iPSNs with the *C9orf72* mutation<sup>10</sup>. In the other study, overexpression of the *C9orf72* HRE in *Drosophila* salivary glands or HeLa cells resulted in retention of poly-A mRNA within the nucleus<sup>12</sup>. Furthermore, a genetic screen indirectly implicated components of the nuclear transport pathway in *C9orf72*-mediated retinal degeneration in *Drosophila*<sup>12</sup>.

A third study published later in 2015 independently identified a subset of NTRs that are modifiers of *C9orf72* dipeptide repeat (DPR) protein toxicity in yeast<sup>13</sup>. Since 2015, multiple studies have been done using exogenous nucleocytoplasmic transport reporters, permeabilized cell assays and genetic screens to understand how pathological DPR proteins produced by the *C9orf72* HRE contribute to disruption of nucleocytoplasmic transport<sup>80–87</sup>. The precise defects identified in *C9orf72* model systems have been reviewed in detail elsewhere<sup>88</sup>.

All studies indicate dysfunction of elements of the nucleocytoplasmic transport machinery, although many of these studies have yielded conflicting results, making it difficult to

interpret exactly how the *C9orf72* HRE and DPR proteins disrupt nucleocytoplasmic transport in human neurons. The conflicting results could be due to the technical challenges and limitations of performing these studies in endogenous and relevant cellular model systems. As such, debate remains about the nature of nucleocytoplasmic transport defects in ALS and the mechanisms that could underlie these defects.

In a study published in 2020, experiments in permeabilized HeLa cells and primary mouse cortical neurons showed that arginine (R)-rich DPR proteins impede the function of importin- $\beta$  in the vicinity of the NPC<sup>80</sup>. Importin- $\alpha$ –importin- $\beta$  complexes facilitate nuclear import of many proteins that contain nuclear localization signals (NLSs). Importin- $\alpha$  binds to NLS sequences in target proteins and importin- $\beta$  binds to importin- $\alpha$  and FG-rich nucleoporins in the NPC to mediate nuclear import of target proteins<sup>33</sup>, such as TDP43 (REF.<sup>89</sup>). Thus, disruptions in importin- $\beta$  function could have detrimental effects on nuclear protein import and might contribute to TDP43 pathology in ALS. Although the study in HeLa cells relied on the artificial expression of short, fluorescently labelled DPR proteins in non-living cells, the result suggests that future studies of DPR protein-mediated NTR disruption could provide novel insights into the mechanistic basis of nucleocytoplasmic transport disruption in *C9orf72* ALS–FTD. Furthermore, some evidence suggests that hyperosmotic stress impedes cargo unloading in a similar way to DPR protein overexpression. In non-neuronal mammalian cells, fluorescent nucleocytoplasmic transport reporters accumulated along the nuclear rim upon sorbitol stress and, to a lesser extent, poly(GR) overexpression<sup>90</sup>, an observation that is similar to poly(GR)-mediated and poly(PR)-mediated defects in importin- $\alpha$  and importin- $\beta$  cargo unloading in the vicinity of the NPC<sup>80</sup>. However, the relevance of these artificial cellular stress model systems to true human neurodegenerative disease remains unclear. Studies are needed to ascertain whether physiologically relevant cellular stressors and stress granule assembly functionally affects nucleocytoplasmic transport via similar mechanisms that involve importin- $\alpha$  and importin- $\beta$  in human neurons.

Though early studies of nucleocytoplasmic transport in ALS focused on *C9orf72*, nucleocytoplasmic transport is now being investigated in the context of other rare inherited forms of ALS, including those associated with TDP43, FUS and PFN1. The use of fluorescent reporters and static or dynamic FRAP imaging in three independent studies has identified defects in nuclear protein transport in iPSNs or primary mouse cortical neurons that express mutant TDP43 (REF.<sup>4</sup>), FUS<sup>11</sup> or PFN1 (REF.<sup>8</sup>). Moreover, overexpression of TDP43 variants in primary mouse cortical neurons led to an increase in nuclear levels of poly-A mRNA, suggesting that TDP43 overexpression impairs global protein and mRNA trafficking between the nucleus and cytoplasm. However, the studies of PFN1 and TDP43 were based on artificial overexpression of mutant constructs in primary mouse cortical neurons; whether endogenous levels of mutant PFN1 or TDP43 or cytoplasmic wild-type TDP43 pathology disrupt nucleocytoplasmic transport in human neuronal systems remains to be seen, as extrapolation from non-neuronal and non-mammalian systems to human diseases is difficult, especially when evaluating NPCs, the composition of which varies by cell type<sup>26–28</sup>. Moreover, these studies did not determine the mechanism by which nucleocytoplasmic transport is impaired in TDP43, FUS, and PFN1 model systems. Studies

are needed to ascertain whether nucleocytoplasmic defects result from NPC injury and/or disruptions in NTR function.

### **NPC disruption.**

To date, most studies of nuclear transport in ALS have focused on functional nucleocytoplasmic transport itself, primarily through the use of reporter constructs. However, the NPC tightly governs active and passive nucleocytoplasmic transport. It controls active nucleocytoplasmic transport through interactions between nucleoporins that contain FG repeat domains (FG-Nups) and NTRs and passive nucleocytoplasmic transport by the integrity of the FG-Nup diffusion barrier within the central channel of the NPC, which normally allows macromolecules of >40–60 kDa to freely diffuse through the NPC. Given that FG-Nups are anchored within the NPC via scaffolding nucleoporins, the overall composition and integrity of the NPC is essential for maintaining nucleocytoplasmic transport and other cellular functions<sup>1,2,21</sup>.

Initial studies in sporadic and *C9orf72* ALS–FTD post-mortem human tissue and in mouse models of ALS suggested that mislocalization and cytoplasmic accumulation of the NPC-associated protein RANGAP1 and a subset of nucleoporins, including NUP107, NUP205 and FG-nucleoporins, contribute to deficits in nucleocytoplasmic transport (FIG. 2; TABLE 1). However, these studies provided little direct functional evidence that cytoplasmic nucleoporin pathology is linked to nucleocytoplasmic transport deficiencies<sup>10,91–95</sup>. Moreover, in a later study, quantification of RANGAP1 pathology in post-mortem human tissue identified no difference in the prevalence of abnormalities between controls and individuals with *C9orf72* ALS<sup>91</sup>, highlighting the necessity of accompanying end-stage pathology studies with robust quantification rather than just crude visual observations when performing histology to identify novel disease pathologies. Nonetheless, histological evidence of protein pathology does not necessarily indicate a functional defect, so the presence or absence of pathology that involves a single protein involved in nucleocytoplasmic transport cannot be used in isolation to draw conclusions about nucleocytoplasmic transport function and its contribution to disease.

Subsequent studies in N2A cells, SH-SY5Y cells and mouse primary neurons that overexpressed wild-type or mutant TDP43 or PFN1 have revealed cytoplasmic mislocalization of nucleoporins and NPC-associated proteins<sup>4,8,96</sup> (TABLE 1). Intriguingly, overexpression of wild-type TDP43, ALS-associated mutant TDP43 or the carboxy-terminal fragment of TDP43 elicited differential nucleoporin and NPC protein pathology in N2A cells and primary mouse cortical neurons<sup>4</sup>, suggesting that alterations in the NPC and nucleocytoplasmic transport are TDP43 variant-specific. In addition, in a study of FUS-associated ALS iPSNs, the nuclear rim staining patterns of POM121 and NUP62 were altered<sup>11</sup>. The decreased nuclear rim immunoreactivity could plausibly be concomitant with cytoplasmic mislocalization of NUP62, although no direct evidence of this was provided<sup>11</sup>.

Each of these pathology studies evaluated only a small number of nucleoporins and NPC-associated proteins and they fall short of linking cytoplasmic accumulations to defects in the NPC and functional changes in nucleocytoplasmic transport. For example, this cytoplasmic pathology could simply reflect dysregulation of cytoplasmic pools of nucleoporins that

has little impact on the composition and function of the NPC. For this reason, none of these studies provides conclusive evidence that cytoplasmic accumulation of nucleoporins and nucleocytoplasmic transport proteins forms the mechanistic basis of dysfunctional nucleocytoplasmic transport or alters expression of nucleoporins within the NPC itself in ALS.

By contrast, injury to the neuronal NPC itself has been demonstrated in a study of a large number of iPSCs that expressed endogenous levels of the *C9orf72* HRE<sup>5</sup>; this injury was characterized by reduced levels of eight specific nucleoporins within the nucleoplasm and NPCs without a change in overall NPC number or distribution<sup>5</sup>. Importantly, a nearly identical NPC injury has also been observed in iPSCs derived from patients with sporadic ALS<sup>97</sup>, an observation that is consistent with the notion that familial and sporadic ALS are often clinically and pathologically indistinguishable<sup>67</sup>. Both of these studies involved the use of super-resolution structured illumination microscopy to accurately and reproducibly resolve individual NPC spots<sup>98</sup> and to examine millions of nuclei from a large number of different patient cell lines. Collectively, these two studies illustrate that NPC injury is initiated by reduction of the transmembrane nucleoporin POM121 from the neuronal NPC, which affects overall NPC composition and nucleocytoplasmic transport function, leading to downstream alterations in TDP43 function and localization and reductions in overall neuronal survival<sup>5,97</sup>.

Most studies of NPC and nucleocytoplasmic transport dysfunction in *C9orf72* ALS have centred on the toxicity of DPR proteins rather than repeat RNA<sup>88</sup>, possibly because early studies in *Drosophila* indicated that pathological repeat RNA is not toxic<sup>99</sup>. However, *Drosophila* lacks the gene that encodes POM121 (REFS<sup>1,100,101</sup>) so overt toxicity might not have been observed in *Drosophila* models that expressed only repeat RNA because the POM121 protein is critical for the initiation of NPC injury in human neurons. Consistent with this hypothesis, a study conducted in human iPSCs concluded that pathological repeat RNA is sufficient to induce NPC injury through reduction of POM121 in human iPSCs<sup>5</sup>. Taken together, studies in *C9orf72* ALS model systems suggest that repeat RNA and DPR proteins lead to impairment of nucleocytoplasmic transport via independent mechanisms — repeat RNA initiates an NPC injury cascade, whereas DPR proteins impair nucleocytoplasmic transport, possibly via pathological interactions with NTRs. However, studies are needed to understand the different cellular and molecular events that trigger reductions in POM121 in sporadic ALS that are dependent on *C9orf72* repeat RNA in *C9orf72* ALS. Moreover, whether *C9orf72*-mediated deficits in the NPC and in nucleocytoplasmic transport that were initially identified in spinal neurons and post-mortem motor cortex tissue<sup>5,10</sup> are also present in neurons that are involved in *C9orf72* FTD (for example, frontal cortex neurons) remains unclear.

Although the nature of defects in the NPC in ALS have been characterized, the mechanisms that give rise to these alterations are less well studied. Two biological pathways have been linked to NPC injury and the cytoplasmic accumulation of nucleoporins and NPC-associated proteins: degradation mediated by CHMP7 and the endosomal sorting complex required for transport (ESCRT) III complex<sup>97,102</sup>, and stress granule assembly<sup>90</sup>. The ESCRT-III-related protein CHMP7, which recruits the ESCRT-III complex and VPS4 to the nuclear envelope,

has a role in NPC turnover in yeast and non-neuronal mammalian cells<sup>103–106</sup>. Multimodal imaging of iPSNs from patients with familial or sporadic ALS has demonstrated that nuclear accumulation of CHMP7 is sufficient to initiate NPC injury<sup>97,102</sup> and could, therefore, be the fundamental disease-initiating pathway in ALS. The studies in iPSNs from patients with sporadic ALS demonstrated that the characteristic loss of nuclear TDP43 function and localization clearly occurs downstream of NPC injury<sup>97</sup>, suggesting that TDP43 dysfunction and mislocalization is a later biological event in ALS pathophysiology. The mechanisms that underlie pathological nuclear accumulation of CHMP7 in ALS remain unknown, but these studies highlight that the ESCRT-III pathway is a potent mediator of early pathogenic events in ALS; the pathway could have similar importance in related neurodegenerative disorders<sup>97,102</sup>.

Given that cytoplasmic accumulations of nucleoporins and NPC-associated proteins are prevalent in multiple models of ALS and that these accumulations seem to be independent of NPC injury itself, distinct mechanisms are likely to regulate cytoplasmic nucleoporin pathologies. Consistent with previous work that suggested that nuclear protein export can be abrogated by oxidative stress<sup>107</sup>, a study of multiple immortalized cell lines has shown that many nucleoporins and nucleocytoplasmic transport proteins can be sequestered in stress granules<sup>90</sup>. This study also showed that stress granule assembly can affect nucleocytoplasmic transport function<sup>90</sup> but it remains unclear whether this effect is the direct result of nucleoporin and nucleocytoplasmic transport protein sequestration in stress granules and whether this phenomenon is more broadly applicable to post-mitotic human neurons and, therefore, human disease.

Studies in iPSNs and post-mortem tissue from patients suggest that only a subset of nucleoporins are reproducibly reduced from neuronal NPCs in ALS<sup>5,97</sup>. However, these nucleoporins span multiple subcomplexes of the NPC and their functions include maintenance of NPC structure and organization, facilitation of nucleocytoplasmic transport, and regulation of genome organization and gene expression<sup>1–3,21</sup>, so reduced expression of these specific nucleoporins in the NPC is likely to directly and/or indirectly affect several cellular processes. For example, NUP50 has roles in protein import and transcriptional regulation<sup>54</sup>, whereas TPR is involved in mRNA export<sup>43</sup>. Future research should delineate the precise cellular defects induced by loss of specific nucleoporins in human neurons and determine how these disruptions contribute to disease pathogenesis. Moreover, collective nucleocytoplasmic transport impairments downstream of NPC injury could disrupt the import and replenishment of nucleoporins and NPC-associated proteins, leading to end-stage cytoplasmic accumulations in a process that compounds the initial injury to the NPC (FIG. 3).

## Nucleocytoplasmic transport in AD and FTD

AD and FTD — the two most common forms of dementia — are characterized by cognitive decline and memory loss that result from the progressive degeneration of neurons in the hippocampus and, in FTD, the frontal cortex. Mutations in the genes that encode amyloid precursor protein (APP) and presenilin (PSEN) are associated with AD<sup>108,109</sup> and mutations in *C9orf72* and the genes that encode tau and progranulin are linked to FTD<sup>71,72,110–112</sup>. The



presence of amyloid- $\beta$  plaques is the hallmark pathology of AD<sup>113–116</sup>, but cytoplasmic accumulations of TDP43 and tau are present in both AD and FTD<sup>113,117–121</sup>. The relationship between TDP43 pathology and alterations in the NPC and nucleocytoplasmic transport is discussed above; in this section, we focus on tau-mediated abnormalities in the NPC and nuclear lamina and in nucleocytoplasmic transport.

Although tau inclusions — known as neurofibrillary tangles — within neuronal cell bodies are a common pathological feature of AD and FTD, the mechanisms that lead to this pathology and the cellular consequences are poorly understood. Neurofibrillary tangles occur near the nuclear envelope<sup>122</sup>, raising the possibility that they interfere with NPC function and/or NPC and nuclear lamina organization. Indeed, one study found that NUP62 and NUP98, but not NUP54 or POM121, were present in perinuclear tau aggregates in post-mortem human brain tissue and in mouse models of FTD-tau<sup>6</sup>. In addition, NUP98 can promote the aggregation of tau in vitro<sup>6</sup> and seems to aggregate in NPCs and the nuclear envelope in AD and FTD<sup>6,123</sup>. However, the relationship between these phenomena and defects in nucleocytoplasmic transport in cellular models of FTD-tau remain unclear. Intriguingly, in a primary neuron model of FTD-tau, knockdown of NUP98 restored the localization of RAN GTPase<sup>6</sup>. These findings suggest that sequestration of NUP98 within tau aggregates does not lead to loss of the function of NUP98 in nucleocytoplasmic transport; instead, NUP98-mediated aggregation of tau might affect nucleocytoplasmic transport via currently unknown mechanisms. Therefore, additional work is needed to determine whether cytoplasmic or nuclear pools of NUP98 promote tau aggregation, to understand the contribution of altered NPC permeability and NTR function to disruption of nucleocytoplasmic transport, and to identify whether local or global changes occur in NPC accessibility and function. Moreover, work is needed to understand whether tau-associated alterations in specific nucleoporins translate into a reduction of these proteins in the NPC, as observed in *C9orf72* ALS–FTD<sup>5</sup>, or local aggregation in the vicinity of a subset of NPCs, perhaps owing to altered structural integrity of the nucleus as a result of, for example, abnormal nuclear lamina pathology.

Several studies of post-mortem human brain tissue, iPSCs and *Drosophila* have demonstrated that nuclear lamina morphology is abnormal in AD and FTD<sup>6,123–125</sup>. The nuclear lamina interacts with several nuclear envelope proteins, including lamina-associated polypeptide (Lap2) and lamin B receptor and is critical for maintenance of chromatin organization and positioning, thereby facilitating transcription and export of messenger ribonucleoprotein (mRNP) complexes through NPCs<sup>126</sup>. In iPSCs, nuclear lamina invaginations that are similar to those observed in AD and FTD occur as a result of microtubule depolymerization<sup>123</sup>, which disrupts the interactions of the linker of the nucleus and cytoskeleton (LINC) complex. This complex normally maintains nuclear integrity and positioning by anchoring the nuclear membranes to cytoplasmic micro tubules, actin and intermediate filaments<sup>127</sup>. The presence of mutant tau within these invaginations<sup>123</sup> raises the possibility that tau mislocalization affects microtubule dynamics and contributes to disruption of nuclear membrane morphology. Moreover, in post-mortem human brain tissue, these nuclear lamina invaginations contain NPCs and LAP2 (REF.<sup>125</sup>), suggesting that altered nuclear morphology can affect NPC and lamina functions. Indeed, toxic accumulation of mRNA has been observed in nuclear lamina

invaginations<sup>124</sup>, and heterochromatin loss<sup>128</sup> occurs in *Drosophila* models of FTD-tau. In *Drosophila*, pharmacological or genetic reduction of mRNA export mitigates tau toxicity<sup>124</sup>.

Taken together, these recent findings suggest that mutations in tau result in its mislocalization to the perinuclear space where NUP98 facilitates its aggregation, leading to impaired microtubule dynamics that deform the nuclear lamina and initiate local disruption of chromatin organization and mRNA export within invaginations. However, additional work is needed to fully define the sequence of pathological events in AD and FTD. Furthermore, future studies are necessary to directly link altered nuclear lamina morphology with impaired nuclear function in AD and FTD.

## Nucleocytoplasmic transport in HD

HD is an inherited, autosomal dominant neurodegenerative disorder that is characterized by degeneration of medium spiny neurons within the striatum. Clinically, HD manifests as choreiform movements and dementia. The cause is a CAG trinucleotide repeat expansion in the first exon of the *HTT* gene, which encodes the huntingtin protein. Expansions of >40 repeats are fully penetrant, and longer expansions are linked to earlier disease onset and greater severity<sup>129,130</sup>. The repeat expansion leads to production of huntingtin protein that contains poly-glutamine (polyQ) tracts and is consequently aggregate-prone. However, as with the *C9orf72* HRE, the *HTT*CAG repeat can lead to repeat-associated non-AUG (RAN) translation that produces poly-alanine (polyA), poly-serine (polyS), poly-leucine (polyL) and poly-cysteine (polyC) proteins that accumulate in the brain<sup>131</sup>. However, the molecular mechanisms through which these protein products contribute to neurodegeneration remain largely unknown.

Given that cytoplasmic protein aggregation is known to affect nucleocytoplasmic transport of protein and RNA<sup>132</sup>, early studies of nucleocytoplasmic transport dysfunction in models of HD have centred on characterization of NPC and nucleocytoplasmic transport pathology that results from accumulation of mutant huntingtin protein. Two studies showed that a subset of nucleoporins and nucleocytoplasmic transport proteins, including NUP62, NUP88, RANGAP1 and GLE1, co-accumulate with mutant huntingtin in mouse models of HD<sup>7,9</sup>. Furthermore, studies in mouse models of HD showed that the extent of RANGAP1 pathology and huntingtin aggregates are dependent on age and expression level of mutant huntingtin protein<sup>7,9</sup>. Studies of post-mortem human tissue revealed RANGAP1 and NUP62 alterations, but the pathology was distinct from that in mice<sup>7,9</sup>. In the mouse models, a few nucleoporins and nucleocytoplasmic transport proteins co-aggregated with mutant huntingtin protein, whereas in end-stage human tissue, mislocalization was more subtle, accumulations of proteins were small but more numerous, and expression of RANGAP1 and NUP62 even seemed to be increased<sup>7,9</sup>. These findings highlight the complexity of authentic human disease in comparison with defined genetic mouse models. Additional findings that are consistent with the idea that pathology is cell-type-specific and species-specific include abnormal nuclear membrane distribution of RANGAP1 in human neuronal precursor cells in HD<sup>7</sup>, and severe cytoplasmic mislocalization of RANGAP1 and NUP62 in HD iPSCs<sup>9</sup>. In a comparison of RANGAP1 and NUP62 pathology in post-mortem tissue from patients with juvenile and adult-onset forms of HD, pathology was more severe in

the juvenile form of the disease<sup>9</sup>, suggesting that a greater extent of this pathology is associated with more severe disease. However, as discussed above, a study of RANGAP1 pathology in post-mortem tissue from patients with *C9orf72* ALS<sup>91</sup> demonstrated that simple quantification of abnormal-looking cells is not sufficient for accurate quantification of nucleoporin and nucleocytoplasmic transport protein pathology, especially in scenarios where cell-type-specific labels are not employed. Nevertheless, the method of quantification used in this HD study might provide a better estimate of patient-to-patient and mouse-to-mouse variability than studies in ALS, AD, FTD and HD models, in which individual cells or nuclei are counted as biological replicates. For all imaging-based studies across neurodegenerative disease models, in the future it may be best to represent and analyse datasets as superplots<sup>133</sup> that depict the full spread of data points across all samples analysed. Another important consideration is that in any nucleoporin or nuclear membrane pathology study in mouse or human tissue, the entire 3D structure of the nucleus should be assessed where possible to avoid mischaracterization on the basis of single *z*-plane sections. The importance of this approach was demonstrated in *C9orf72* ALS: nucleoporin reduction and nuclear lamina pathology were more robustly and accurately characterized in studies in which the 3D structure was analysed than in studies in which single 2D *z*-plane sections were analysed<sup>5,134</sup>. This 3D characterization enabled the investigators to conclude that nucleoporin reduction occurs throughout NPCs within the entire nucleus with no change to nuclear lamina structure, at least that is detectable with light microscopy.

Studies of post-mortem tissue from patients with HD and of mouse models have revealed nuclear membrane abnormalities in addition to nucleoporin and nucleocytoplasmic transport protein pathology<sup>7</sup>. However, whether these abnormalities reflect ageing-associated nuclear membrane folding or pathological nuclear membrane invagination remains unclear. Age-dependent nuclear mRNA retention has been observed in mouse models of HD<sup>7</sup> and altered subcellular distribution of RAN GTPase and the S-tdTomato nucleocytoplasmic transport reporter<sup>9</sup> has been observed in iPSN models of HD. Together, these observations indicate global defects in nucleocytoplasmic transport. While NUP62, NUP88, RANGAP1 and GLE1 have defined roles in nucleocytoplasmic transport<sup>40,135–140</sup>, neither study provided any evidence that pathological alterations and/or accumulations of these proteins in HD directly affect nuclear mRNA export or protein import and export.

Quantitative proteomics analysis of non-neuronal cell lines that overexpress proteins involved in neurodegenerative disease suggests that wild-type huntingtin protein associates with NTRs, such as importins  $\beta$ 1, 4, 7 and 9, whereas mutant huntingtin protein associates with RANGAP1 and RAE1 (REF.<sup>141</sup>). However, these studies did not address the functional implications of these associations. Whether sequestration of these nucleoporins and nucleocytoplasmic transport proteins reflects their decreased expression within or association with the NPC itself or reflects accumulation from non-NPC associated pools remains unclear. Therefore, future studies are needed to unravel the functional contribution of nucleoporin pathology to the pathophysiology of HD.

## Diseases caused by NPC mutations

Genetic mutations in some nucleoporins and nucleocytoplasmic transport proteins cause cell-type-specific neurological diseases; for example: mutations in NUP62 are implicated in infantile bilateral striatal necrosis, which affects the caudate nucleus and putamen; mutations in NUP214 can cause progressive encephalopathy and cortical atrophy<sup>20</sup>; and mutations in GLE1 are linked to the fetal motor neuron disease human lethal congenital contracture syndrome 1 (REF.<sup>18</sup>). Although not addressed in this Review, mutations in some nucleoporins have been linked to other non-neurological, cell-type-specific diseases<sup>142,143</sup> (TABLE 2).

Although mutations in these nucleoporins and NPC-associated proteins are known to cause system-specific neurological disease, little is known about the functional implications of the mutations. At the RNA level, these proteins are widely expressed in CNS and non-CNS tissues<sup>26</sup>. However, the composition of nucleoporins and NPC-associated proteins in different cells is not known, especially in the CNS, so variations in the expression and ratio of specific nucleoporins and NPC-associated proteins could contribute to cell-type-specific vulnerability to disease.

GLE1 is an NPC-associated protein with roles in nuclear mRNA export, initiation of translation and termination of translation<sup>135,144,145</sup>. Disease-associated mutations in GLE1 disrupt its oligomerization, thereby impairing nuclear mRNA export<sup>146</sup>. NUP62 and NUP214 are FG-repeat-containing nucleoporins that reside, respectively, within the central channel and the cytoplasmic ring and filaments (FIG. 1) to facilitate bidirectional transport. The functional consequences of NUP62 mutations are unknown. However, in fibroblasts, mutations in NUP214 reduce overall NUP214 and NUP88 protein levels without affecting the number and density of NPCs. In addition, in fibroblasts that express mutant NUP214, nuclear protein import and mRNA export are impaired and a high proportion of NPCs have so-called plugs in the central channel. What these plugs are is unknown — one hypothesis is that they are mRNPs that have become trapped during transport through the pore or are transported more slowly, enabling their visualization in NUP214-mutant fibroblasts. These findings suggest that NUP214 mutations affect the passage of large cargo through the NPC<sup>19</sup>, but future experiments are necessary to understand the precise disruptions to passive and active nucleocytoplasmic transport that result from these mutations. Furthermore, the mechanism by which these functional alterations lead to cell-type-specific pathology remains unclear. Cell-specific expression of these nucleoporins and/or their cellular functions could render specific cell types more susceptible than others to the effects of these rare genetic mutations.

The fact that nucleoporin mutations cause cell-type-specific neurological disease suggests that defects in the NPC and nucleocytoplasmic transport are sufficient to initiate disease. However, few studies have been carried out to test this hypothesis, primarily owing to a lack of mechanistic studies in the context of mutant nucleoporins. In order to determine whether mutations in nucleoporins or NTRs are sufficient to initiate disease cascades in a cell-type-specific manner, studies are needed to comprehensively assess the effects of

nucleoporin mutations on NPC composition, nucleo cytoplasmic transport, downstream cellular functions and cellular viability.

## Laminopathy in neurodegenerative disease

The nuclear lamina is composed of lamin A/C and lamin B proteins, and provides structural integrity to the nucleus, organizes heterochromatin in the vicinity of the NPC, and is involved in mechanotransduction via interactions with the LINC complex<sup>147</sup>. Laminopathy has been described in diseases that affect the brain and/or muscle cells. For example, >400 mutations have been identified in *LMNA*, which encodes lamin A, and these mutations are implicated in a wide range of cellular disorders, including Hutchinson–Guilford progeria syndrome, muscular dystrophy, and Charcot–Marie–Tooth disease<sup>148–150</sup>. Lamin B1 duplications are associated with adult-onset autosomal dominant leukodystrophy<sup>151</sup>. Collectively, mutations or duplications in lamin genes alter the integrity of the nuclear lamina, resulting in nuclear membrane invaginations and premature cell ageing<sup>147,152,153</sup>. However, how nuclear lamina abnormalities contribute to neurodegeneration in these diseases and more broadly is unclear<sup>7,8,123,134</sup>. Studies that include age-related controls are needed to address whether observed disruptions of the nuclear lamina are related to physiological ageing or pathological processes. For example, one study of iPSNs and *C9orf72* ALS–FTD suggested that nuclear lamina invaginations are an age-related phenomenon and not a pathological consequence of the *C9orf72* HRE<sup>134</sup>. Other aspects that need to be investigated are the mechanisms that lead to nuclear lamina folds and/or invaginations and, perhaps most importantly, how these folds and invaginations disrupt NPC composition, nucleocytoplasmic transport, chromatin accessibility and gene expression.

## Age-related changes in NPCs

Ageing is a risk factor for neurodegenerative diseases, and age-related disruptions to the NPC and nucleocytoplasmic transport are thought to be exacerbated in neurodegenerative disease<sup>4,6,7,9,10,12,13</sup>. Few studies have examined age-related declines in NPC integrity and nucleocytoplasmic transport function, but non-dividing human neurons are likely to accumulate age-related damage to NPCs given that they do not undergo frequent rounds of nucleoporin turnover during cell division, as do mitotic cells. Indeed, multiple studies have suggested that, although the overall number of NPCs remains consistent in ageing rat brains, NPC composition changes with age<sup>154–156</sup>. Specifically, quantitative proteomics analysis has shown that scaffold nucleoporins are extremely long-lived in ageing rat brains, whereas a subset of primarily FG-repeat-containing nucleoporins are exchanged more frequently<sup>156</sup>. Consistent with this molecular analysis, FRAP analyses in rat kidney cells have revealed that different nucleoporins have different residence times within the NPC, ranging from seconds to days<sup>157</sup>. Use of electron microscopy has revealed that the overall density of NPCs declines in the ageing rat dentate gyrus but remains fairly stable in hippocampal CA1 neurons<sup>158,159</sup>, raising the possibility that changes in NPC composition and dynamics with age are cell-type-specific. On the basis of these findings, the slow accumulation of nucleoporin pathology and nucleoporin variants might be expected to eventually lead to dysfunctional nucleocytoplasmic transport and ultimately increase cellular stress in neurodegeneration.

Functionally, NPCs are known to become more ‘leaky’ with age<sup>154</sup>. However, whether this change results from compositional changes within the NPC or the loss of permeability barrier function and/or integrity remains unclear. Studies in fibroblasts suggest that expression of proteins involved in nucleocytoplasmic transport decreases during ageing<sup>160,161</sup> and that nuclear protein import declines<sup>161</sup>. However, whether these alterations directly affect NPC function or whether age-related declines in nucleocytoplasmic transport result from multiple cellular defects — as is likely to be the case for neurodegenerative disease — is unknown.

Nuclear lamina integrity can also deteriorate with age and in age-related disease<sup>162</sup> and could affect NPC functions, such as nucleocytoplasmic transport. Age-associated nuclear envelope invaginations can result in dysfunctional nucleocytoplasmic transport via accumulation of NPCs<sup>124,125</sup>, but a weakened lamina network also often causes nuclear envelope ruptures, which reduce nuclear–cytoplasmic compartmentalization<sup>162,163</sup>. Furthermore, nuclear envelope integrity is partly maintained by contact with the cytoskeleton via the LINC complex<sup>147</sup> and loss of LINC complexes can facilitate nuclear envelope weakening and lead to ruptures<sup>164</sup>. Together, these observations raise the possibility that LINC complex and nuclear envelope disruption contribute to age-related neurodegenerative declines in nucleocytoplasmic transport. Indeed, in primary mouse neurons that overexpressed the *C9orf72* HRE or mutant PFN1, pharmacologically induced actin depolymerization altered the localization of RANGAP1, FG-repeat-containing nucleoporins and RAN GTPase in primary mouse motor neurons, whereas promotion of actin polymerization partially rescued nucleocytoplasmic transport defects<sup>8</sup>. Future work is needed to determine the mechanism by which actin dynamics contribute to nucleocytoplasmic transport in human neurons, but these studies suggest that age-related declines in overall nuclear integrity contribute to neurodegenerative disease pathogenesis.

## Therapeutic approaches

Where genetic alterations in NPC or nucleocytoplasmic transport proteins contribute to defects in nucleocytoplasmic transport, elimination of the genetic abnormalities by reducing expression of mutant genes would be the most specific therapeutic approach. CRISPR technology enables specific targeting of genetic mutations<sup>165,166</sup>, and a scenario in which specific mutations in nucleoporins or other proteins that lead to NPC dysfunction are eliminated with CRISPR-based strategies can be envisioned. CRISPR technology has been used to remove pathological *C9orf72* repeat expansions in iPSCs, which led to reversal of several *C9orf72*-associated phenotypes<sup>167</sup>, highlighting the potential of this new technology. Currently, however, the most common approach to therapeutic targeting of gene mutations is the use of antisense oligonucleotides (ASOs) to eliminate production of mutant protein via RNase H degradation of RNA transcripts<sup>168,169</sup>. Results from initial preclinical studies in iPSCs with *C9orf72* mutations and in mouse models<sup>170,171</sup> suggest that targeting the *C9orf72* HRE can mitigate molecular hallmarks of disease, including the formation of repeat RNA foci and production of DPR proteins. Subsequent studies in iPSCs with *C9orf72* mutations have shown that ASOs that selectively target *C9orf72* repeat RNA can alleviate NPC injury and mislocalization of RAN GTPase<sup>5,10</sup>, highlighting the contribution of NPC injury and nucleocytoplasmic transport dysfunction to disease pathogenesis. An international

phase I clinical trial of intrathecal administration of an ASO that specifically targets the G<sub>4</sub>C<sub>2</sub> sense repeat strand of the *C9orf72* mutation (BIIB078) was recently completed<sup>172</sup>. Therapies that modulate the antisense C<sub>4</sub>G<sub>2</sub> repeat strand or the C9ORF72 protein have not yet been explored.

In the absence of a known genetic mutation — as in sporadic ALS — therapies that directly target NPC injury and nucleocytoplasmic dysfunction could prove beneficial in neurodegenerative diseases. Owing to the fact that the involvement of nucleocytoplasmic transport is an emerging concept in our understanding of neurodegenerative disease pathophysiology, few therapeutic studies have been conducted to date. However, in a study published in 2021, use of iPNSs from patients with sporadic or *C9orf72* ALS demonstrated that the use of ASOs to reduce expression of an upstream initiator of NPC injury in ALS — CHMP7 — restored NPC composition and function, mitigated downstream deficits in TDP43 function and localization, and improved neuronal survival without overt toxicity<sup>97</sup>. Functional nucleocytoplasmic transport could also be targeted downstream of NPC injury; for example, the compound KPT-350 inhibits exportin-1 function, thereby preventing nuclear protein export, and variations of this compound have been used to rescue nucleocytoplasmic transport deficits in multiple models of ALS and HD<sup>4,8–10,90</sup>. Primarily as a result of these preclinical studies, a phase I clinical trial of oral KPT-350 (also known as BIIB100) is being carried out in patients with ALS<sup>173</sup>. Theoretically, small molecules that increase RAN GTPase activity could also increase nuclear transport capacity in neurodegeneration. Together, these early preclinical studies suggest that direct targeting of NPC injury and nucleocytoplasmic transport dysfunction in the absence of known genetic mutations could be a viable therapeutic strategy for neurodegeneration.

## Conclusions

Considerable progress has been made in uncovering pathological changes in the NPC and nucleocytoplasmic transport in neurodegenerative disease but much work is still needed to understand how these alterations affect cellular function and vulnerability and to determine whether NPC and nucleocytoplasmic transport pathology is sufficient to initiate neurodegeneration and/or propagate the cellular injury. Despite the fact that the structure and organization of the NPC is conserved from yeast to flies to mice to humans, its overall composition is highly variable. For example, the transmembrane nucleoporin POM121 is not present in yeast or flies, and rodent POM121 has only ~60% protein sequence homology with human POM121, possibly undermining the interpretation of non-human models in relation to authentic disease. Moreover, expression of POM121 is highly variable across different human cell types<sup>26,27</sup>. In addition to the fact that genetic mutations in specific nucleoporins can cause cell-type-specific diseases<sup>142,143</sup> (TABLE 2), this variability in nucleoporin expression raises the fascinating possibility that NPC heterogeneity contributes to the cell-type specificity of neurodegenerative disease. To address this possibility, studies are needed to understand the composition and stoichiometry of nucleoporins within cell-type-specific NPCs across the CNS.

The mechanisms by which nucleoporin and NTR disruptions contribute to defects in nucleocytoplasmic transport and/or gene expression in neurodegenerative disease remain

largely unknown. One interesting insight that has been gained is that a *POM121* gene duplication results in production of POM121 and soluble POM121 proteins, which independently mediate nucleocytoplasmic transport and transcription, respectively<sup>174</sup>. This study raises the intriguing possibility of a two-hit model, whereby alterations in a specific nucleoporin change NPC composition and functionality and could also lead to accumulation of the nucleoporin in the cytoplasm, ultimately leading to a loss of normal function and a gain of toxic cytoplasmic function, as has been proposed for TDP43 (REF.<sup>175</sup>).

This insight highlights the fact that, in order to understand how NPC injury and nucleocytoplasmic transport dysfunction contribute to disease pathogenesis, nucleoporin and NPC-associated protein pathology in the cytoplasm, the nucleus and the NPC itself must be comprehensively defined. Furthermore, emerging evidence shows that nucleoporins have cytoplasmic functions<sup>176</sup> and NTRs have non-transport-related functions<sup>14–16</sup>, making it critical to understand whether the cytoplasmic, NPC or nucleoplasmic functions of nucleoporins are disrupted in and contribute to disease pathogenesis. Nonetheless, existing evidence demonstrates that alterations to the NPC, nucleoporins and nucleocytoplasmic transport are early and prominent pathogenic events in ALS, AD, FTD and HD, and highlights the potential for therapeutic targeting of these alterations for the treatment of neurodegenerative disease.

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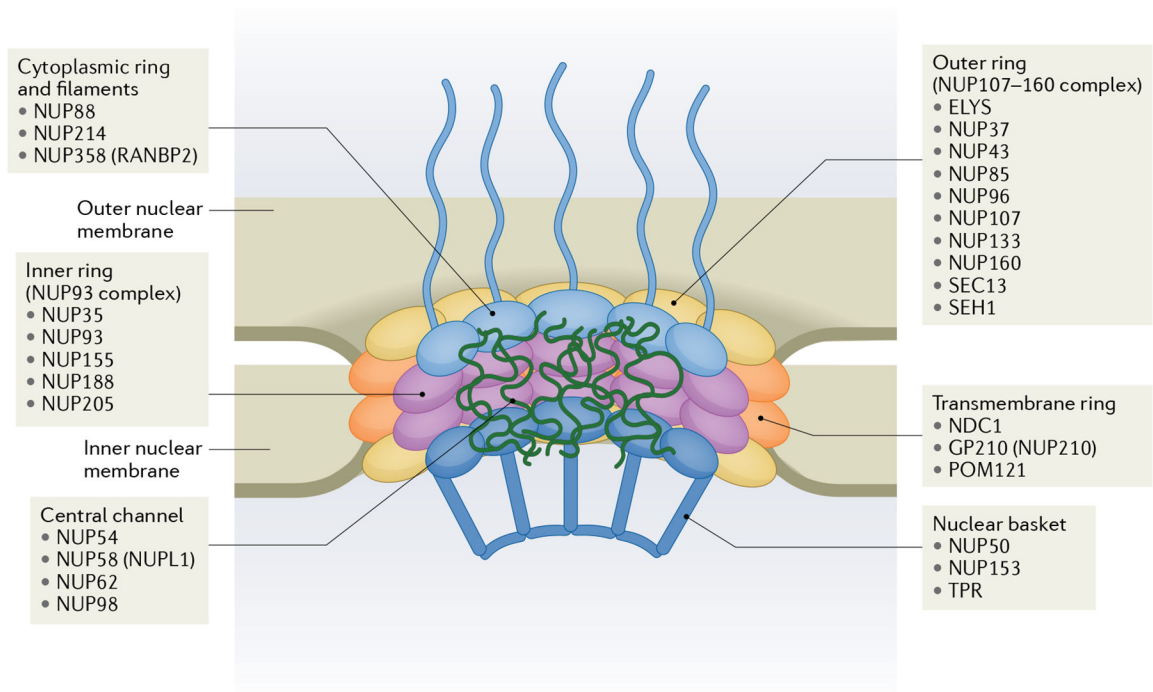
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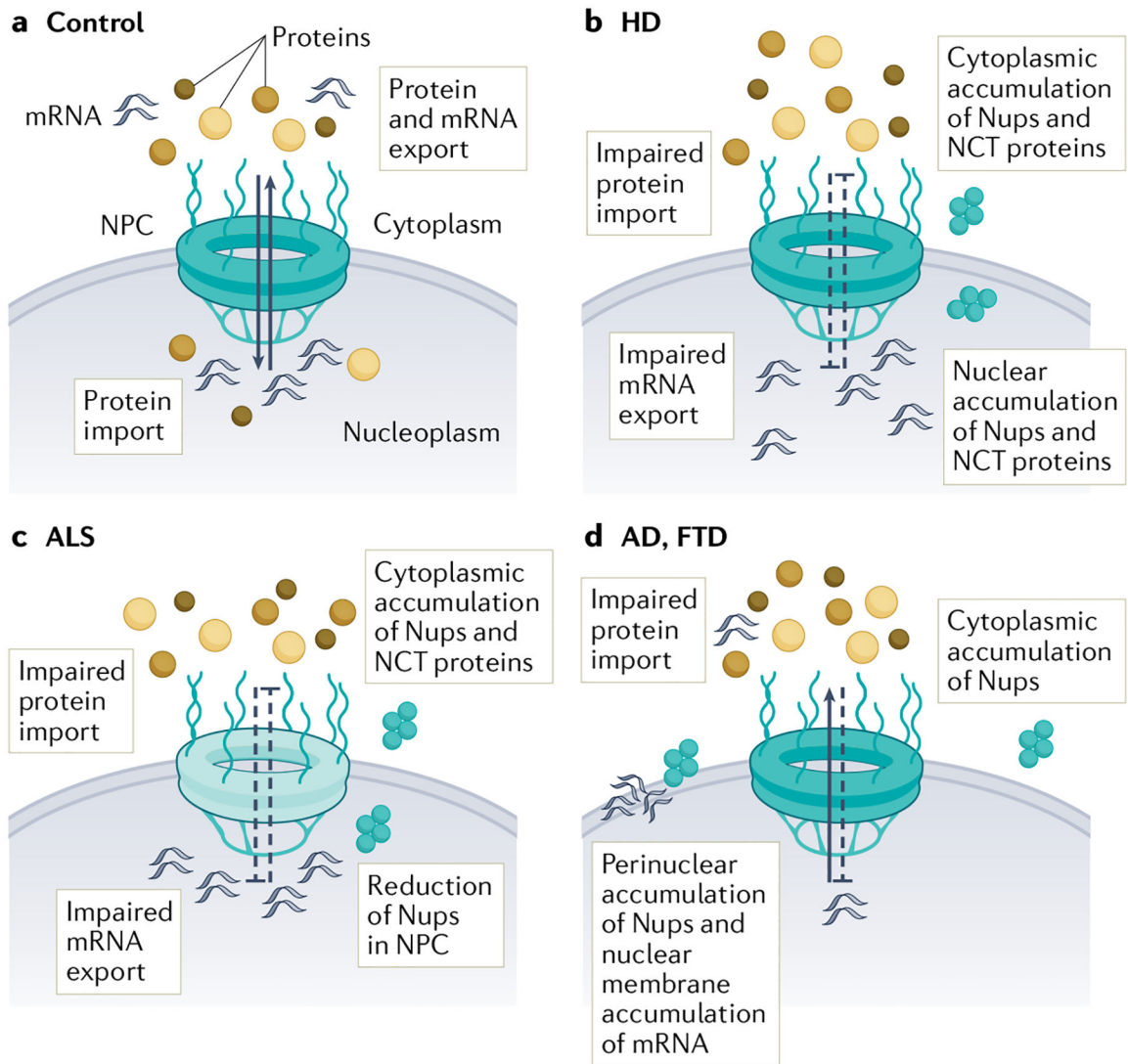
**Key points**

- The nuclear pore complex (NPC), which is made up of multiple nucleoporin proteins, mediates nucleocytoplasmic transport, genome organization and gene expression.
- Accumulating evidence suggests that defects in the NPC and nucleocytoplasmic transport contribute to, or possibly initiate, neurodegenerative diseases such as amyotrophic lateral sclerosis, dementia and Huntington disease.
- Cell-type-specific NPC composition might underlie differential cellular vulnerability in neurological diseases.
- Specific nucleoporin mutations can cause a wide range of neurological disorders, including a Huntington disease-like motor neuron disease.
- Therapeutic strategies with antisense oligonucleotides and small molecules to repair NPC defects or restore altered nucleocytoplasmic transport are in development.



**Fig. 1 |. Overview of nuclear pore complex structure and subcomplexes.**

The main subcomplexes of the nuclear pore complex are the cytoplasmic ring and filaments, the outer ring, the inner ring, the transmembrane ring, the central channel and the nuclear basket. Each subcomplex consists of multiple nucleoporins, listed as bullet points for each subcomplex. Adapted from REF.<sup>188</sup>, Springer Nature Ltd.



**Fig. 2 | Alterations in the nuclear pore complex and nucleocytoplasmic transport in neurodegenerative diseases.**

**a** | Under physiological conditions, mRNA and protein are transported out of and into the nucleus via the nuclear pore complex (NPC). **b** | In Huntington disease (HD), import and export through the NPC is impaired, leading to impaired protein import and mRNA export. In addition, a subset of nucleoporins (Nups) and nuclear pore-associated proteins with roles in nucleocytoplasmic transport (NCT) are present in nuclear and cytoplasmic aggregates (TABLE 1). **c** | In amyotrophic lateral sclerosis (ALS), specific Nups (TABLE 1) are reduced from neuronal NPCs, in a manner dependent on CHMP7 and the ESCRT-III complex, with no change in overall NPC number or structure. Consequently, import and export through the NPC is impaired. Moreover, a handful of Nups and nucleocytoplasmic transport proteins (TABLE 1) accumulate in the cytoplasm via unknown mechanisms. **d** | In Alzheimer disease (AD) and frontotemporal dementia (FTD), cytoplasmic and perinuclear accumulation of a small number of Nups (TABLE 1) occurs. In addition, accumulation of mRNA within nuclear membrane invaginations and impairments in protein import have

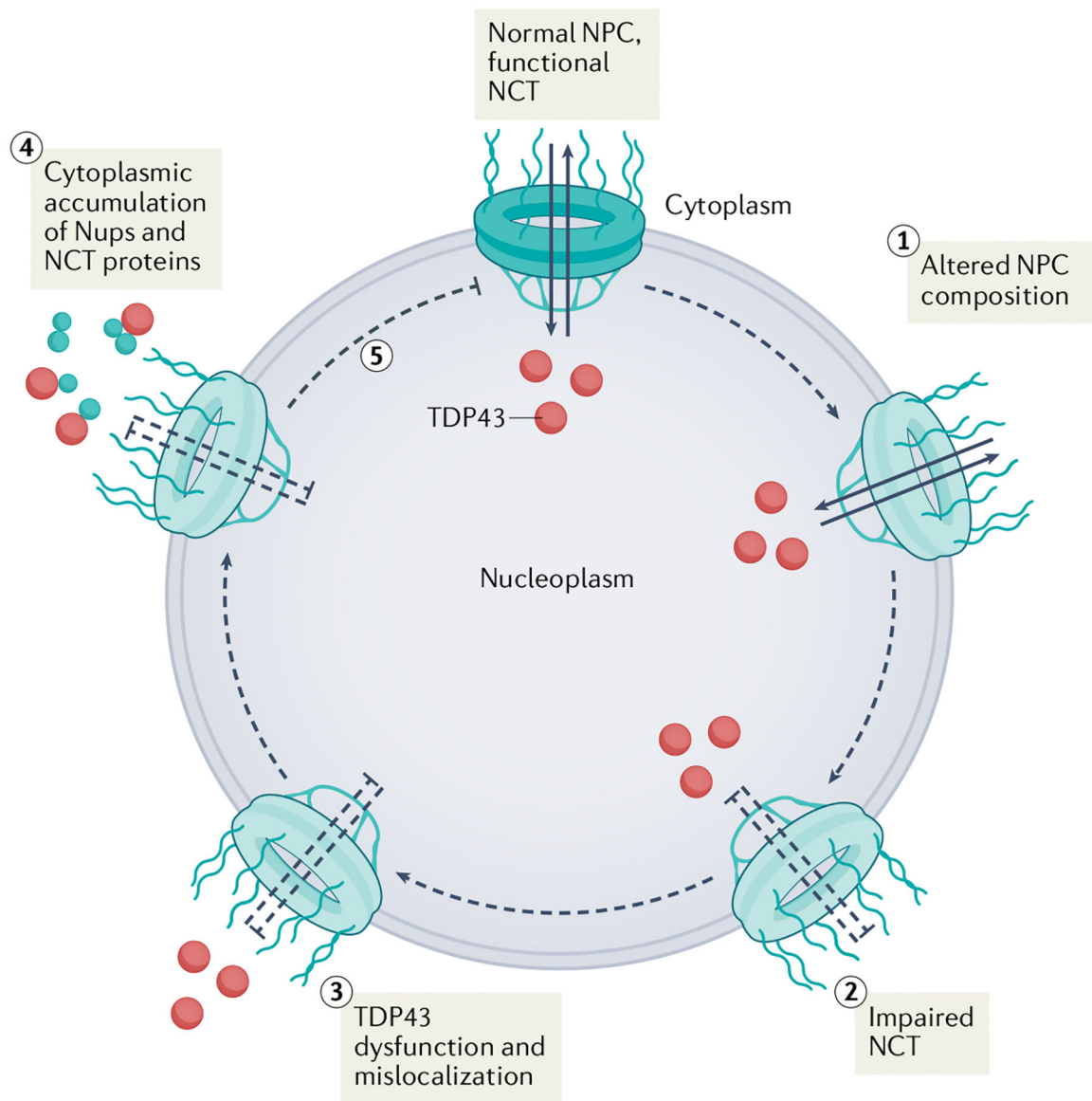
been described, although the biological implications are unknown and the mechanistic link between all these pathologies remains unclear.

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**Fig. 3 |. Pathological progression of changes to the nuclear pore complex and nucleocytoplasmic transport in amyotrophic lateral sclerosis.**

Aberrant nuclear retention of the ESCRT-III-associated protein CHMP7 initiates nuclear pore injury characterized by the reduction in specific nucleoporins (Nups) from the nuclear pore complex (NPC), leading to an altered composition of the NPC (1). Disruption of the NPC in this way alters functional nucleocytoplasmic transport (NCT) (2), which ultimately leads to loss of TAR DNA-binding protein 43 (TDP43) function within the nucleus and translocation of TDP43 from the nucleus to the cytoplasm (3). Impaired NCT might result in cytoplasmic accumulation of TDP43, Nups and nuclear transport receptors in end-stage disease (4). Impaired nuclear import might then inhibit restoration of the NPC composition and integrity (5), thereby exacerbating the process.

Summary of nucleoporin and nuclear transport receptor alterations in neurodegenerative disease models

Table 1 |

Proteins	Model system	Alterations	Biological impact	Refs
<i>Amyotrophic lateral sclerosis</i>				
NUP62	FUS-ALS iPSN model	Altered nuclear rim staining pattern; possible cytoplasmic mislocalization	Unclear — might affect FUS phase separation	11
NUP98	N2A cells that overexpress TDP43 C-terminal fragment	Probable reduction in levels in the nucleus	Unknown	4
NUP107	Post-mortem motor cortex tissue from patients with <i>C9orf72</i> ALS	Cytoplasmic mislocalization	Unknown	10
NUP205	Fibroblasts that express mutant TDP43	Probable reduction in levels in the nucleus	Unknown	4
NUP205	Post-mortem frontal and motor cortex tissue from patients with <i>C9orf72</i> ALS, TDP43 ALS and sporadic ALS	Cytoplasmic mislocalization	Unknown	4,10
POM121	AAV GFP-(GR) <sub>200</sub> mice	Subtle cytoplasmic mislocalization and/or co-accumulation with (GR) <sub>200</sub> ; no obvious reduction in levels in the nucleus	Unclear in mice	95
POM121	Primary spinal neurons that overexpress PFN1 variants	Cytoplasmic mislocalization	Unknown	8
POM121	FUS-ALS iPSN model	Altered nuclear rim staining pattern	Unknown	11
RANGAP1	Primary spinal neurons that overexpress PFN1 variants; fibroblasts that express mutant <i>C9orf72</i> ; post-mortem motor cortex tissue from patients with <i>C9orf72</i> ALS	Cytoplasmic mislocalization	Unclear — might contribute to deficient nucleocytoplasmic transport	8,10
RANGAP1	Primary cortical neurons that overexpress TDP43 variants; <i>C9orf72</i> ALS iPSN model; post-mortem motor cortex tissue from patients with <i>C9orf72</i> ALS; AAV (G <sub>4</sub> C <sub>2</sub> ) <sub>140</sub> mice; AAV GFP-(PR) <sub>50</sub> mice	Altered nuclear rim staining pattern	Unclear — might contribute to deficient nucleocytoplasmic transport	4,10,92,94
POM121 and RANGAP1	AAV GFP-(GA) <sub>50</sub> mice	Intranuclear co-accumulation with (GA) <sub>50</sub> ; no obvious reduction in nuclear envelope staining	Unknown	93
NUP98, importin- $\alpha$ 5, KPN2	AAV GFP-(GR) <sub>200</sub> mice	Cytoplasmic mislocalization and/or co-aggregation with (GR) <sub>200</sub>	Unclear — might contribute to deficient nucleocytoplasmic transport	95
POM121, NUP133, NUP50, NUP153, TPR	iPSN model of sporadic ALS	Reduction in levels in the NPC	Altered cellular distribution of RAN GTPase; impaired nucleocytoplasmic transport; TDP43 dysfunction and mislocalization	97
POM121, NDC1, GP210, NUP133, NUP107, NUP50, TPR, NUP98	<i>C9orf72</i> ALS iPSN model; post-mortem motor cortex and spinal cord tissue from patients with <i>C9orf72</i> ALS	Reduction in levels in the NPC	Altered cellular distribution of RAN GTPase; impaired nucleocytoplasmic transport; TDP43 dysfunction and mislocalization	5,97

Proteins	Model system	Alterations	Biological impact	Refs
NUP50, NUP62, NUP93, NUP98, NUP107, NUP214, TPR, GLE1	Primary cortical neurons that overexpress TDP43 variants	Cytoplasmic mislocalization and/or co-aggregation with TDP43 variants	Unknown	4
NUP35, NUP43, NUP58, NUP62, NUP88, NUP93, NUP98, NUP107, NUP153, NUP155, NUP160, NUP205, NUP214, NUP358, TPR, Aladin, hCG1, POM121, GP210, XPO5, NXF1, GLE1	N2A cells that overexpress TDP43 C-terminal fragment	Cytoplasmic mislocalization and/or co-aggregation with TDP43 C-terminal fragment	Unknown	4
<b>Alzheimer disease and frontotemporal dementia</b>				
NUP62	Post-mortem human hippocampal tissue	Perinuclear accumulation	Unknown	6
NUP98	Tg4510 mice; post-mortem human hippocampal tissue; IPSNs that express mutant tau	Perinuclear accumulation, possibly within nuclear membrane invaginations	Contributes to altered RAN GTPase localization, which might affect nucleocytoplasmic transport; promotes tau aggregation	6,123
<b>Huntington disease</b>				
GLE1	R6/2 mice; HTT <sup>Q175</sup> mice	Intranuclear accumulation	Unknown — might reduce RNA export	7
NUP62	R6/2 mice; post-mortem cortical and striatal human tissue; iPSN model of HD	Intranuclear accumulation; possible increase in expression; cytoplasmic mislocalization	Unknown	9
NUP88	HTT <sup>Q175</sup> mice	Intranuclear accumulation	Unknown	9
RANGAP1	R6/2 mice; HTT <sup>Q175</sup> mice; post-mortem cortical and striatal human tissue; human neuronal progenitor cells; iPSN model of HD	Intranuclear accumulation; possible increase in expression; abnormal nuclear distribution; abnormal nuclear membrane distribution; cytoplasmic mislocalization	Unknown	7,9

AAV, adeno-associated virus; ALS, amyotrophic lateral sclerosis; FUS, fused in sarcoma; GA, glycine–alanine dipeptide repeat protein; GFP, green fluorescent protein; GP210, transmembrane nucleoporin; GR, glycine–arginine dipeptide repeat protein; HD, Huntington disease; Htt, huntingtin; iPSN, induced pluripotent stem cell-derived neuron; KPNA2, karyopherin- $\alpha$  2; N2A, neuro2A; NDC1, transmembrane nucleoporin; NPC, nuclear pore complex; NXF1, nuclear RNA export factor 1; PFN1, profilin 1; POM121, transmembrane nucleoporin; RANGAP1, RAN GTPase-activating protein 1; TDP43, TAR DNA-binding protein 43; TPR, translocated promoter region nuclear basket nucleoporin; XPO5, exportin 5.

## Summary of selected cell-type-specific or organ-specific diseases resulting from mutations in nucleoporins or NPC-associated proteins

Table 2 |

Disease	Mutated protein	Cell type	Phenotype	Refs
Allgrove (AAA) syndrome	Aladin	CNS motor neurons; multiple peripheral cell types	Motor neuron disease, achalasia, adrenal deficiency, alacrima	177–180
Human lethal congenital contracture syndrome 1	GLE1	CNS motor neurons	Infantile motor neuron disease, weakness, death	18
Lethal arthrogryposis with anterior horn cell disease				
Striatal nigral degeneration	NUP62	Striatal neurons	Huntington-like disease	17
Fetal akinesia	NUP88	Muscle	Muscle atrophy	181
Steroid-resistant nephrotic syndrome	NUP93, NUP205, XPO5, NUP107	Kidney	Renal pathology, diffuse mesangial sclerosis, loss of renal function	182
Intellectual disability and general developmental delay	NUP107	CNS and kidney	Simplified cortical gyri, undeveloped frontal lobes, glomerulosclerosis	183
Atrial fibrillation	NUP155	Heart	Childhood death	184
Acute febrile encephalopathy	NUP214	Purkinje cells, cortex	Febrile-induced ataxia, progressive cortical neurodegeneration	19,20
Encephalitis and autoimmune myositis	NUP358	CNS and PNS	Encephalopathy, myopathy often after viral infection	185
Limb-girdle muscular dystrophy 1F	TNPO3	Muscle	Selective muscle weakness	186
Intellectual disability	TPR	Unknown	White matter changes with delayed myelination, gliosis, cerebellar atrophy, microcephaly, ataxia	187

GLE1, mRNA export factor GLE1; TNPO3, transportin 3; TPR, translocated promoter region nuclear basket protein; XPO5, exportin 5.