NUCLEUS
2024, VOL. 15, NO. 1, 2314297
https://doi.org/10.1080/19491034.2024.2314297

Taylor & Francis
Taylor & Francis Group

Nuclear pore dysfunction and disease: a complex opportunity

Charlotte M. Fare and Jeffrey D. Rothstein

Department of Neurology and Brain Science Institute, Johns Hopkins University, Baltimore, MD, USA

ABSTRACT

The separation of genetic material from bulk cytoplasm has enabled the evolution of increasingly complex organisms, allowing for the development of sophisticated forms of life. However, this complexity has created new categories of dysfunction, including those related to the movement of material between cellular compartments. In eukaryotic cells, nucleocytoplasmic trafficking is a fundamental biological process, and cumulative disruptions to nuclear integrity and nucleocytoplasmic transport are detrimental to cell survival. This is particularly true in post-mitotic neurons, where nuclear pore injury and errors to nucleocytoplasmic trafficking are strongly associated with neurodegenerative disease. In this review, we summarize the current understanding of nuclear pore biology in physiological and pathological contexts and discuss potential therapeutic approaches for addressing nuclear pore injury and dysfunctional nucleocytoplasmic transport.

ARTICLE HISTORY
Received 27 November 2023
Revised 24 January 2024
Accepted 30 January 2024

KEYWORDS
Neurodegenerative disease; nuclear pore complex; nucleocytoplasmic transport; nucleoporin; nuclear envelope; therapeutics

Introduction

Eukaryotic life depends on the controlled distribution of cytoplasmic and nuclear materials. When this partitioning is disrupted, organisms experience wide-ranging damage caused by genomic instability, an activated inflammatory response, and apoptosis [1–4]. A substantial body of evidence indicates that nuclear pore injury and nucleocytoplasmic trafficking (NCT) defects are a shared feature of neurodegenerative diseases. Indeed, nuclear pore complexes (NPCs) and NCT are disrupted in Alzheimer's disease (AD) [5–14], Parkinson's disease (PD) [15–20], Huntington's disease (HD) [21–23], and amyotrophic lateral sclerosis and frontotemporal dementia (ALS/FTD) [24–50]. Interestingly, NCT defects and NPC deterioration also occur in traumatic brain injury [51], as well as during normal aging [52–54], suggesting that the compromised segregation of nuclear and cytoplasmic materials is a general feature of neuronal damage. Moreover, mutations to the proteins that make up the nuclear pore, collectively known as nucleoporins (Nups), are associated with an array of diseases, affecting multiple organ systems. Thus, maintenance of the NPC and NCT is critical for preserving cell health, a fact that is made particularly apparent in cell populations with long-lived nuclei, such as neurons. In this review, we cover recent advances in our understanding of the structure and function of the NPC, the unique problems faced by neurons in preserving NPC and NCT integrity, the role of Nups and NCT in disease, and potential opportunities for therapeutic intervention in diseases where the NPC and NCT are impaired.

Nuclear Pore Structure and Function

To facilitate the exchange of material between the cyto- and nucleoplasm, the nuclear envelope (NE) is dotted with NPCs, which are multi-protein channels made up of ~ 1,000 individual Nups [55]. At ~ 110 MDa, the NPC is a massive structure with a diameter of ~120 nm, and the number of NPCs per nucleus ranges from hundreds to well over 10,000 [56,57]. Neuronal nuclei, like many cells, typically have ~ 2000–5000 NPCs, although other cells of the central nervous system, such as oligodendroglia, may have different numbers of NPCs [41,58]. The NPC can be subdivided into six domains: the cytoplasmic filaments; the coat nucleoporin complex (also known as the Y-complex or Nup107-Nup160 complex); the inner ring; the central channel; the transmembrane or pore membrane proteins (POMs); and

CONTACT Jeffrey D. Rothstein jrothst1@jh.edu Department of Neurology and Brain Science Institute, Johns Hopkins University, Building 855 North Wolfe Street, Room 270, 2nd Floor, Baltimore, MD 21205, USA

the nuclear basket [55,59,60] (Figure 1(a)). The core scaffold of the NPC consists of the outer coat, inner ring, and central channel and is symmetrical, with eight-fold rotational pseudo-symmetry around the central channel of the pore, and two-fold symmetry across the NE [55,59–62] (Figure 1(b)). On the cytoplasmic face of the NPC core are the cytoplasmic filaments, and the Nups on the nuclear face of the NPC comprise the nuclear basket [55,59]. These sets of Nups are also known as asymmetric Nups because they are predominantly found on only one side of the NPC [55,59,61].

The Nups that make up the NPC are diverse and include proteins that serve a structural role (e.g., the coat nucleoporin complex) as well as natively unstructured Nups (e.g., phenylalanine-glycine (FG)-Nups of the central channel [63–67]) which directly interact with transported molecules. Together, the NPC acts as a barrier that can selectively gate the movement of cargo based on size and biochemical properties. Molecules that are below ~ 40 kDa can passively move through the NPC, whereas larger molecules require assistance by binding to dedicated nuclear transport receptors (NTRs) [55]. Efforts to understand the discerning nature of the NPC have found that the FG-Nups within the central channel of the pore are critical for enabling this selectivity due to their distinctive emergent properties [63–70]. Similar to what is observed in cells [71,72], purified FG-Nups can undergo liquid–liquid phase separation to form dense liquid-like condensates and solid-like hydrogels *in vitro*, both of which can be modified by NTRs [63,68,69,73]. Thus, the proteins within the central channel of the NPC form a biophysical and biochemical barrier that demonstrates selective permeability to transport proteins [72,74,75].

In addition to forming a barrier between the nucleus and cytoplasm, some Nups have direct involvement in the transport of specific cargo. Cytoplasmic Nup358 (also known as RanBP2) is required for the import of DNA methyltransferase 1 associated protein 1 (DMAP-1) [76], and nuclear Nup153 promotes the import of the DNA damage response protein, 53BP1 [77,78]. Additionally, cytoplasmic Nup42 (also known as NLP-1) cooperates with Exportin-1 (CRM1) to facilitate nuclear export [79]. Several Nups also play roles outside of the NPC and NCT. For instance, Nups in the coat nucleoporin complex, the inner ring, and the nuclear basket interact with chromatin and regulate gene expression [80–84]. Nups also play roles in cell migration [85–88], cell signaling [88–90], the immune response [91,92], and autophagy [93,94].

a.

Cytoplasmic Filaments			
AAAS	DDX19	Gle1	Nup42*
Nup88	Nup214*	Nup358*	Rae1
Coat Nucleoporin Complex			
ELYS	Nup37	Nup43	Nup85
Nup96	Nup107	Nup133	Nup160
Sec13	Seh1		
Inner Ring			
Nup53	Nup93	Nup155	Nup188
Nup205			
Central Channel			
Nup54*	Nup58*	Nup62*	Nup98*
Transmembrane			
NDC1	Nup210	POM121*	
Nuclear Basket			
Nup50*	Nup153*	TPR*	

*Contain FG repeats

b.

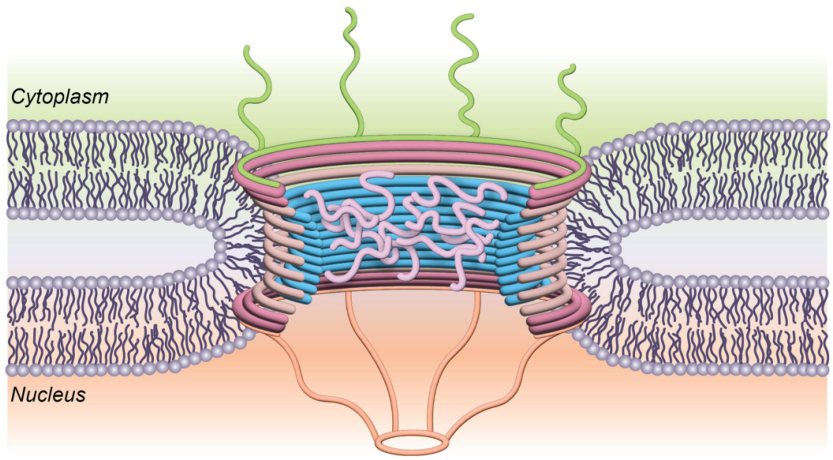

Figure 1. The nuclear pore complex is a large macromolecular structure. (a) The nuclear pore complex (NPC) is comprised of six subdomains: the cytoplasmic filaments, the coat nucleoporin complex, the inner ring, the central channel, the transmembrane nucleoporins, and the nuclear basket. Many phenylalanine-glycine (FG)-Nups (indicated by an asterisk) are found in the central channel. However, FG-Nups are also found at the asymmetric cytoplasmic and nuclear faces of the NPC. (b) The NPC sits within the double membrane of the nucleus, and the NPC core demonstrates two-fold symmetry across the nuclear envelope, with the asymmetric cytoplasmic filaments and nuclear basket Nups projecting into their corresponding cellular compartments.

Neuronal Nuclei

NPCs are essential structures, and thus they must be actively maintained. In mitotic cells, NPCs are disassembled during cell division and reassembled in the new daughter cells [95–97]. As part of the process of building new nuclei, Nups are subject to quality control mechanisms to preserve NPC integrity across generations [1,98–100]. Neurons, however, do not divide, and therefore the integrity of neuronal NPCs is not monitored via the same strategies as those used by dividing cells [101–103]. Instead, Nup integrity is preserved by a variety of alternative means, including the activity of protein chaperones [104–106], nuclear import receptors [35,48,107], and members of the endosomal sorting complexes required for transport (ESCRT)-III family [44,46,100,103,108,109]. These quality control processes guard against protein misfolding, oxidative stress, DNA damage, and other cellular stressors [110].

Because the quality of NPCs in non-dividing cells is constantly under surveillance, Nups have different lifetimes within neuronal nuclei. For example, scaffolding Nups are very long-lived, persisting in NPCs for periods spanning months to years in the brains of an *in vivo* rat model [111]. In this model, even the relatively mobile FG-Nup, Nup98, had a lifespan of several months [111]. In cell culture, however, turnover rates may be more rapid, with Nups being replaced on a timescale of hours to days [52,102]. Still, for both *in vivo* and *in vitro* models, different Nups demonstrate variable lifetimes with Nups that form the scaffold of the NPC generally having less rapid turnover [52,112]. Thus, Nup renewal in non-dividing cells is not a wholesale event, but instead occurs in an ad hoc fashion [102]. As such, neurons face a particular challenge with respect to NPC integrity, as these long-lived proteins must be monitored and maintained over decades to prevent NPC injury and dysfunction.

Nuclear Pore Injury in Neurodegenerative Disease

Given the specific burden placed on neurons to maintain NPC health, and the central role of the NPC and NCT in integral biological processes, it is not surprising that NPC and NCT defects can be a feature of neurodegenerative diseases. In this section, we will cover NPC and NCT dysfunction in Alzheimer's disease and other tauopathies, Parkinson's disease, Huntington's disease, and ALS/FTD.

Alzheimer's Disease and Other Tauopathies

Tauopathies are a broad class of neurodegenerative disorders that often result in behavioral changes, memory defects, and dementia [113]. AD is the most notorious tauopathy, but this group of diseases also includes FTD, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), and others [113]. At the cellular level, tauopathies are characterized by the accumulation of tau protein aggregates in the brain [113]. In healthy neurons, tau binds to microtubules and stabilizes the cytoskeleton [11,113,114], and the affinity of tau for microtubules is regulated by its phosphorylation [113]. In several tauopathies, specific sites on tau become hyperphosphorylated, impairing the interaction between tau and microtubules, leading to microtubule destabilization and tau mislocalization [9,11,14,113,114].

In AD, tau hyperphosphorylation is correlated with the severity of neurodegeneration [9,113]. When tau is hyperphosphorylated, it interacts with the central channel Nups, Nup62, and Nup98, leading to their co-aggregation with tau in the cytoplasm and subsequent defects in NCT [9,11,14]. Nup98 cytoplasmic mislocalization occurs in other tauopathies as well, including FTD, CBD, and progressive supranuclear palsy (PSP) [12]. In model systems, Nup98 exacerbates tau aggregation, suggesting that initial co-aggregation of Nups and tau could initiate a cascade of NCT dysfunction [9]. Phosphorylated tau can also be imported into the nucleus by NTRs, which results in the mislocalization of other proteins and nuclear injury [115]. Interestingly, the degree to which the nuclear protein TFEB (an autophagy-related transcription factor) is mislocalized to the cytoplasm increases with the extent of tau hyperphosphorylation in AD brains [116]. As TFEB is important for lysosomal biogenesis, this finding indicates a progressive loss

of both efficient NCT and general proteostasis in relation to tau hyperphosphorylation [116].

Pathological tau mutations can further impact Nup levels and localization. In human embryonic kidney cells (HEK) cells, expression of the disease-associated Tau^{P301L} mutant leads to increased cytoplasmic levels of multiple Nups, including cytoplasmic filament Nups, Nup88 and Nup214; coat Nups, Nup85, Nup107, Nup133, and Nup160; inner ring Nups, Nup155, Nup188, and Nup205; central channel Nup, Nup98; transmembrane Nup, Nup210; and nuclear basket Nups, Nup50 and Nup153 [117]. These changes in Nup localization are accompanied by NE invagination, reduced lamin levels, and altered chromatin condensation, indicative of severe nuclear injury [117]. As a consequence, expression of Tau^{P301L} results in defective nuclear transport and an altered epigenomic landscape, leading to cell stress [117]. In other studies, the expression of disease-associated mutant tau in neurons derived from human induced pluripotent stem cells (iPSCs) also compromises NCT, leading to the mislocalization of NCT reporters [114].

Intriguingly, the phosphorylation and mislocalization of disease-associated tau mutants also correspond with abnormal microtubule growth patterns [114]. Whereas the growing ends of microtubules in wild-type cells project into the cell body, the projections of microtubules in cells expressing mutant tau grow into the nucleus, deforming the NE and leading to harmful mechanical stress [114]. Specifically, in iPSC-derived neurons from FTD-Tau patients, NPCs are found within laminar invaginations and cells show aberrant NCT [114]. Thus, pathological tau can affect NCT directly by interacting with components of the NPC and NE, and indirectly, by abandoning its role in cytoskeletal organization.

Some tauopathies exhibit stereotypical compound pathology, which can worsen NCT deficits [113]. For example, AD is also characterized by the accumulation of aggregates containing amyloid-β (Aβ), both inside and outside of the cell [118]. Nuclear Aβ has been described in cell culture and in mouse tissue, where it can directly interact with the genome to affect gene expression [119]. Localization of Aβ to the nucleus can be induced by oxidative stress [120] and antibiotic treatment [121], but the mechanism by which it enters the nucleus is not known. However, oligomers of Aβ are less than 40 kDa in size [122], and thus these species may passively diffuse through the NPC [119]. Another tauopathy that frequently involves other proteins is FTD, which is discussed in more detail below.

Parkinson's Disease

PD is a progressive neurodegenerative disease that presents with movement abnormalities (e.g., tremor, slow movement, rigidity) and, in some cases, fatigue, psychosis, and dementia [123]. These symptoms develop due to a loss of dopaminergic neurons within the substantia nigra, and the surviving cells in patient tissue harbor cytoplasmic aggregates of the protein α-synuclein [123]. These aggregates are also known as Lewy bodies (LBs) and contain a diverse collection of proteins including protein chaperones; proteasomal subunits; tau; the nuclear import receptor, Importin 7; and nuclear RNA-binding proteins (RBPs) such as TDP-43 and hnRNPA2/B1 [17,124]. Thus, the accumulation of material in LBs may lead to (or result from) defects in NCT.

Although most PD cases are sporadic, ~10–15% are inherited, and mutations to proteins such as Parkin and LRRK2 lead to nuclear injury [15,16,18–20,123]. Parkin is a ubiquitin-protein ligase, and one of its targets is the cytoplasmic Nup, Nup358 [15]. In cell culture, when wild-type Parkin is overexpressed, Nup358 levels are significantly decreased, and this decrease is affected in a proteasome-dependent manner [15]. On the other hand, when a dominant-negative Parkin mutant is overexpressed, levels of Nup358 are only modestly decreased, indicating that active Parkin functionality may regulate Nup358 abundance [15]. As Parkin mutations likely lead to a loss-of-function [123], these data suggest that Nup358 quantity and quality may be impacted in PD.

By contrast, PD-associated LRRK2 mutations typically enhance enzymatic activity [18]. LRRK2 is a kinase that normally localizes to membranes, including the nuclear membrane [16,19]. However, in affected tissue from patients with PD, LRRK2 colocalizes with LBs [16], and

hyperactive disease-associated mutants of LRRK2 interact less with the NE protein Lamin A/C [19]. Expression of these hyperactive LRRK2 mutants leads to nuclear membrane deformations *in vitro* and *in vivo*, phenocopying experimental knockdown of LRRK2 in cell culture [18,19]. These results suggest that overactive LRRK2 dissociates from the NE, damaging the nucleus through negligence. Indeed, LRRK2-null mice show signs of nuclear damage such as accelerated genomic instability, neurodegeneration, and motor defects [20]. Additionally, cultured dopaminoceptive striatal spiny projection neurons from both LRRK2 mutant and null mice have abnormal nuclear morphology [20]. Together, these findings suggest that PD-associated LRRK2 mutants have impaired interactions with the NE, leading to nuclear injury and cell death.

Huntington's Disease

HD is an inherited form of neurodegeneration related to the expansion of a CAG trinucleotide repeat in the *HTT* gene [125]. Translation of these CAG repeats produces huntingtin protein (Htt) containing a poly-glutamine (polyQ) tract that can be dozens of residues long [21–23,125]. PolyQ-expanded Htt forms pathological inclusions within neuronal nuclei, affecting cells in the striatum and cortex [21–23,125]. Cell death in these regions leads to disturbed movement, cognitive decline, and death [125].

Early studies found that polyQ Htt aggregates sequester the central channel Nup, Nup62 [126], and that mutant Htt disrupts the NE [127]. Later experiments showed that, in addition to Nup62, mutant Htt also interacts with the cytoplasmic filament Nups, Nup88 and Gle1 [21–23]. Furthermore, in cells expressing polyQ-expanded Htt, the NE protein, Lamin B1, and key components of the Ran gradient that facilitate directional nucleocytoplasmic transport (NCT), Ran-GTP and RanGAP1, are all mislocalized [21–23]. Collectively, these changes lead to defective NCT, increased DNA damage, and cell death [21,22].

Interestingly, Htt was recently identified to have a proline-tyrosine nuclear localization signal (PY-NLS) that is recognized by the nuclear import receptors, Karyopherin β1/β2 (Kapβ1/2) [128]. Additional work has found that Htt also interacts with several other NTRs [129,130]. NTRs can act as protein chaperones to modify the physical state of their cargo [35,43,131–136], but they can also become co-aggregated with client proteins [34,48,137,138]. As such, whether nuclear import receptors are implicated in HD etiology would be an informative question to pursue.

To date, investigations into how NCT is affected in HD have centered on the Htt protein. However, evidence indicates that the RNA from which Htt is translated forms toxic intranuclear inclusions [139–143]. In studies that focused on the G_4C_2 hexanucleotide repeat expansion (HRE) in the *C9ORF72* gene (discussed in more detail below), the G_4C_2 HRE RNA forms aggregates which colocalize with RanGAP1 [33]. Thus, repeat RNAs can impair NCT as well. However, whether expanded Htt mRNAs sequester components of the NPC or NCT machinery remains an unexplored area of research.

Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

ALS and FTD are two related diseases which exist on a clinical and genetic spectrum [144–146]. ALS describes a fatal motor neuron disease in which progressive loss of motor neurons in the brain and spinal cord leads to muscle weakness, respiratory failure, and death [145]. In contrast, FTD is not fatal on its own, and its presentation is markedly heterogeneous, making the disease difficult to diagnose [147]. Prominent clinical presentations of FTD include changes to behavior and personality, emotional dysregulation, repetitive behaviors, and aphasia [147]. However, early reports indicated that a subset of ALS and FTD patients display overlapping symptoms, causing people to hypothesize that these two diseases were linked [147]. Approximately 50% of ALS patients have very mild cogitative deficits, whereas ~ 10% of patients can have significant signs of both FTD and ALS [148], largely due to the mutation in C9orf72. Both ALS and FTD are largely sporadic in etiology, with mutations in the C9orf72 gene as the most common gene causing both ALS and FTD.

The initial molecular evidence that ALS and FTD share underlying pathological mechanisms came with the identification of ubiquitinated inclusions of the RNA-binding protein (RBP) TDP-43 in postmortem brain tissue from both ALS and FTD patients [144,149–153]. Since this observation, the aggregation of many other RBPs has been tied to ALS and FTD, including FUS, hnRNPA1, and hnRNPA2B1 [144,154–162]. However, the major link between ALS and FTD is the G_4C_2 HRE in the first intron of the *C9ORF72* gene, which produces toxic RNA molecules, deleterious dipeptide repeat protein (DPR) species via repeat associated non-AUG (RAN) translation, and may also lead to haploinsufficiency, or loss or gain of function of the C9orf72 protein [33,41–43,138,163–170]. It is estimated that 20–50% of people with familial ALS and FTD (fALS/FTD) and 5–10% of people with sporadic ALS/FTD (sALS/FTD) have the *C9ORF72* HRE (C9-ALS/FTD), making it the most prevalent genetic contributor to these diseases [144,164,171–173].

Many of the proteins implicated in ALS/FTD have roles in regulating RNA [157,174], and although the function of the C9orf72 protein is not fully understood, the RNA and protein species produced from its G_4C_2 HRE do interact with RBPs and other RNA molecules to disrupt RNA metabolism [175–181]. SOD1, another ALS-related protein that is not strictly classified as an RBP, also interacts with known RBPs [182–185]. Furthermore, SOD1 may bind to some RNA molecules [186], and some studies have found that SOD1 mutations can alter levels of certain RNA species, although this is likely an indirect effect [187]. Overall, these findings have led to the understanding that ALS/FTD can result from loss-of-function and gain-of-toxicity mechanisms related to the mislocalization and aggregation of specific proteins involved in RNA biology [188–191]. As RBPs are depleted from the nucleus, their normal functions in mRNA metabolism are lost, leading to mis-splicing events and changes in mRNA levels [35,41,44,178,192–198]. Meanwhile, aggregated proteins in the cytoplasm can be inherently toxic, as reducing levels of aggregated proteins such as FUS can be protective [199,200]. Furthermore, protein aggregates cause toxic secondary effects by sequestering other proteins and mRNA species, leading to extensive dysfunction [32,34,35,37,38,42,43,47,48,137,201–204]. Notably, although ALS is characterized by protein aggregation in general, the proteome of the inclusions is not uniform, suggesting potential disease heterogeneity [205–207].

Among the proteins that are co-sequestered in cytoplasmic aggregates formed in ALS/FTD are Nups and components of the NCT machinery. For example, cytoplasmic Nups, coat Nups, inner ring Nups, central channel Nups, and basket Nups were all found to co-aggregate with pathological TDP-43 C-terminal fragments (CTFs) [34]. Moreover, multiple studies looking at full-length TDP-43 and the DPRs produced via repeat-associated non-AUG (RAN)-translation from the G_4C_2 HRE indicate that TDP-43 and DPRs co-aggregate, and that these aggregates also contain central channel Nups, Nup54, Nup62, and Nup98; as well as transmembrane Nup, POM121; and nuclear basket Nup, Nup153 [47,138]. Interestingly, with the exception of POM121, each of the Nups that were shown to co-aggregate with TDP-43 and DPRs contain FG-domains [55], underscoring the disease relevance of these domains [42,47,208,209]. Even in the absence of TDP-43, DPRs can interact with Nups to impair NCT, associating with Nups found throughout the NPC [42,209–211]. However, one must be cautious in extrapolating conclusions about human pathophysiology based on *in vitro* experiments involving DPRs. For example, although some studies relate DPR expression to pathological phenotypes, in authentic human C9orf72 iPSCs, DPRs play no role in disrupting the NPC or NCT [41]. Rather, the C9orf72 repeat RNA itself is the cause of NPC damage and defective NCT [41]. Moreover, there have not yet been any studies showing DPR-induced defects to the NPC or to NCT in human neuronal cells. Still, reducing C9orf72 levels can also perturb NCT and instigate NPC defects [212], supporting a hypothesis that haploinsufficiency of the C9orf72 protein might contribute to C9-ALS /FTD pathology.

In iPSC-derived spinal motor neurons from ALS patients expressing FUS coding variants, Nup62 and POM121 show an atypically

clustered localization, and this phenotype can be corrected by reverting FUS to its wild-type sequence [45]. In cell culture, mutant SOD1 is depleted from the nucleus relative to the wild-type protein [213], and in mice expressing mutant human SOD1, nuclear architecture and transport are disrupted [214,215]. Namely, outer coat Nup, Nup107; inner ring Nup, Nup205; transmembrane Nup, Nup210; and basket Nup, Nup50 each shows accumulation over time in both the nucleus and the cytoplasm of murine motor neurons expressing human $SOD1^{G93A}$ [215]. These results were validated in sALS patient tissue, where RanGAP1, Nup210, and Nup50 demonstrate increased cytoplasmic localization [215].

NTRs are also trapped within cytoplasmic aggregates in ALS/FTD, impairing their critical role in facilitating NCT. For example, TDP-43 CTFs co-aggregate with the nuclear export factor Nxf1 and the protein exporter XPO5, whereas increased expression of the nuclear import receptor Karyopherin β1 (Kapβ1) reduces TDP-43 CTF aggregate levels [34]. Expression of Kapβ1 can also reduce TDP-43 pathology in *Drosophila* models, improving locomotive phenotypes and prolonging lifespan [48]. However, aggregates of arginine-containing DPRs (R-DPRs) contain Kapα1, Kapβ1, XPO1, and XPO2 [42]. Furthermore, in brain tissue from mice expressing GFP-tagged $poly(GR)_{200}$, poly(GR) inclusions colocalized with both Importin α5 (Impα5) and Karyopherin α2 (Kapα2) [138]. Thus, the relative degree of NTR activity and aggregate burden may play a consequential role in disease progression. This balance is especially important in cases with TDP-43 and DPR co-pathology, as DPRs can promote the aggregation of TDP-43 [43,138,216]. However, biochemical studies with recombinant protein found that Kapβ2, which does not interact with TDP-43 but does interact with R-DPRs, prevents R-DPRs from enhancing TDP-43 aggregation [43]. Kapβ2 also acts as a chaperone for its physiological cargo, including the ALS/FTD-related RBPs, FUS, hnRNPA1, and hnRNPA2/B1, but the efficacy of this activity depends on the strength of the interaction between Kapβ2 and the PY-NLS of its client [29,35,133,135,136,200,217,218]. Indeed, PY-NLS mutations lead to persistent NCT defects and cause highly aggressive forms of ALS [26,219–222].

Although cytoplasmic TDP-43 aggregates certainly may contribute to NPC and/or NCT disruption in ALS, emerging data suggest that loss of nuclear TDP-43 is another central defect, reflecting upstream disruption of the NPC and resultant errors in NCT. In studies of hiPSC-derived spinal neurons from large numbers of sporadic and C9orf72 ALS/FTD individuals, loss of POM121 as well as overall disruption of both the NPC and NCT precedes the loss of nuclear TDP-43 and the resultant appearance of aberrant RNA species that reflect this loss of function [223]. Furthermore, analysis of human brain tissue revealed that cytoplasmic TDP-43 aggregates in human brain are rare, whereas nuclear loss of TDP-43 is more common in affected brain regions [223]. These *in vitro* and *in vivo* data indicate that disruption of the NPC is a common upstream defect in these disorders.

Genetic variation within Nups is associated with ALS/FTD as well [224,225]. For instance, the cytoplasmic Nup, Gle1, was found to have disease-specific mutations in a small cohort of ALS patients [225]. Further *in vitro* and *in vivo* analyses indicated that these Gle1 mutants exert a loss-of-function phenotype [225]. More recently, researchers undertook transcriptome-wide association study on a dataset including thousands of ALS patient and control samples [224,226]. In addition to genes known to be implicated in ALS, such as *C9ORF72*, the group also identified *NUP50* as a disease-associated transcript [224]. The group performed several subsequent analyses on independent sets of data from ALS/FTD patients and confirmed that Nup50 variants were significantly correlated with disease [224]. They found both coding and non-coding risk variants in Nup50, and showed that Nup50 levels are lower in ALS patient samples and in iPSC-derived neurons from ALS patients relative to controls, leading the researchers to hypothesize that decreased levels of Nup50 may be deleterious [224]. Indeed, motor defects, shortened neuromuscular junctions (NMJs), and impaired axonal branching of motor neuron all result from knockdown of Nup50 in living organisms [224].

Importantly, depletion of Nups from the NPC also occurs in cases where no known pathological genetic variation has been established, and Nups can be depleted at the NPC through reduced expression [227], and through Nup mislocalization or degradation [41,44]. Recent work comparing *in vitro* data collected using iPSC-derived motor neurons and patient outcomes revealed that *NUP188* expression levels were decreased in patients with more aggressive forms of ALS [227]. In an earlier comprehensive study, multiple iPSC lines from patients with sALS without any disease-associated mutations, outer coat Nup, Nup133; transmembrane Nup, POM121; and nuclear basket Nups, Nup50, Nup153, and TPR were all found to have reduced nuclear abundance [44] along with decreased NCT fidelity. Compellingly, the reduction of these Nups from the NPC occurs without pronounced cytoplasmic accumulation of TDP-43, despite evidence for TDP-43 loss-of-function at the mRNA-level [44]. These results strongly suggest, as detailed above, that NPC injury precedes TDP-43 pathology, and in both C9-ALS/FTD and sALS, loss of POM121 from the nucleus is a critical upstream event in the cascade of disease-associated dysfunction [41,44]. Interestingly, previous work in this model showed that the loss of Nups from the nucleus was not related to changes in Nup mRNA levels [41].

Follow-up studies revealed that one route by which NPC disruption can occur is via nuclear accumulation of the ESCRT-III protein, CHMP7 [44]. CHMP7 is understood to serve a role in maintaining NPC homeostasis, suggesting that the cell is sensing and responding to NPC injury [44,108]. In sporadic and familial ALS iPS models, CHMP7 was found to initiate the NPC disruption, and CHMP7 nuclear accumulation and NPC defects were also observed in patient brain tissue, validating these *in vitro* observations [41,44]. However, it is not yet known what NPC injury, if any, is initiating CHMP7 nuclear accumulation, and whether CHMP7 nuclear accumulation directly or indirectly leads to Nup reduction remains to be elucidated. Thus, understanding what leads to pathological Nup depletion is an active area of research. Therefore, it will be important to determine whether the expression of genes that encode for components of the NPC or proteins involved in NCT is affected in disease states. Nevertheless, the fundamental role of NPC injury appears to be a core upstream defect in sporadic and C9orf72 ALS.

Cytoskeletal abnormalities can also impair the NPC and NCT in ALS. Mutations to Profilin 1 (PFN1), which regulates actin growth; tubulin alpha protein, TUBA4A; and the kinesin family member, KIF5A, have been found in both fALS and sALS [228–230]. Mutated cytoskeletal proteins alter microtubule dynamics [231] and cause damage to NPCs and the nuclear membrane [39], leading to compromised NCT [39,231]. Similarly, ALS-associated mutations to proteins within the nuclear membrane, such as vesicle-associated membrane protein-associated protein B (VAPB), also can be detrimental to the NPC [232,233]. VAPB is generally thought to reside in the ER, but was recently shown to also localize to the inner nuclear membrane where it interacts with components of the protein complexes that link the nucleoskeleton and cytoskeleton (LINC complexes) as well as the NPC via ELYS (also known as AHCTF1) in the coat Nucleoporin complex, and basket Nups, Nup153 and Tpr [233]. These findings complement earlier work demonstrating that ALS-related VAPB mutants impair ER-Golgi trafficking, resulting in cytoplasmic retention of cytoplasmic filament Nup214 and transmembrane Nup210 [232].

Nucleoporin Variation and Disease

Nup coding variation is associated with numerous diseases and a broad array of phenotypes (Table 1, Figure 2). In this section, we describe Nup mutations in each domain of the NPC and the consequences of these mutations on NPC function and biology.

Cytoplasmic Filaments

In addition to ALS, mutations to the cytoplasmic Nup Gle1 cause fetal motoneuron disease, potentially by decreasing Gle1 nuclear localization [238–240]. Among other cytoplasmic Nups, Nup88 mutations cause lethal fetal akinesia deformation sequence (FADS), a disease

Table 1. A summary of disease-associated Nup coding variants.

	Nup	Coding Variant(s)	Disease	Experimental Observations	Refs.
Cytoplasmic Filaments	AAAS (Aladin)	Q15K; H71fs * 92; W84X; R119*; Q145*; F157fs * 171; H160R; R230*; Q237*; S263P; R286*; W295*; R312*; V313A; S328fs * 362; V369fs * 382; S382fs * 413; Q387*; E398fs * 424; Q456*; Q456fs * 492; R342*; S463fs * 549; W474*; R478*	Triple-A syndrome (Allgrove syndrome)	Normal NPC structure and NTR localization, some mutations result in mislocalized AAAS (HeLa cells and patient-derived fibroblasts)	[234–237]
	Gle1	S70*; R697C	Amyotrophic Lateral Sclerosis (ALS)	Decreased mRNA levels, neuronal cell death (patient lymphoblast cells; zebrafish)	[225]
		T144_E145insPFQ; R569H; V617M; I684T	Lethal congenital contracture syndrome 1 (LCCS1) and lethal arthrogryposis with anterior horn cell disease (LAAHD)	Specific loss of Gle1 at the nucleus (patient-derived fibroblasts)	[238–240]
	Nup88	D434Y; R509*; E634del	Fetal akinesia deformation sequence	Impaired locomotive behavior, loss-of-function, disrupted interaction with other Nups, premature lethality (HeLa and C2C12 cells; zebrafish)	[241]
	Nup214	R38C; L68del; D154G; P525Lfs *6; P387S	Encephalopathy and microcephaly (including IIAE9)	Decreased Nup214 and Nup88 at the nucleus, blocked NPC channel, abnormal nuclear morphology, impaired NCT, increased sensitivity to heat stress (patient-derived fibroblasts)	[242–244]
	Nup358 (RANBP2)	T585M; T653I; I656V	Acute necrotizing encephalopathy (ANE1)	Reduced interaction with COX11 (purified protein), impaired interactions with GW182/TNRC6 and associated miRNA pathway defects (HEK293T cells)	[245–247]
Coat Nucleoporin Complex	Nup37	R306*	Steroid-resistant nephrotic syndrome (SRNS)	Reduced mRNA and protein levels, co-depletion of Nup107 and Nup160, reduced NPC density, altered chromatin organization, deformed nuclei (patient-derived fibroblasts)	[248]
	Nup85	A477V; A581P; R645W	SRNS	Weakened interactions with Nup160, early lethality (HEK293T cells; zebrafish)	[248]
	Nup107	M101I; D157Y; E360Gfs *6; D447N; D831A	Early-childhood-onset SRNS	Reduced Nup107 and Nup133 protein levels, reduced Nup107:Nup133 binding, mislocalized Nup107 (purified protein; patient-derived fibroblasts)	[249,250]
		M101I; E341Gfs *3; E710del; Y889C	SRNS	Reduced mRNA and protein levels, reduced interaction with Nup133, co-depletion of Nup37 and Nup160 (HEK293T and patient lymphoblastoid cells)	[248]
	Nup133	R231G; L1055S; S974R	SRNS	Reduced binding to Nup107 (HEK293T cells)	[248]
	Nup160	E803K; R1173*	SRNS	Abnormal nuclear volume, some mutations affect NPC localization and nuclear morphology (*Drosophila*)	[251]

(*Continued*)

Table 1. (Continued).

	Nup	Coding Variant(s)	Disease	Experimental Observations	Refs.
Inner Ring	Nup93	R388W; K442Nfs *14; G591V; Y629C	SRNS	Reduced localization to the nuclear envelope, fail to form NPCs, reduce interaction with Imp7 (HEK293 cells and cultured human podocytes)	[252]
	Nup155	R391H	Atrial fibrillation	Reduced accumulation at the nuclear envelope, reduced nuclear envelope permeability, inhibition of Hsp70 mRNA export, reduced Hsp70 expression (COS7 and HeLa cells)	[253]
	Nup188	Y96*; Q113*	'Nup188 insufficiency syndrome'	N/A	[254]
		I302Vfs *7; W630*; W1048*; Q1360*; R1678Pfs *13;	Brain malformation, dysmorphic features, visual impairment, heart anomalies, hypotonia, progressive microcephaly	Reduced Nup188 mRNA and protein levels, defective NCT for both canonical and non-canonical nuclear import (patient-derived fibroblasts)	[255]
	Nup205	F1995S	SRNS	Reduced interaction with Nup93 (cultured human podocytes)	[252]
Central Channel	Nup54	I358S; K376E; Q471del; Q472del; L474F	Infantile striatonigral degeneration	Proper localization, but reduced levels of Nup54, Nup62, and Nup58 (patient-derived fibroblasts)	[256]
	Nup62	Q391P	Recessive infantile bilateral striatal necrosis	Normal nuclear localization (U2OS and patient lymphoblastoid cells)	[257]
Nuclear Basket	Nup50	Q20C; F58fs; R45C; R72C; G114D; Y156C; P179A; K275E; R448W	ALS	Reduced Nup50 protein levels (patient lymphoblast cells)	[224]
	TPR	V859_D870del; R2209*	Ataxia, microcephaly, and intellectual disability	Decreased TPR levels, decreased colocalization to NPCs, increase in NPC density, reduced nuclear mRNA levels (patient-derived fibroblasts)	[258]

A table listing the known disease-associated Nup coding variants, including their subdomain within the nuclear pore complex, the specific coding variants, the associated diseases, experimental observations that have been made for the mutations, and references.

characterized by reduced fetal movement, potentially as a result of defective NMJ formation [241]. FADS Nup88 mutations have been shown to reduce the extent to which Nup88 can interact with other Nups in the NPC, which may be destabilizing [241]. Meanwhile, mutations to cytoplasmic Nup214 or Nup358 cause encephalopathy, including acute infection-induced encephalopathy-9 (IIAE9) [242–246], and acute necrotizing encephalopathy (ANE1) [247]. Similarly, mutations to AAAS (also known as Aladin) lead to Triple-A syndrome, which is also typified by microcephaly, as well as neurological impairment, muscle weakness, and neuropathy [234–237]. The symptoms of Triple-A syndrome can also overlap with those of ALS, with some patients showing amyotrophy in the face, neck, and distal limbs [259–261]. For each of these encephalitic diseases, mutations in the associated Nup affect protein interaction networks within and outside of the NPC, Nup localization, and NCT [236,242,243,247].

Coat Nucleoporin Complex

The described mutations to the Nups of the coat nucleoporin complex (i.e., Nup37, Nup85, Nup107, Nup133, and Nup160) exclusively lead to steroid-resistant nephrotic syndrome (SRNS), with Nup107-SRNS patients also presenting with microcephaly [249–251]. SRNS can also result from mutations to the inner ring Nups, Nup93, and Nup205 [248,252]. In line with the highly interdependent structure of the NPC, mutations to individual coat Nups cause general coat Nup dysfunction [248]. For example, mutations to Nup37 and Nup133 both lead to a reduction in Nup107 levels in cells, whereas mutations in Nup107 are associated with reduced levels of Nup37, Nup133, and Nup160 [248]. Coat nucleoporin mutations also affect protein–protein interactions, such as Nup85-Nup160 interactions and Nup107-Nup133 interactions. As the central structural foundation for the NPC [55], disruptions to the levels or integrity of the coat nucleoporin complex are understandably harmful for the NPC. However, it is unclear why coat nucleoporin complex Nup mutations appear to target the renal system so acutely.

Inner Ring Nups

Unlike outer coat Nups, mutations to the Nups of the inner ring are associated with a relatively diverse set of diseases. As opposed to the aforementioned mutations to Nup93 and Nup205, Nup155 mutations, for example, result in atrial fibrillation (AF), a cardiac disease that can lead to stroke and heart failure [253]. In cell culture, AF Nup155 mutations affect Nup155 localization and lead to reduced NE permeability, with the protein chaperone Hsp70 in particular showing decreased mRNA export and nuclear import [253]. In a mouse model where one copy of *NUP155* is knocked out, mice display AF symptoms, suggesting that Nup155 mutations result in a loss-of-function phenotype [253]. Mutations in Nup188 can result in heart abnormalities as well, but also cause or are associated with neurologic and muscular defects [254,255,262]. In patient cell lines, pathogenic Nup188 mutations lead to reduced Nup188 levels and defects in nuclear import [255].

Central Channel

In the central channel, Nup54 mutations have been linked to infantile striatonigral degeneration, a disease that results in dystonia, ataxia, spasms, and difficulty swallowing [256]. Interestingly, disease-related Nup54 mutations are clustered in the C-terminus of the protein, which interacts with Nup62 [256]. Separate work had previously identified Nup62 mutations which lead to bilateral striatal necrosis, a neurodegenerative disorder that affects the caudate nucleus and putamen of the basal ganglia [257]. The phenotypes of patients with Nup54 and Nup62 mutations are remarkably similar [256], suggesting that proper interaction between central channel Nups is critical for neurological and motor functioning.

Transmembrane Nups

As yet, there are no pathological mutations to transmembrane Nups listed on the UniProt database [263]. However, mislocalization and changes in expression levels of transmembrane Nups can

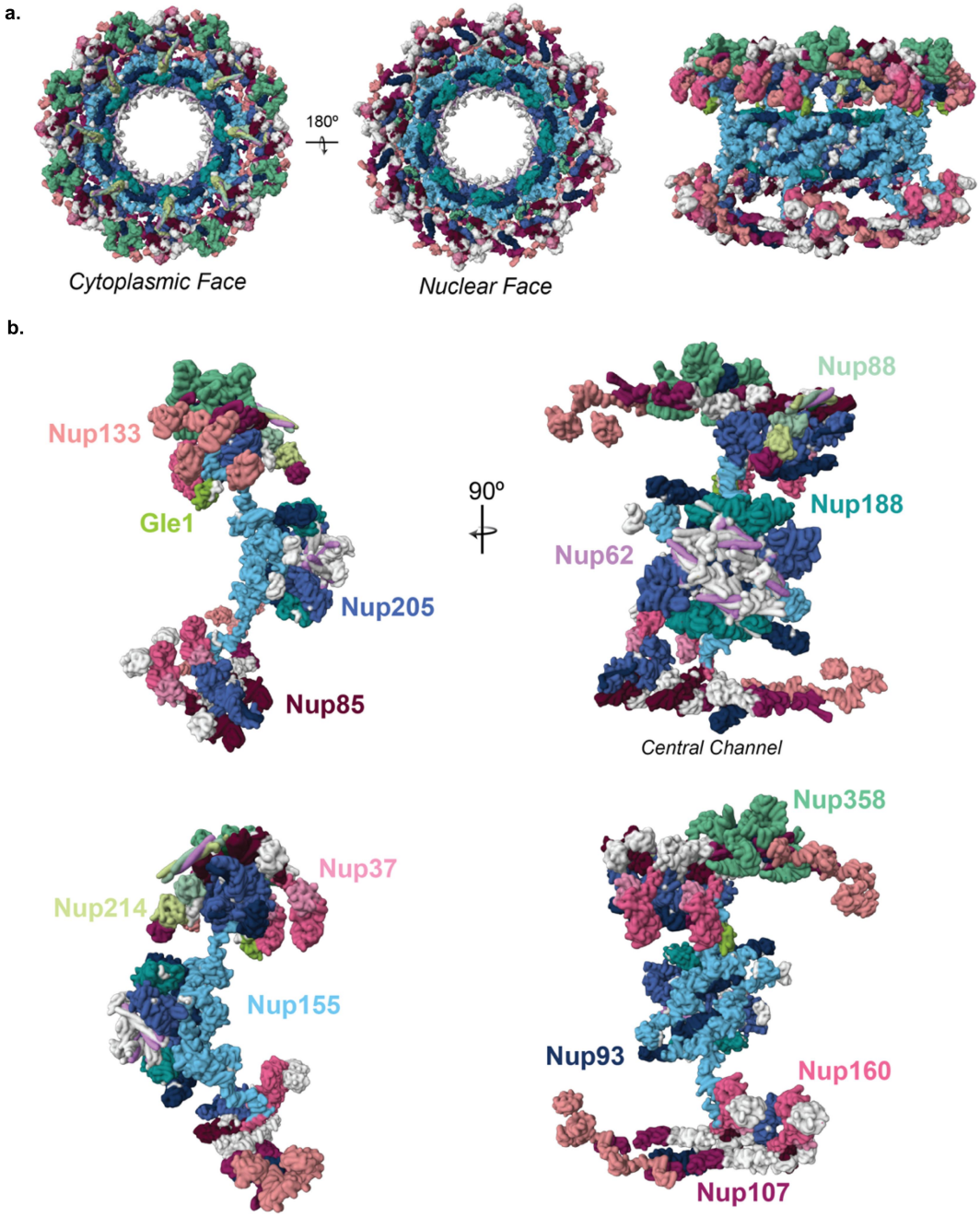

Figure 2. Mutations to the nucleoporins of the nuclear pore complex are associated with a diverse set of diseases. (a) From left to right, the symmetrical core of the nuclear pore complex (NPC) shown from its cytoplasmic and nuclear faces, as well as from within the plane of the nuclear envelope. Nucleoporins (Nups) that have not been identified to be mutated in disease are shown in white. Mutated Nups are shown in different colors, labeled on an NPC monomer in (b). Among cytoplasmic Nups, Gle1 is shown in lime, Nup88 is mint green, Nup214 is light green, and Nup358 is seafoam green. For outer coat Nups, Nup37 is light pink, Nup85 is dark purple, Nup107 is fuchsia, Nup133 is salmon, and Nup160 is pink. Of the inner ring Nups, Nup93 is navy, Nup155 is sky blue, Nup188 is teal, and Nup205 is dark periwinkle. The central channel Nup, Nup62, is shown in lilac. Additional Nups with disease associated mutants that are not included in these structures are: cytoplasmic Nup, AAAS; basket Nups, Nup50 and TPR. Structures shown are PDB: 7TBL [59].

have pathological effects, as discussed with POM121 and Nup210 in ALS [41,215]. Transmembrane Nups have also been implicated in cardiomyopathy [264], infertility [265], endometriosis [266], a number of cancers [267–271]. In these diseases, Nup overexpression is often observed, and there is evidence for widespread disruption to biological processes [272].

Nuclear Basket

Within the nuclear basket, aside from the recently identified ALS-linked Nup50 variants, TPR mutations can lead to microcephaly, ataxia, and intellectual disabilities [258]. In patient cells, these TPR mutations lead to decreased protein levels, reducing the amount of nuclear mRNA and increasing the number of NPCs per nucleus [258].

Nuclear Envelope

Although the NE is not a component of the NPC itself, NPCs are embedded in the NE surrounding the nucleoplasm [55]. As such, defects to the NE also have pathological consequences, as with the ALS-associated VAPB mutant described above [232]. One significant class of NE-associated disorders is laminopathies, which are related to mutations in the proteins that comprise the filamentous network of lamins on the nuclear face of the inner nuclear membrane [273]. There are many laminopathies, including muscular dystrophy, neuropathies like Charcot-Marie-Tooth disease, diseases of premature aging (e.g., Hutchinson-Gilford progeria syndrome [HGPS]), and demyelination of the central nervous system [273]. Disease-associated lamin mutations can disrupt interactions between Nups and the NE [274–276], impair NCT [274], and lead to aberrant NPC distribution [277].

Another major source of NE-related dysfunction is caused by mutations to the LINC complex. LINC complexes connect the nuclear lamina to the cytoskeleton via inner and outer nuclear membrane proteins containing, respectively, SUN and KASH domains [278]. The LINC complex is critical for NPC distribution, with SUN1 playing an especially key role [279,280]. Indeed, mutations to SUN1 are associated with muscular dystrophy [281,282], and may modify the pathogenicity of laminopathies [283].

Intriguingly, in laminopathy models, ESCRT-III proteins are recruited to the NE by ALIX and CHMP7, underscoring the role of ESCRT-III in preserving NE and NPC integrity [284,285]. Moreover, recent work has shown that SUN1 contributes to CHMP7 nuclear accumulation in models of ALS, and reducing SUN1 expression prevents CHMP7 accumulation and subsequent pathological NPC injury [44]. Thus, the relationship between the proteins associated with the NE and NPC biology is an area that warrants further investigation.

Mutation vs. Variation

Disease-causing mutations have been identified in roughly half of human Nups, but there may be additional mutations that have not yet been described. Studies in which specific Nups are experimentally reduced suggest that mutations which lead to Nup loss-of-function would be detrimental. Indeed, NPC number, distribution, and function are impaired if levels of ELYS or Nup98 protein are reduced [286,287]. Additionally, knocking out Nup210 in mice reduces muscle regeneration after injury, and results in an increase in centrally nucleated muscle fibers [288]. Centrally nucleated fibers are a characteristic trait of muscle dystrophy, indicating that Nup210 is involved in muscular repair [288]. Other mouse studies show that deletion of Nup358 in motor neurons results in ALS pathology, including gross motor deficits and cellular evidence of disrupted NCT [289]. Thus, mutations that deplete Nup levels would likely be injurious.

Aside from bona fide mutations, it may also be the case that Nup coding variation is benign in some situations, and pathological in others. For example, the central channel of the NPC becomes constricted upon energy depletion [290], which can happen during neurodegenerative diseases in which mitochondrial activity is perturbed [291]. Aberrant NPC constriction may amplify modest Nup abnormalities, leading to NPC and NCT dysfunction. Additionally, stresses such as protein misfolding can result in NE budding [292], potentially impacting NPC structure by creating mechanical stress. It is well-established that mechanical stress can induce NE remodeling, and recurrent remodeling may reveal Nup defects [108,293–295]. Moreover, prolonged nuclear stress could inappropriately trigger NPC repair mechanisms, which may have deleterious consequences [44,46,108,109].

Therapeutic Approaches

The overwhelming evidence that NPC and NCT dysfunction plays a central role in neurodegenerative and other diseases makes therapeutically targeting the NPC a provocative approach. However, given the essential relationship between NPC functionality and cell survival, one must be cautious when targeting this complex. Many disease-causing Nup variants exhibit loss-of-function phenotypes due to decreased protein levels and impaired interaction with other proteins within the NPC (Table 1). Additionally, even in the absence of mutation, depletion of Nups from the NPC is pathological [41,44–47]. Thus, one potential avenue for addressing identified pathological Nup mutants would be to use adeno-associated viral (AAV)-mediated delivery of the wild-type Nup sequence [296–299]. Recent innovations in AAV-based therapeutics have made the prospect of using this technique a tractable option for diseases affecting the nervous system [299–302]. However, researchers delivering Nup sequences via AAV would need to monitor for any side effects related to overexpression of the affected Nup, as high levels of individual Nups can be damaging [87,88,92,303,304] and cell-specific targeting might be necessary. Additionally, many individual Nups are large, spanning over 1,000 amino acids [55], which may make packaging these sequences into AAVs a non-trivial endeavor [305,306]. Conversely, if a Nup mutant shows a gain-of-function phenotype, as with the carcinogenic overexpression of Nups [307], antisense oligonucleotide (ASO) or small interfering RNA (siRNA) methods can be used to reduce the expression of toxic Nups [308].

Previous studies have shown that one approach to address loss of Nups from the NPC may be to artificially express specific Nups [10,41]. However, as the stoichiometry of Nups is critical for NPC functionality [53,59,309], gene therapy approaches targeting Nups may not always be effective. As an alternative, efforts to resolve the aggregates into which Nups are sequestered could liberate Nups, restoring their functionality [310–313]. Disaggregation can be achieved directly by reducing levels of aggregation-prone molecules, such as TDP-43 [314,315], FUS [200], and SOD1 [316,317]. Aggregation can also be mitigated indirectly by enhancing the activity of endogenous chaperones, such as NTRs [35,43,48,310,318–320].

Another therapeutic option may focus on enhancing the stability of Nups themselves. Nups are stabilized by the post-translational modification, O-linked β-N-acetylglucosamine (O-GlcNAc) [321–324]. Indeed, when Nups are de-O-GlcNAcylated, Nup protein levels throughout the NPC decrease [321,323]. Furthermore, when Nups are not properly O-GlcNAcylated, the selectivity barrier of the NPC is impaired, leading to leaky nuclear import [323]. In mouse models of HD, Nup O-GlcNAc levels are significantly lower in cortical cells, and treating primary cortical neurons expressing pathogenic polyQ Htt with an O-GlcNAcase (OGA) inhibitor to reduce O-GlcNAc removal improves cell viability and reverses NCT defects [22]. Thus, whether the NPC is aberrantly O-GlcNAcylated in other diseases will be an informative line of inquiry, and therapeutics that alter O-GlcNAcylation of the NPC could hold promise. Researchers have also recently achieved high-resolution structures for the NPC [55,59–61,74], and these structures can be used to model coding variation or to perform small-molecule docking simulations to generate therapeutic compounds to address structural vulnerabilities [325,326].

Given the emerging data on a role for ESCRT-III proteins contributing to NPC/NCT defects in disease, regulation of ESCRT-III proteins might be a possible therapeutic approach. However, the directionality of such interventions will depend on many factors. For example, in several settings, decreasing levels of the ESCRT-III proteins that monitor Nup integrity, as well as the related ATPase, Vps4, has been shown to be highly protective. Normally, Vps4 and ESCRT-III proteins transiently survey the NPC for quality control purposes [1,108,109]. In both fALS and sALS, however, Vps4 and the ESCRT-III protein, CHMP7, become enriched at the nucleus [44,327]. Moreover, in the case of CHMP7, its nuclear accumulation precedes the subsequent loss of Nups from the NPC [44], and decreasing levels of either Vps4 or CHMP7 mitigates

pathological phenotypes [44,46]. Studies employing siRNA, ASOs, or Trim21-driven protein degradation to reduce CHMP7 levels were all shown to repair NCT defects and prevent downstream cellular stress and cytotoxicity in studies performed using large numbers of patient neuronal cell lines [44,223]. These results suggest that the ESCRT-III pathway is hyperactively modifying the NPC in disease, leading to Nup mislocalization or degradation, and that dampening this activity could be beneficial. Why the activation of this pathway occurs in C9orf72 and sporadic ALS is unclear, and identifying the instigating factor or factors that prompt ESCRT-III recruitment to the NPC will be the target of future investigations. Understanding what elevates the ESCRT-III pathway to this vigilant state will be critical for leveraging its members as therapeutic agents.

Mutations to another ESCRT-III protein, CHMP2B, have also been linked to ALS/FTD [328–334]. In cell culture, animal models, and patient tissue, expression of CHMP2B mutants results in the accumulation of p62 inclusions, enlarged endosomes, stalled endolysosomes, and lysosomal dysfunction [331,335–338]. Moreover, mice expressing disease-associated CHMP2B mutants show reduced survival, whereas CHMP2B-null mice do not have any survival defects, suggesting a gain-of-function phenotype [336]. Indeed, although CHMP2B does not localize to the nucleus in sALS patient-derived cells [327], knockdown of CHMP2B restores Nup levels and prevents cell death in a *Drosophila* model of C9-ALS/FTD [46].

By contrast, overexpression of ESCRT-III proteins may be protective in other disease contexts, such as tauopathies. For example, to find protein modifiers of tau self-assembly, researchers employed a cell-based screen and found that increasing CHMP7, LEMD2, and LEMD3 levels reduced tau aggregation [339]. LEMD2 and LEMD3 are two NE proteins that interact with CHMP7 [108,340], suggesting that enhanced ESCRT-III surveillance activity can also be beneficial [339].

The ESCRT-III pathway may also be a therapeutic target in PD. Recently, by screening a peptide library to find candidate molecules that prevent α-synuclein oligomerization, researchers discovered a novel interaction between α-synuclein and CHMP2B [341]. They showed that α-synuclein binds CHMP2B, leading to endolysosomal dysfunction [341]. By abrogating this interaction, the researchers were able to reduce α-synuclein levels, restore autophagic degradation, and preserve cell viability [341]. In fact, there are several links between autolysosomal dysfunction and NCT pathology. In studies of a polyQ ataxia, dentatorubral-pallidoluysian atrophy (DRPLA), autophagic stalling is associated with nuclear accumulation of p62, cytoplasmic accumulation of LaminB1, and NE ruffling [342]. As autophagy is involved in maintaining proteostasis [343], inadequate autophagic flux may exacerbate NCT dysfunction by enabling the accumulation of harmful materials.

The pathology of neurodegenerative disease compromises many biological processes, and thus it may be productive to investigate ancillary pathways, such as autophagy, to address issues in NPC homeostasis. To this end, several groups have studied the cytoplasmic mislocalization of the autophagic transcription factor, TFEB [94,116,344,345]. TFEB regulates the expression of lysosomal proteins, and studies in brain tissue from AD and ALS patients showed that this protein was mislocalized in disease [116], indicating convergence between defects in NCT and autophagy. Further experiments performed in non-human C9-ALS/FTD models demonstrated that expression of the G_4C_2 HRE leads to TFEB mislocalization, thus impairing lysosomal function [344].

In the same year these findings were published, a separate group also working with C9-ALS/FTD models found that expression of the autophagy-related molecular chaperone, sigma non-opioid intracellular receptor 1 (Sigmar1) stabilizes cytoplasmic filament Nups, Nup358 and Nup214; central channel Nup, Nup62; and basket Nup, Nup50, upon $(G_4C_2)_{31}$ RNA expression, corresponding with reduced toxicity [346]. Additional studies revealed that Sigmar1 localizes to the nuclear pore, where it associates with the transmembrane Nup, POM121, and the nuclear import receptor responsible for importing TFEB, Kapβ1 [94,346]. Transfecting motor neuron-like NSC-34 cells with $(G_4C_2)_{31}$ RNA alone led to dissociation of Sigmar1 from POM121 and Kapβ1, reducing POM121

stability [94]. However, the overexpression of Sigmar1 prevented the G_4C_2-related depletion of POM121 protein levels, suggesting Sigmar1 chaperones POM121 [94]. Additionally, Sigmar1 overexpression restores Kapβ1-mediated nuclear import of TFEB, promoting autophagy [94]. Moreover, two Sigmar1 agonists, pridopidine and fluvoxamine, each promote POM121 expression and restore TFEB nuclear localization, and pridopidine protects against cell death [94,345]. Encouragingly, pridopidine has also been identified to have therapeutic potential in AD [347], PD [348], and HD [349]. Whether Sigmar1 agonists function via the NPC and NCT across neurodegenerative diseases is an evocative hypothesis and calls for further mechanistic studies.

Given the centrality of the NPC to biology, there are a number of factors that must be considered when designing and applying any therapeutic strategy. First, one must identify the cell type(s) affected in disease. For example, a patient with basal ganglion pathology (e.g., bilateral striatal necrosis, HD) may require a different treatment than someone suffering from diseases involving motor neurons (e.g., ALS) or disorders of the heart or kidney. Second, therapeutic approaches must target the appropriate biological mechanism. Indeed, although there is convergence of pathological phenotype among disorders related to the NPC, the underlying biological maleficence can be highly disparate. In ALS, for example, addressing the NPC injury caused by a PFN1 mutation (i.e., nuclear injury caused by cytoskeletal destabilization [39]) may require an alternative approach than the NPC injury that occurs in C9-ALS and sporadic ALS (e.g., sequestration of Nups and NCT factors [42,47,138,175,176,210], ESCRT-III hyperactivity [44,327]).

Conclusions and Open Questions

Proper delineation of nuclear and cytoplasmic environments within the cell is critical for eukaryotic life, and its disruption is deadly. Here, we provide a summary of what is known about the architecture of the NPC and its roles in cell functioning, and outline the unique challenges faced by neurons in maintaining NPC and NCT integrity. We also describe what happens when neurons succumb to these challenges. Namely, we detail the existing evidence for NPC and NCT defects in neurodegenerative diseases and enumerate several Nup mutations associated with disease. Finally, we provide a discussion of potential modalities for therapeutically targeting the NPC. Still, several open questions remain with respect to the NPC and NCT in disease. First is the primordial question of which occurs first: NPC injury or defective NCT? That is, do insults to the NPC instigate NCT deficits, or does the mislocalization of aggregation-prone proteins lead to the sequestration of vulnerable Nups, destabilizing the NPC? Alternatively, are both events happening simultaneously in response to a shared stressor? To address the defects observed in disease, it will be essential to understand the order of events, and whether this pathological sequence varies based on genetic or environmental factors.

To that end, another unresolved question is: what is the best way to model and study the human NPC? Because Nup turnover and quality control mechanisms differ between dividing and non-dividing cells, one must carefully consider the hypothesis being tested when selecting a cellular system. Additionally, the number and composition of NPCs can vary across cell type [309], adding another layer of complexity to understanding these structures. Furthermore, although the global structure of the NPC is conserved across eukaryotes, there are significant differences in both sequence and number of subunits across species [55]. Even between mammals there can be substantial sequence variation. For example, between the human and mouse sequences of the Nup214 protein, there is only 76.5% identity [263,350]. POM121 and Nup50 protein sequences also diverge substantially between humans and mice, with 67.3% and 77.9% shared identity, respectively [263,350]. Compared to an average shared identity of ~ 85% between mouse and human protein sequences [351], Nups can be quite variable. And, these variations may exert a multiplicative influence, as each Nup is present in multiple copies, with some Nups appearing up to 32 times in a single NPC [55,309]. These differences may make rodent models poor representations of the of the human disease cell biology. Therefore, newer human cell-based models such as patient derived iPSC lines or 2D and 3D organoid approaches [352–354] may be more suitable

for understanding the dysfunction of NPC and NCT in human neurological diseases.

In summary, NPC fitness and reliable NCT are essential for life. Numerous diseases develop when these processes are compromised, including many currently incurable neurodegenerative disorders. Targeting the NPC is therefore a promising approach for understanding and addressing the causes and consequences of disease.

Acknowledgments

We thank Muzi (Andrew) Du and S. Can Akerman for their feedback on this review.

Disclosure statement

JDR has pending patents on 1) increasing/restoring expression of POM121 for mitigation of NPC injury and TDP-43 dysfunction in neurodegeneration, 2) CHMP7 therapy (ASO, protein degradation, siRNA) in ALS, dementia (AD/FTD), neurodegeneration, and other neurological disorders, and 3) other relevant pending patents regarding nuclear biology and neurodegeneration.

Funding

This work was supported by: Answer ALS (JDR), NIH NIA R01 RF1AG062171 (JDR), Chan Zuckerberg Foundation (JDR), NIH NINDS 2P01NS084974, R01 NS122236 (JDR) R35 NS132179 (JDR), ALS Association (JDR), Muscular Dystrophy Association (JDR), Virginia Gentlemen Foundation (JDR), US Dept of Defense HT94252310136 (JDR), and F Prime (JDR).

Author contributions

CMF and JDR prepared the manuscript concept, outline, and draft. All authors reviewed and edited the manuscript.

ORCID

Charlotte M. Fare http://orcid.org/0000-0003-0394-6435
Jeffrey D. Rothstein http://orcid.org/0000-0003-2001-8470

References

[1] Webster BM, Lusk CP. Border safety: quality control at the nuclear envelope. Trends Cell Biol. 2016;26:29–39. doi:10.1016/j.tcb.2015.08.002

[2] Robijns J, Houthaeve G, Braeckmans K, et al. Loss of nuclear envelope integrity in aging and disease. Int Rev Cell Mol Biol. 2018;336:205–222.

[3] Lindenboim L, Zohar H, Worman HJ, et al. The nuclear envelope: target and mediator of the apoptotic process. Cell Death Discov. 2020;6(1):29. doi: 10.1038/s41420-020-0256-5

[4] Gauthier BR, Comaills V. Nuclear envelope integrity in health and disease: consequences on genome instability and inflammation. IJMS. 2021;22(14):7281. doi: 10.3390/ijms22147281

[5] Metuzals J, Robitaille Y, Houghton S, et al. Paired helical filaments and the cytoplasmic-nuclear interface in Alzheimer's disease. J Neurocytol. 1988;17(6):827–833. doi: 10.1007/BF01216709

[6] Lee HG, Ueda M, Miyamoto Y, et al. Aberrant localization of importin α1 in hippocampal neurons in alzheimer disease. Brain Res. 2006;1124(1):1–4. doi: 10.1016/j.brainres.2006.09.084

[7] Sheffield LG, Miskiewicz HB, Tannenbaum LB, et al. Nuclear pore complex proteins in Alzheimer disease. J Neuropathol Exp Neurol. 2006;65(1):45–54. doi: 10.1097/01.jnen.0000195939.40410.08

[8] Mastroeni D, Chouliaras L, Grover A, et al. Reduced RAN expression and disrupted transport between cytoplasm and nucleus; a key event in Alzheimer's disease pathophysiology. *PLoS One*. 2013;8(1):e53349. doi: 10.1371/journal.pone.0053349

[9] Eftekharzadeh B, Daigle JG, Kapinos LE, et al. Tau Protein Disrupts Nucleocytoplasmic Transport in Alzheimer's Disease. Neuron. 2018;99(5):925–940 e927. doi: 10.1016/j.neuron.2018.07.039

[10] Leone L, Colussi C, Gironi K, et al. Altered Nup153 expression impairs the function of cultured hippocampal neural stem cells isolated from a mouse Model of Alzheimer's disease. Mol Neurobiol. 2019;56(8):5934–5949. doi: 10.1007/s12035-018-1466-1

[11] Diez L, Kapinos LE, Hochmair J, et al. Phosphorylation but not oligomerization drives the accumulation of Tau with Nucleoporin Nup98. Int J Mol Sci. 2022;23(7):3495. doi: 10.3390/ijms23073495

[12] Dickson JR, Frosch MP, Hyman BT. Altered localization of nucleoporin 98 in primary tauopathies. Brain Commun. 2023;5(1):fcac334. doi: 10.1093/braincomms/fcac334

[13] Donnaloja F, Limonta E, Mancosu C, et al. Unravelling the mechanotransduction pathways in Alzheimer's disease. J Biol Eng. 2023;17(1):22. doi: 10.1186/s13036-023-00336-w

[14] Nag N, Tripathi T. Tau–FG-nucleoporin98 interaction and impaired nucleocytoplasmic transport in Alzheimer's disease. Brief Funct Genomics. 2023;22(2):161–167. doi: 10.1093/bfgp/elac022

[15] Um JW, Min DS, Rhim H, et al. Parkin ubiquitinates and promotes the degradation of RanBP2. J Biol Chem. 2006;281(6):3595–3603. doi: 10.1074/jbc.M504994200

[16] Alegre-Abarrategui J, Ansorge O, Esiri M, et al. LRRK2 is a component of granular alpha-synuclein pathology in the brainstem of Parkinson's disease. Neuropathol

Appl Neurobiol. 2008;34:272–283. doi:10.1111/j.1365-2990.2007.00888.x

[17] Kokoulina P, Rohn TT. Caspase-cleaved transactivation response DNA-binding protein 43 in Parkinson's disease and dementia with Lewy bodies. Neurodegener Dis. 2010;7(4):243–250. doi: 10.1159/000287952

[18] Liu GH, Qu J, Suzuki K, et al. Progressive degeneration of human neural stem cells caused by pathogenic LRRK2. Nature. 2012;491(7425):603–607. doi: 10.1038/nature11557

[19] Shani V, Safory H, Szargel R, et al. Physiological and pathological roles of LRRK2 in the nuclear envelope integrity. Hum Mol Genet. 2019;28:3982–3996. doi: 10.1093/hmg/ddz245

[20] Chen X, Xie C, Tian W, et al. Parkinson's disease-related Leucine-rich repeat kinase 2 modulates nuclear morphology and genomic stability in striatal projection neurons during aging. Mol Neurodegener. 2020;15(1):12. doi: 10.1186/s13024-020-00360-0

[21] Gasset-Rosa F, Chillon-Marinas C, Goginashvili A, et al. Polyglutamine-Expanded Huntingtin Exacerbates Age-Related Disruption of Nuclear Integrity and Nucleocytoplasmic Transport. Neuron. 2017;94(1):48–57.e44. doi: 10.1016/j.neuron.2017.03.027

[22] Grima JC, Daigle JG, Arbez N, et al. Mutant huntingtin disrupts the nuclear pore complex. Neuron. 2017;94(1):93–107 e106. doi: 10.1016/j.neuron.2017.03.023

[23] Lange J, Wood-Kaczmar A, Ali A, et al. Mislocalization of nucleocytoplasmic transport proteins in human Huntington's disease PSC-Derived striatal neurons. Front Cell Neurosci. 2021;15:742763. doi: 10.3389/fncel.2021.742763

[24] Pesiridis GS, Lee VM, Trojanowski JQ. Mutations in TDP-43 link glycine-rich domain functions to amyotrophic lateral sclerosis. Hum Mol Genet. 2009;18(R2):R156–R162. doi: 10.1093/hmg/ddp303

[25] DeJesus-Hernandez M, Kocerha J, Finch N, et al. De Novo truncating FUS gene mutation as a cause of sporadic amyotrophic lateral sclerosis. Hum Mutat. 2010;31(5):E1377–E1389. doi: 10.1002/humu.21241

[26] Dormann D, Rodde R, Edbauer D, et al. ALS-associated fused in sarcoma (FUS) mutations disrupt Transportin-mediated nuclear import. EMBO J. 2010;29(16):2841–2857. doi: 10.1038/emboj.2010.143

[27] Ito D, Seki M, Tsunoda Y, et al. Nuclear transport impairment of amyotrophic lateral sclerosis-linked mutations in FUS/TLS. Ann Neurol. 2011;69(1):152–162. doi: 10.1002/ana.22246

[28] Niu C, Zhang J, Gao F, et al. FUS-NLS/Transportin 1 complex structure provides insights into the nuclear targeting mechanism of FUS and the implications in ALS. PLoS One. 2012;7(10):e47056. doi: 10.1371/journal.pone.0047056

[29] Zhang ZC, Chook YM. Structural and energetic basis of ALS-causing mutations in the atypical proline–tyrosine nuclear localization signal of the fused in sarcoma protein (FUS). Proc Natl Acad Sci, USA. 2012;109(30):12017–12021. doi: 10.1073/pnas.1207247109

[30] Baron DM, Kaushansky LJ, Ward CL, et al. Amyotrophic lateral sclerosis-linked FUS/TLS alters stress granule assembly and dynamics. Mol Neurodegener. 2013;8(1):30. doi: 10.1186/1750-1326-8-30

[31] Kim HJ, Kim NC, Wang Y-D, et al. Mutations in prion-like domains in hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy and ALS. Nature. 2013;495(7442):467–473. doi: 10.1038/nature11922

[32] Vance C, Scotter EL, Nishimura AL, et al. ALS mutant FUS disrupts nuclear localization and sequesters wild-type FUS within cytoplasmic stress granules. Hum Mol Genet. 2013;22(13):2676–2688. doi: 10.1093/hmg/ddt117

[33] Zhang K, Donnelly CJ, Haeusler AR, et al. The C9orf72 repeat expansion disrupts nucleocytoplasmic transport. Nature. 2015;525(7567):56–61. doi: 10.1038/nature14973

[34] Chou CC, Zhang Y, Umoh ME, et al. TDP-43 pathology disrupts nuclear pore complexes and nucleocytoplasmic transport in ALS/FTD. Nat Neurosci. 2018;21(2):228–239. doi: 10.1038/s41593-017-0047-3

[35] Guo L, Kim HJ, Wang H, et al. Nuclear-import receptors reverse aberrant phase transitions of RNA-Binding proteins with prion-like domains. Cell. 2018;173(3):677–692 e620. doi: 10.1016/j.cell.2018.03.002

[36] Zhang K, Daigle JG, Cunningham KM, et al. Stress granule assembly disrupts nucleocytoplasmic transport. Cell. 2018;173(4):958–971 e917. doi: 10.1016/j.cell.2018.03.025

[37] Aizawa H, Yamashita T, Kato H, et al. Impaired nucleoporins are present in sporadic amyotrophic lateral sclerosis motor neurons that exhibit mislocalization of the 43-kDa TAR DNA-Binding protein. J Clin Neurol. 2019;15(1):62–67. doi: 10.3988/jcn.2019.15.1.62

[38] Gasset-Rosa F, Lu S, Yu H, et al. Cytoplasmic TDP-43 De-mixing Independent of stress granules drives inhibition of nuclear import, loss of nuclear TDP-43, and cell death. Neuron. 2019;102(2):339–357.e7. doi: 10.1016/j.neuron.2019.02.038

[39] Giampetruzzi A, Danielson EW, Gumina V, et al. Modulation of actin polymerization affects nucleocytoplasmic transport in multiple forms of amyotrophic lateral sclerosis. Nat Commun. 2019;10(1):3827. doi: 10.1038/s41467-019-11837-y

[40] Tyzack GE, Luisier R, Taha DM, et al. Widespread FUS mislocalization is a molecular hallmark of amyotrophic lateral sclerosis. Brain. 2019;142(9):2572–2580. doi: 10.1093/brain/awz217

[41] Coyne AN, Zaepfel BL, Hayes L, et al. G4C2 repeat RNA initiates a POM121-mediated reduction in specific nucleoporins in C9orf72 ALS/FTD. Neuron. 2020;107(6):1124–1140 e1111. doi: 10.1016/j.neuron.2020.06.027

[42] Hayes LR, Duan L, Bowen K, et al. C9orf72 arginine-rich dipeptide repeat proteins disrupt karyopherin-mediated nuclear import. Elife. 2020;9. doi: 10.7554/eLife.51685

[43] Hutten S, Usluer S, Bourgeois B, et al. Nuclear import receptors directly bind to Arginine-Rich Dipeptide repeat proteins and suppress their pathological interactions. Cell Rep. 2020;33(12):108538. doi: 10.1016/j.celrep.2020.108538

[44] Coyne AN, Baskerville V, Zaepfel BL, et al. Nuclear accumulation of CHMP7 initiates nuclear pore complex injury and subsequent TDP-43 dysfunction in sporadic and familial ALS. Sci Transl Med. 2021;13(604). doi: 10.1126/scitranslmed.abe1923

[45] Lin YC, Kumar MS, Ramesh N, et al. Interactions between ALS-linked FUS and nucleoporins are associated with defects in the nucleocytoplasmic transport pathway. Nat Neurosci. 2021;24(8):1077–1088. doi: 10.1038/s41593-021-00859-9

[46] Dubey SK, Maulding K, Sung H, et al. Nucleoporins are degraded via upregulation of ESCRT-III/Vps4 complex in Drosophila models of C9-ALS/FTD. Cell Rep. 2022;40(12):111379. doi: 10.1016/j.celrep.2022.111379

[47] Gleixner AM, Verdone BM, Otte CG, et al. NUP62 localizes to ALS/FTLD pathological assemblies and contributes to TDP-43 insolubility. Nat Commun. 2022;13(1):3380. doi: 10.1038/s41467-022-31098-6

[48] Khalil B, Chhangani D, Wren MC, et al. Nuclear import receptors are recruited by FG-nucleoporins to rescue hallmarks of TDP-43 proteinopathy. Mol Neurodegener. 2022;17(1):80. doi: 10.1186/s13024-022-00585-1

[49] Vanneste J, Vercruysse T, Boeynaems S, et al. Cellular stress induces nucleocytoplasmic transport deficits independent of stress granules. Biomedicines. 2022;10(5):1057. doi: 10.3390/biomedicines10051057

[50] Spead O, Zaepfel BL, Rothstein JD. Nuclear Pore Dysfunction in Neurodegeneration. Neurotherapeutics. 2022;19(4):1050–1060. doi: 10.1007/s13311-022-01293-w

[51] Anderson EN, Morera AA, Kour S, et al. Traumatic injury compromises nucleocytoplasmic transport and leads to TDP-43 pathology. Elife. 2021;10. doi: 10.7554/eLife.67587

[52] D'Angelo MA, Raices M, Panowski SH, et al. Age-dependent deterioration of nuclear pore complexes causes a loss of nuclear integrity in postmitotic cells. Cell. 2009;136(2):284–295. doi: 10.1016/j.cell.2008.11.037

[53] Rempel IL, Crane MM, Thaller DJ, et al. Age-dependent deterioration of nuclear pore assembly in mitotic cells decreases transport dynamics. Elife. 2019;8. doi: 10.7554/eLife.48186

[54] Park JH, Ryu SJ, Kim BJ, et al. Disruption of nucleocytoplasmic trafficking as a cellular senescence driver. Exp Mol Med. 2021;53(6):1092–1108. doi: 10.1038/s12276-021-00643-6

[55] Lin DH, Hoelz A. The structure of the nuclear pore complex (an update). Annu Rev Biochem. 2019;88(1):725–783. doi: 10.1146/annurev-biochem-062917-011901

[56] Maul GG, Deaven L. Quantitative determination of nuclear pore complexes in cycling cells with differing DNA content. J Cell Bio. 1977;73(3):748–760. doi: 10.1083/jcb.73.3.748

[57] Garcia-Segura LM, Lafarga M, Berciano MT, et al. Distribution of nuclear pores and chromatin organization in neurons and glial cells of the rat cerebellar cortex. J Comp Neurol. 1989;290(3):440–450. doi: 10.1002/cne.902900311

[58] Jamali T, Jamali Y, Mehrbod M, et al. Nuclear pore complex: biochemistry and biophysics of nucleocytoplasmic transport in health and disease. Int Rev Cell Mol Biol. 2011;287:233–286.

[59] Bley CJ, Nie S, Mobbs GW, et al. Architecture of the cytoplasmic face of the nuclear pore. Science. 2022;376(6598):eabm9129. doi: 10.1126/science.abm9129

[60] Fontana P, Dong Y, Pi X, et al. Structure of cytoplasmic ring of nuclear pore complex by integrative cryo-EM and AlphaFold. Science. 2022;376(6598):eabm9326. doi: 10.1126/science.abm9326

[61] Petrovic S, Samanta D, Perriches T, et al. Architecture of the linker-scaffold in the nuclear pore. Science. 2022;376(6598):eabm9798. doi: 10.1126/science.abm9798

[62] Lutzmann M, Kunze R, Buerer A, et al. Modular self-assembly of a Y-shaped multiprotein complex from seven nucleoporins. EMBO J. 2002;21(3):387–397. doi: 10.1093/emboj/21.3.387

[63] Frey S, Gorlich D. A saturated FG-repeat hydrogel can reproduce the permeability properties of nuclear pore complexes. Cell. 2007;130(3):512–523. doi: 10.1016/j.cell.2007.06.024

[64] Patel SS, Belmont BJ, Sante JM, et al. Natively unfolded nucleoporins gate protein diffusion across the nuclear pore complex. Cell. 2007;129(1):83–96. doi: 10.1016/j.cell.2007.01.044

[65] Schmidt HB, Görlich D. Nup98 FG domains from diverse species spontaneously phase-separate into particles with nuclear pore-like permselectivity. Elife. 2015;4. doi: 10.7554/eLife.04251

[66] Li C, Goryaynov A, Yang W. The selective permeability barrier in the nuclear pore complex. Nucleus. 2016;7(5):430–446. doi: 10.1080/19491034.2016.1238997

[67] Ng SC, Biswas A, Huyton T, et al. Barrier properties of Nup98 FG phases ruled by FG motif identity and inter-FG spacer length. Nat Commun. 2023;14(1):747. doi: 10.1038/s41467-023-36331-4

[68] Frey S, Richter RP, Gorlich D. FG-rich repeats of nuclear pore proteins form a three-dimensional meshwork with hydrogel-like properties. Science. 2006;314(5800):815–817. doi: 10.1126/science.1132516

[69] Hulsmann BB, Labokha AA, Gorlich D. The permeability of reconstituted nuclear pores provides direct evidence for the selective phase model. Cell. 2012;150(4):738–751. doi: 10.1016/j.cell.2012.07.019

[70] Celetti G, Paci G, Caria J, et al. The liquid state of FG-nucleoporins mimics permeability barrier properties of nuclear pore complexes. J Cell Bio. 2020;219(1). doi: 10.1083/jcb.201907157

[71] Denning DP, Patel SS, Uversky V, et al. Disorder in the nuclear pore complex: the FG repeat regions of nucleoporins are natively unfolded. *Proc Natl Acad Sci, USA*. 2003;100(5):2450–2455. doi: 10.1073/pnas.0437902100

[72] Yu M, Heidari M, Mikhaleva S, et al. Visualizing the disordered nuclear transport machinery in situ. Nature. 2023;617(7959):162–169. doi: 10.1038/s41586-023-05990-0

[73] Kalita J, Kapinos LE, Zheng T, et al. Karyopherin enrichment and compensation fortifies the nuclear pore complex against nucleocytoplasmic leakage. J Cell Bio. 2022;221(3). doi: 10.1083/jcb.202108107

[74] Ibanez de Opakua A, Geraets JA, Frieg B, et al. Molecular interactions of FG nucleoporin repeats at high resolution. Nat Chem. 2022;14(11):1278–1285. doi: 10.1038/s41557-022-01035-7

[75] Kapinos LE, Huang B, Rencurel C, et al. Karyopherins regulate nuclear pore complex barrier and transport function. J Cell Bio. 2017;216(11):3609–3624. doi: 10.1083/jcb.201702092

[76] Wälde S, Thakar K, Hutten S, et al. The nucleoporin Nup358/RanBP2 promotes nuclear import in a cargo- and transport receptor-specific manner. Traffic. 2012;13(2):218–233. doi: 10.1111/j.1600-0854.2011.01302.x

[77] Lemaître C, Fischer B, Kalousi A, et al. The nucleoporin 153, a novel factor in double-strand break repair and DNA damage response. Oncogene. 2012;31(45):4803–4809. doi: 10.1038/onc.2011.638

[78] Moudry P, Lukas C, Macurek L, et al. Nucleoporin NUP153 guards genome integrity by promoting nuclear import of 53BP1. Cell Death Differ. 2012;19(5):798–807. doi: 10.1038/cdd.2011.150

[79] Waldmann I, Spillner C, Kehlenbach RH. The nucleoporin-like protein NLP1 (hCG1) promotes CRM1-dependent nuclear protein export. J Cell Sci. 2012;125(1):144–154. doi: 10.1242/jcs.090316

[80] Gozalo A, Duke A, Lan Y, et al. Core components of the nuclear pore bind distinct states of chromatin and contribute to polycomb repression. Mol Cell. 2020;77(1):67–81.e67. doi: 10.1016/j.molcel.2019.10.017

[81] Kadota S, Ou J, Shi Y, et al. Nucleoporin 153 links nuclear pore complex to chromatin architecture by mediating CTCF and cohesin binding. Nat Commun. 2020;11(1):2606. doi: 10.1038/s41467-020-16394-3

[82] Ibarra A, Benner C, Tyagi S, et al. Nucleoporin-mediated regulation of cell identity genes. Genes Dev. 2016;30(20):2253–2258. doi: 10.1101/gad.287417.116

[83] Labade AS, Karmodiya K, Sengupta K. HOXA repression is mediated by nucleoporin Nup93 assisted by its interactors Nup188 and Nup205. *Epigenet Chromatin*. 2016;9(1):54. doi: 10.1186/s13072-016-0106-0

[84] Zhu X, Qi C, Wang R, et al. Acute depletion of human core nucleoporin reveals direct roles in transcription control but dispensability for 3D genome organization. Cell Rep. 2022;41(5):111576. doi: 10.1016/j.celrep.2022.111576

[85] Hubert T, Vandekerckhove J, Gettemans J. Exo70-mediated recruitment of nucleoporin Nup62 at the leading edge of migrating cells is required for cell migration. Traffic. 2009;10(9):1257–1271. doi: 10.1111/j.1600-0854.2009.00940.x

[86] Joseph J, Dasso M. The nucleoporin Nup358 associates with and regulates interphase microtubules. *FEBS Lett*. 2008;582(2):190–196. doi: 10.1016/j.febslet.2007.11.087

[87] Makise M, Uchimura R, Higashi K, et al. Overexpression of the nucleoporin Nup88 stimulates migration and invasion of HeLa cells. Histochem Cell Biol. 2021;156(5):409–421. doi: 10.1007/s00418-021-02020-w

[88] Nataraj NB, Noronha A, Lee JS, et al. Nucleoporin-93 reveals a common feature of aggressive breast cancers: robust nucleocytoplasmic transport of transcription factors. Cell Rep. 2022;38(8):110418. doi: 10.1016/j.celrep.2022.110418

[89] Kirsh O, Seeler JS, Pichler A, et al. The SUMO E3 ligase RanBP2 promotes modification of the HDAC4 deacetylase. EMBO J. 2002;21(11):2682–2691. doi: 10.1093/emboj/21.11.2682

[90] Gloerich M, Vliem MJ, Prummel E, et al. The nucleoporin RanBP2 tethers the cAMP effector Epac1 and inhibits its catalytic activity. J Cell Bio. 2011;193(6):1009–1020. doi: 10.1083/jcb.201011126

[91] Faria AM, Levay A, Wang Y, et al. The nucleoporin Nup96 is required for proper expression of interferon-regulated proteins and functions. Immunity. 2006;24(3):295–304. doi: 10.1016/j.immuni.2006.01.014

[92] Monwan W, Kawasaki T, Hasan MZ, et al. Identification of nucleoporin 93 (Nup93) that mediates antiviral innate immune responses. Biochem Biophys Res Commun. 2020;521(4):1077–1082. doi: 10.1016/j.bbrc.2019.11.035

[93] Funasaka T, Tsuka E, Wong RW. Regulation of autophagy by nucleoporin Tpr. Sci Rep. 2012;2(1):878. doi: 10.1038/srep00878

[94] Wang SM, Wu H-E, Yasui Y, et al. Nucleoporin POM121 signals TFEB-mediated autophagy via activation of SIGMAR1/sigma-1 receptor chaperone by pridopidine. Autophagy. 2023;19(1):126–151. doi: 10.1080/15548627.2022.2063003

[95] Chou YY, Upadhyayula S, Houser J, et al. Inherited nuclear pore substructures template post-mitotic pore assembly. Dev Cell. 2021;56(12):1786–1803.e1789. doi: 10.1016/j.devcel.2021.05.015

[96] Kutay U, Jühlen R, Antonin W. Mitotic disassembly and reassembly of nuclear pore complexes. Trends Cell Biol. 2021;31(12):1019–1033. doi: 10.1016/j.tcb.2021.06.011

[97] Otsuka S, Tempkin JOB, Zhang W, et al. A quantitative map of nuclear pore assembly reveals two distinct mechanisms. Nature. 2023;613(7944):575–581. doi: 10.1038/s41586-022-05528-w

[98] Kaganovich D, Kopito R, Frydman J. Misfolded proteins partition between two distinct quality control compartments. Nature. 2008;454(7208):1088–1095. doi: 10.1038/nature07195

[99] Miller SB, Ho C-T, Winkler J, et al. Compartment-specific aggregases direct distinct nuclear and cytoplasmic aggregate deposition. EMBO J. 2015;34(6):778–797. doi: 10.15252/embj.201489524

[100] Koch BA, Staley E, Jin H, et al. The ESCRT-III complex is required for nuclear pore complex sequestration and regulates gamete replicative lifespan in budding yeast meiosis. Nucleus. 2020;11(1):219–236. doi: 10.1080/19491034.2020.1812872

[101] Rujano MA, Bosveld F, Salomons FA, et al. Polarised asymmetric inheritance of accumulated protein damage in higher eukaryotes. PLoS Biol. 2006;4(12):e417. doi: 10.1371/journal.pbio.0040417

[102] Toyama BH, Arrojo e Drigo R, Lev-Ram V, et al. Visualization of long-lived proteins reveals age mosaicism within nuclei of postmitotic cells. J Cell Bio. 2019;218(2):433–444. doi: 10.1083/jcb.201809123

[103] Dultz E, Wojtynek M, Medalia O, et al. The nuclear pore complex: birth, life, and death of a cellular behemoth. Cells. 2022;11(9):1456. doi: 10.3390/cells11091456

[104] Kuiper EFE, Gallardo P, Bergsma T, et al. The chaperone DNAJB6 surveils FG-nucleoporins and is required for interphase nuclear pore complex biogenesis. Nat Cell Biol. 2022;24(11):1584–1594. doi: 10.1038/s41556-022-01010-x

[105] Goodchild RE, Kim CE, Dauer WT. Loss of the dystonia-associated protein torsinA selectively disrupts the neuronal nuclear envelope. Neuron. 2005;48(6):923–932. doi: 10.1016/j.neuron.2005.11.010

[106] Rampello AJ, Laudermilch E, Vishnoi N, et al. Torsin ATPase deficiency leads to defects in nuclear pore biogenesis and sequestration of MLF2. J Cell Bio. 2020;219(6). doi: 10.1083/jcb.201910185

[107] Lowe AR, Tang JH, Yassif J, et al. Importin-β modulates the permeability of the nuclear pore complex in a Ran-dependent manner. Elife. 2015;4. doi: 10.7554/eLife.04052

[108] Thaller DJ, Allegretti M, Borah S, et al. An ESCRT-LEM protein surveillance system is poised to directly monitor the nuclear envelope and nuclear transport system. Elife. 2019;8. doi: 10.7554/eLife.45284

[109] Webster BM, Colombi P, Jäger J, et al. Surveillance of nuclear pore complex assembly by ESCRT-III/Vps4. Cell. 2014;159(2):388–401. doi: 10.1016/j.cell.2014.09.012

[110] Kagias K, Nehammer C, Pocock R. Neuronal responses to physiological stress. Front Genet. 2012;3:222. doi:10.3389/fgene.2012.00222

[111] Toyama BH, Savas J, Park S, et al. Identification of long-lived proteins reveals exceptional stability of essential cellular structures. Cell. 2013;154(5):971–982. doi: 10.1016/j.cell.2013.07.037

[112] Hakhverdyan Z, Molloy KR, Keegan S, et al. Dissecting the structural dynamics of the nuclear pore complex. Mol Cell. 2021;81(1):153–165.e157. doi: 10.1016/j.molcel.2020.11.032

[113] Zhang Y, Wu KM, Yang L, et al. Tauopathies: new perspectives and challenges. Mol Neurodegener. 2022;17(1):28. doi: 10.1186/s13024-022-00533-z

[114] Paonessa F, Evans LD, Solanki R, et al. Microtubules Deform the Nuclear Membrane and Disrupt Nucleocytoplasmic Transport in Tau-Mediated Frontotemporal Dementia. Cell Rep. 2019;26(3):582–593.e585. doi: 10.1016/j.celrep.2018.12.085

[115] Candia RF, Cohen LS, Morozova V, et al. Importin-Mediated pathological tau nuclear translocation causes disruption of the nuclear lamina, TDP-43 mislocalization and cell death. Front Mol Neurosci. 2022;15:888420. doi:10.3389/fnmol.2022.888420

[116] Wang H, Wang R, Xu S, et al. Transcription factor EB is selectively reduced in the nuclear fractions of Alzheimer's and amyotrophic lateral sclerosis brains. Neurosci J. 2016;2016:4732837. doi:10.1155/2016/4732837

[117] Montalbano M, McAllen S, Puangmalai N, et al. RNA-binding proteins Musashi and tau soluble aggregates initiate nuclear dysfunction. Nat Commun. 2020;11(1):4305. doi: 10.1038/s41467-020-18022-6

[118] LaFerla FM, Green KN, Oddo S. Intracellular amyloid-β in Alzheimer's disease. Nat Rev Neurosci. 2007;8(7):499–509. doi: 10.1038/nrn2168

[119] Barucker C, Harmeier A, Weiske J, et al. Nuclear translocation uncovers the amyloid peptide Aβ42 as a regulator of gene transcription. J Biol Chem. 2014;289(29):20182–20191. doi: 10.1074/jbc.M114.564690

[120] Bailey JA, Maloney B, Ge YW, et al. Functional activity of the novel Alzheimer's amyloid β-peptide interacting domain (AβID) in the APP and BACE1 promoter sequences and implications in activating apoptotic genes and in amyloidogenesis. Gene. 2011;488:13–22. doi:10.1016/j.gene.2011.06.017

[121] Gezen-Ak D, Atasoy IL, Candaş E, et al. Vitamin D receptor regulates amyloid beta 1–42 production with protein disulfide isomerase A3. ACS Chem Neurosci. 2017;8(10):2335–2346. doi: 10.1021/acschemneuro.7b00245

[122] Pryor NE, Moss MA, Hestekin CN. Unraveling the early events of amyloid-β protein (Aβ) aggregation: techniques for the determination of Aβ aggregate size.

Int J Mol Sci. 2012;13(3):3038–3072. doi: 10.3390/ijms13033038

[123] Kouli A, Torsney KM, Kuan WL. Chapter 1: Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. Parkinson's disease: pathogenesis and clinical aspect. Stoker, TB, and Greenland JC, editors. Brisbane, Australia: Codon Publications; 2018. p. 3–26.

[124] Xia Q, Liao L, Cheng D, et al. Proteomic identification of novel proteins associated with Lewy bodies. Front Biosci. 2008;13 :3850–3856. doi: 10.2741/2973

[125] McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. Eur J Neurol. 2018;25:24–34. doi:10.1111/ene.13413

[126] Suhr ST, Senut M-C, Whitelegge JP, et al. Identities of sequestered proteins in aggregates from cells with induced polyglutamine expression. J Cell Bio. 2001;153(2):283–294. doi: 10.1083/jcb.153.2.283

[127] Liu KY, Shyu YC, Barbaro BA, et al. Disruption of the nuclear membrane by perinuclear inclusions of mutant huntingtin causes cell-cycle re-entry and striatal cell death in mouse and cell models of Huntington's disease. Hum Mol Genet. 2015;24:1602–1616. doi: 10.1093/hmg/ddu574

[128] Desmond CR, Atwal RS, Xia J, et al. Identification of a karyopherin β1/β2 Proline-Tyrosine nuclear localization signal in huntingtin protein. J Biol Chem. 2012;287(47):39626–39633. doi: 10.1074/jbc.M112.412379

[129] Shirasaki DI, Greiner E, Al-Ramahi I, et al. Network organization of the huntingtin proteomic interactome in mammalian brain. Neuron. 2012;75(1):41–57. doi: 10.1016/j.neuron.2012.05.024

[130] Langfelder P, Cantle JP, Chatzopoulou D, et al. Integrated genomics and proteomics define huntingtin CAG length–dependent networks in mice. Nat Neurosci. 2016;19(4):623–633. doi: 10.1038/nn.4256

[131] Hofweber M, Hutten S, Bourgeois B, et al. Phase separation of FUS is suppressed by its nuclear import receptor and arginine methylation. Cell. 2018;173(3):706–719 e713. doi: 10.1016/j.cell.2018.03.004

[132] Qamar S, Wang G, Randle SJ, et al. FUS phase separation is modulated by a molecular chaperone and methylation of arginine cation-π interactions. Cell. 2018;173(3):720–734 e715. doi: 10.1016/j.cell.2018.03.056

[133] Baade I, Hutten S, Sternburg EL, et al. The RNA-binding protein FUS is chaperoned and imported into the nucleus by a network of import receptors. J Biol Chem. 2021;296:100659. doi: 10.1016/j.jbc.2021.100659

[134] Beijer D, Kim HJ, Guo L, et al. Characterization of HNRNPA1 mutations defines diversity in pathogenic mechanisms and clinical presentation. JCI Insight. 2021;6(14). doi: 10.1172/jci.insight.148363

[135] Fare CM, Rhine K, Lam A, et al. A minimal construct of nuclear-import receptor karyopherin-β2 defines the regions critical for chaperone and disaggregation activity. J Biol Chem. 2022;102806(2):102806. doi: 10.1016/j.jbc.2022.102806

[136] Kim HJ, Mohassel P, Donkervoort S, et al. Heterozygous frameshift variants in HNRNPA2B1 cause early-onset oculopharyngeal muscular dystrophy. Nat Commun. 2022;13(1):2306. doi: 10.1038/s41467-022-30015-1

[137] Woerner AC, Frottin F, Hornburg D, et al. Cytoplasmic protein aggregates interfere with nucleocytoplasmic transport of protein and RNA. Science. 2016;351(6269):173–176. doi: 10.1126/science.aad2033

[138] Cook CN, Wu Y, Odeh HM, et al. C9orf72 poly(GR) aggregation induces TDP-43 proteinopathy. Sci Transl Med. 2020;12(559). doi: 10.1126/scitranslmed.abb3774

[139] de Mezer M, Wojciechowska M, Napierala M, et al. Mutant CAG repeats of huntingtin transcript fold into hairpins, form nuclear foci and are targets for RNA interference. Nucleic Acids Res. 2011;39(9):3852–3863. doi: 10.1093/nar/gkq1323

[140] Bañez-Coronel M, et al. A pathogenic mechanism in Huntington's disease involves small CAG-repeated RNAs with neurotoxic activity. PLoS Genet. 2012;8:e1002481. doi: 10.1371/journal.pgen.1002481

[141] Rué L, Bañez-Coronel M, Creus-Muncunill J, et al. Targeting CAG repeat RNAs reduces Huntington's disease phenotype independently of huntingtin levels. J Clin Invest. 2016;126(11):4319–4330. doi: 10.1172/JCI83185

[142] Ly S, Didiot M-C, Ferguson CM, et al. Mutant huntingtin messenger RNA forms neuronal nuclear clusters in rodent and human brains. Brain Commun. 2022;4:fcac248. doi: 10.1093/braincomms/fcac248

[143] Morelli KH, Wu Q, Gosztyla ML, et al. An RNA-targeting CRISPR–Cas13d system alleviates disease-related phenotypes in Huntington's disease models. Nat Neurosci. 2023;26(1):27–38. doi: 10.1038/s41593-022-01207-1

[144] Ling SC, Polymenidou M, Cleveland DW. Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. Neuron. 2013;79(3):416–438. doi: 10.1016/j.neuron.2013.07.033

[145] van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. Lancet. 2017;390(10107):2084–2098. doi: 10.1016/S0140-6736(17)31287-4

[146] Cividini C, Basaia S, Spinelli EG, et al. Amyotrophic lateral sclerosis–frontotemporal dementia. Neurology. 2021;98(4):e402–415. doi: 10.1212/WNL.0000000000013123

[147] Olney NT, Spina S, Miller BL. Frontotemporal Dementia. Neurol Clin. 2017;35(2):339–374. doi: 10.1016/j.ncl.2017.01.008

[148] Ferrari R, Kapogiannis D, Huey ED, et al. FTD and ALS: a tale of two diseases. Curr Alzheimer Res. 2011;8(3):273–294. doi: 10.2174/156720511795563700

[149] Mackenzie IR, Feldman HH. Ubiquitin immunohistochemistry suggests classic motor neuron disease, motor neuron disease with dementia, and frontotemporal

dementia of the motor neuron disease type represent a clinicopathologic spectrum. J Neuropathol Exp Neurol. 2005;64(8):730–739. doi: 10.1097/01.jnen.0000174335.27708.0a

[150] Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006;314(5796):130–133. doi: 10.1126/science.1134108

[151] Arai T, Hasegawa M, Akiyama H, et al. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun. 2006;351(3):602–611. doi: 10.1016/j.bbrc.2006.10.093

[152] Cairns NJ, Neumann M, Bigio EH, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. Am J Pathol. 2007;171(1):227–240. doi: 10.2353/ajpath.2007.070182

[153] Sreedharan J, Blair IP, Tripathi VB, et al. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. Science. 2008;319(5870):1668–1672. doi: 10.1126/science.1154584

[154] Purice MD, Taylor JP. Linking hnRNP function to ALS and FTD pathology. Front Neurosci. 2018;12:326. doi:10.3389/fnins.2018.00326

[155] Neumann M, Rademakers R, Roeber S, et al. A new subtype of frontotemporal lobar degeneration with FUS pathology. Brain. 2009;132(11):2922–2931. doi: 10.1093/brain/awp214

[156] Mackenzie IR, Rademakers R, Neumann M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. Lancet Neurol. 2010;9(10):995–1007. doi: 10.1016/S1474-4422(10)70195-2

[157] Gitler AD, Shorter J. RNA-binding proteins with prion-like domains in ALS and FTLD-U. Prion. 2011;5(3):179–187. doi: 10.4161/pri.5.3.17230

[158] Couthouis J, Hart MP, Shorter J, et al. A yeast functional screen predicts new candidate ALS disease genes. *Proc Natl Acad Sci, USA*. 2011;108(52):20881–20890. doi: 10.1073/pnas.1109434108

[159] Sun Z, Diaz Z, Fang X, et al. Molecular determinants and genetic modifiers of aggregation and toxicity for the ALS disease protein FUS/TLS. PLoS Biol. 2011;9(4):e1000614. doi: 10.1371/journal.pbio.1000614

[160] Couthouis J, Hart MP, Erion R, et al. Evaluating the role of the FUS/TLS-related gene EWSR1 in amyotrophic lateral sclerosis. Hum Mol Genet. 2012;21(13):2899–2911. doi: 10.1093/hmg/dds116

[161] Daigle JG, Lanson NA, Smith RB, et al. RNA-binding ability of FUS regulates neurodegeneration, cytoplasmic mislocalization and incorporation into stress granules associated with FUS carrying ALS-linked mutations. Hum Mol Genet. 2013;22(6):1193–1205. doi: 10.1093/hmg/dds526

[162] Harrison AF, Shorter J. RNA-binding proteins with prion-like domains in health and disease. Biochem J. 2017;474(8):1417–1438. doi: 10.1042/BCJ20160499

[163] DeJesus-Hernandez M, Mackenzie I, Boeve B, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72(2):245–256. doi: 10.1016/j.neuron.2011.09.011

[164] Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011;72(2):257–268. doi: 10.1016/j.neuron.2011.09.010

[165] Frottin F, Pérez-Berlanga M, Hartl FU, et al. Multiple pathways of toxicity induced by *C9orf72* dipeptide repeat aggregates and G_4C_2 RNA in a cellular model. Elife. 2021;10. doi: 10.7554/eLife.62718

[166] Jovicic A, Mertens J, Boeynaems S, et al. Modifiers of C9orf72 dipeptide repeat toxicity connect nucleocytoplasmic transport defects to FTD/ALS. Nat Neurosci. 2015;18(9):1226–1229. doi: 10.1038/nn.4085

[167] Freibaum BD, Lu Y, Lopez-Gonzalez R, et al. GGGGCC repeat expansion in C9orf72 compromises nucleocytoplasmic transport. Nature. 2015;525(7567):129–133. doi: 10.1038/nature14974

[168] Balendra R, Isaacs AM. C9orf72-mediated ALS and FTD: multiple pathways to disease. Nat Rev Neurol. 2018;14(9):544–558. doi: 10.1038/s41582-018-0047-2

[169] Shi Y, Lin S, Staats KA, et al. Haploinsufficiency leads to neurodegeneration in C9ORF72 ALS/FTD human induced motor neurons. Nat Med. 2018;24(3):313–325. doi: 10.1038/nm.4490

[170] Li J, Lim RG, Kaye JA, et al. An integrated multi-omic analysis of iPSC-derived motor neurons from C9ORF72 ALS patients. iScience. 2021;24(11):103221. doi: 10.1016/j.isci.2021.103221

[171] Byrne S, Elamin M, Bede P, et al. Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study. Lancet Neurol. 2012;11(3):232–240. doi: 10.1016/S1474-4422(12)70014-5

[172] Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012;11(4):323–330. doi: 10.1016/S1474-4422(12)70043-1

[173] Umoh ME, Fournier C, Li Y, et al. Comparative analysis of C9orf72 and sporadic disease in an ALS clinic population. Neurology. 2016;87(10):1024–1030. doi: 10.1212/WNL.0000000000003067

[174] King OD, Gitler AD, Shorter J. The tip of the iceberg: RNA-binding proteins with prion-like domains in neurodegenerative disease. Brain Res. 2012;1462:61–80. doi:10.1016/j.brainres.2012.01.016

[175] Donnelly CJ, Zhang P-W, Pham J, et al. RNA toxicity from the ALS/FTD C9ORF72 expansion is mitigated by antisense intervention. Neuron. 2013;80(2):415–428. doi: 10.1016/j.neuron.2013.10.015

[176] Lee YB, Chen H-J, Peres J, et al. Hexanucleotide repeats in ALS/FTD form length-dependent RNA foci, sequester RNA binding proteins, and are neurotoxic. Cell Rep. 2013;5(5):1178–1186. doi: 10.1016/j.celrep.2013.10.049

[177] Mori K, Lammich S, Mackenzie IRA, et al. hnRNP A3 binds to GGGGCC repeats and is a constituent of p62-positive/TDP43-negative inclusions in the hippocampus of patients with C9orf72 mutations. Acta Neuropathol. 2013;125(3):413–423. doi: 10.1007/s00401-013-1088-7

[178] Conlon EG, Lu L, Sharma A, et al. The C9ORF72 GGGGCC expansion forms RNA G-quadruplex inclusions and sequesters hnRNP H to disrupt splicing in ALS brains. Elife. 2016;5. doi: 10.7554/eLife.17820

[179] Lee KH, Zhang P, Kim HJ, et al. C9orf72 dipeptide repeats impair the assembly, dynamics, and function of membrane-less organelles. Cell. 2016;167(3):774–788. e717. doi: 10.1016/j.cell.2016.10.002

[180] Boeynaems S, Bogaert E, Kovacs D, et al. Phase separation of C9orf72 dipeptide repeats perturbs stress granule dynamics. Mol Cell. 2017;65(6):1044–1055.e1045. doi: 10.1016/j.molcel.2017.02.013

[181] Yin S, Lopez-Gonzalez R, Kunz RC, et al. Evidence that C9ORF72 dipeptide repeat proteins associate with U2 snRNP to cause Mis-splicing in ALS/FTD patients. Cell Rep. 2017;19(11):2244–2256. doi: 10.1016/j.celrep.2017.05.056

[182] Lu L, Zheng L, Viera L, et al. Mutant Cu/Zn-superoxide dismutase associated with amyotrophic lateral sclerosis destabilizes vascular endothelial growth factor mRNA and downregulates its expression. J Neurosci. 2007;27(30):7929–7938. doi: 10.1523/JNEUROSCI.1877-07.2007

[183] Lu L, Wang S, Zheng L, et al. Amyotrophic lateral sclerosis-linked mutant SOD1 sequesters hu antigen R (HuR) and TIA-1-related protein (TIAR): implications for impaired post-transcriptional regulation of vascular endothelial growth factor. J Biol Chem. 2009;284(49):33989–33998. doi: 10.1074/jbc.M109.067918

[184] Da Ros M, Deol HK, Savard A, et al. Wild-type and mutant SOD1 localizes to RNA-rich structures in cells and mice but does not bind RNA. J Neurochem. 2021;156(4):524–538. doi: 10.1111/jnc.15126

[185] Rosen DR. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993;364(6435):362. doi: 10.1038/364362c0

[186] Chen H, Qian K, Du Z, et al. Modeling ALS with iPSCs reveals that mutant SOD1 misregulates neurofilament balance in motor neurons. Cell Stem Cell. 2014;14(6):796–809. doi: 10.1016/j.stem.2014.02.004

[187] Menzies FM, Grierson AJ, Cookson MR, et al. Selective loss of neurofilament expression in Cu/Zn superoxide dismutase (SOD1) linked amyotrophic lateral sclerosis. J Neurochem. 2002;82(5):1118–1128. doi: 10.1046/j.1471-4159.2002.01045.x

[188] Winklhofer KF, Tatzelt J, Haass C. The two faces of protein misfolding: gain- and loss-of-function in neurodegenerative diseases. EMBO J. 2008;27(2):336–349. doi: 10.1038/sj.emboj.7601930

[189] Blokhuis AM, Groen EJ, Koppers M, et al. Protein aggregation in amyotrophic lateral sclerosis. Acta Neuropathol. 2013;125(6):777–794. doi: 10.1007/s00401-013-1125-6

[190] Kim G, Gautier O, Tassoni-Tsuchida E, et al. ALS genetics: gains, losses, and implications for future therapies. Neuron. 2020;108(5):822–842. doi: 10.1016/j.neuron.2020.08.022

[191] Xue YC, Ng CS, Xiang P, et al. Dysregulation of RNA-Binding Proteins in Amyotrophic Lateral Sclerosis. Front Mol Neurosci. 2020;13:78. doi: 10.3389/fnmol.2020.00078

[192] Zhou Y, Liu S, Liu G, et al. ALS-associated FUS mutations result in compromised FUS alternative splicing and autoregulation. PLoS Genet. 2013;9(10):e1003895. doi: 10.1371/journal.pgen.1003895

[193] Coady TH, Manley JL. ALS mutations in TLS/FUS disrupt target gene expression. Genes Dev. 2015;29(16):1696–1706. doi: 10.1101/gad.267286.115

[194] Hans F, Glasebach H, Kahle PJ. Multiple distinct pathways lead to hyperubiquitylated insoluble TDP-43 protein independent of its translocation into stress granules. J Biol Chem. 2020;295(3):673–689. doi: 10.1016/S0021-9258(17)49926-1

[195] Humphrey J, Birsa N, Milioto C, et al. FUS ALS-causative mutations impair FUS autoregulation and splicing factor networks through intron retention. Nucleic Acids Res. 2020;48(12):6889–6905. doi: 10.1093/nar/gkaa410

[196] Brown AL, Wilkins OG, Keuss MJ, et al. TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A. Nature. 2022;603(7899):131–137. doi: 10.1038/s41586-022-04436-3

[197] Ma XR, Prudencio M, Koike Y, et al. TDP-43 represses cryptic exon inclusion in the FTD–ALS gene UNC13A. Nature. 2022;603(7899):124–130. doi: 10.1038/s41586-022-04424-7

[198] Koike Y, Pickles S, Estades Ayuso V, et al. TDP-43 and other hnRNPs regulate cryptic exon inclusion of a key ALS/FTD risk gene, UNC13A. PLoS Biol. 2023;21(3):e3002028. doi: 10.1371/journal.pbio.3002028

[199] Scekic-Zahirovic J, Sendscheid O, El Oussini H, et al. Toxic gain of function from mutant FUS protein is crucial to trigger cell autonomous motor neuron loss. EMBO J. 2016;35(10):1077–1097. doi: 10.15252/embj.201592559

[200] Korobeynikov VA, Lyashchenko AK, Blanco-Redondo B, et al. Antisense oligonucleotide silencing of FUS expression as a therapeutic approach in amyotrophic lateral sclerosis. Nat Med. 2022;28(1):104–116. doi: 10.1038/s41591-021-01615-z

[201] An H, Litscher G, Watanabe N, et al. ALS-linked cytoplasmic FUS assemblies are compositionally

different from physiological stress granules and sequester hnRNPA3, a novel modifier of FUS toxicity. Neurobiol Dis. 2022;162:105585. doi: 10.1016/j.nbd.2021.105585

[202] Jun MH, Ryu H-H, Jun Y-W, et al. Sequestration of PRMT1 and Nd1-L mRNA into ALS-linked FUS mutant R521C-positive aggregates contributes to neurite degeneration upon oxidative stress. Sci Rep. 2017;7(1):40474. doi: 10.1038/srep40474

[203] Tsai YL, Coady TH, Lu L, et al. ALS/FTD-associated protein FUS induces mitochondrial dysfunction by preferentially sequestering respiratory chain complex mRNAs. Genes Dev. 2020;34(11–12):785–805. doi: 10.1101/gad.335836.119

[204] Nag N, Tripathi T. Mislocalization of Nup62 contributes to TDP-43 proteinopathy in ALS/FTLD. ACS Chem Neurosci. 2022;13(17):2544–2546. doi: 10.1021/acschemneuro.2c00480

[205] Vance C, Rogelj B, Hortobagyi T, et al. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. Science. 2009;323(5918):1208–1211. doi: 10.1126/science.1165942

[206] Huang EJ, Zhang J, Geser F, et al. Extensive FUS-immunoreactive pathology in juvenile amyotrophic lateral sclerosis with basophilic inclusions. Brain Pathol. 2010;20(6):1069–1076. doi: 10.1111/j.1750-3639.2010.00413.x

[207] Keller BA, Volkening K, Droppelmann CA, et al. Co-aggregation of RNA binding proteins in ALS spinal motor neurons: evidence of a common pathogenic mechanism. Acta Neuropathol. 2012;124(5):733–747. doi: 10.1007/s00401-012-1035-z

[208] Ader C, Frey S, Maas W, et al. Amyloid-like interactions within nucleoporin FG hydrogels. Proc Natl Acad Sci U S A. 2010;107(14):6281–6285. doi: 10.1073/pnas.0910163107

[209] Shi KY, Mori E, Nizami ZF, et al. Toxic PR_n poly-dipeptides encoded by the *C9orf72* repeat expansion block nuclear import and export. Proc Natl Acad Sci U S A. 2017;114(7):E1111–E1117. doi: 10.1073/pnas.1620293114

[210] Zhang YJ, Gendron TF, Grima JC, et al. C9ORF72 poly(GA) aggregates sequester and impair HR23 and nucleocytoplasmic transport proteins. Nat Neurosci. 2016;19(5):668–677. doi: 10.1038/nn.4272

[211] Lin Y, Mori E, Kato M, et al. Toxic PR Poly-Dipeptides Encoded by the C9orf72 repeat expansion target LC domain polymers. Cell. 2016;167(3):789–802.e712. doi: 10.1016/j.cell.2016.10.003

[212] McGoldrick P, Lau A, You Z, et al. Loss of C9orf72 perturbs the Ran-GTPase gradient and nucleocytoplasmic transport, generating compositionally diverse importin β-1 granules. Cell Rep. 2023;42:112134. doi:10.1016/j.celrep.2023.112134

[213] Zhong Y, Wang J, Henderson MJ, et al. Nuclear export of misfolded SOD1 mediated by a normally buried NES-like sequence reduces proteotoxicity in the nucleus. Elife. 2017;6. doi: 10.7554/eLife.23759

[214] Gertz B, Wong M, Martin LJ. Nuclear localization of human SOD1 and mutant SOD1-specific disruption of survival motor neuron protein complex in transgenic amyotrophic lateral sclerosis mice. J Neuropathol Exp Neurol. 2012;71(2):162–177. doi: 10.1097/NEN.0b013e318244b635

[215] Shang J, Yamashita T, Nakano Y, et al. Aberrant distributions of nuclear pore complex proteins in ALS mice and ALS patients. Neuroscience. 2017;350:158–168. doi: 10.1016/j.neuroscience.2017.03.024

[216] Nonaka T, Masuda-Suzukake M, Hosokawa M, et al. C9ORF72 dipeptide repeat poly-GA inclusions promote intracellular aggregation of phosphorylated TDP-43. Hum Mol Genet. 2018;27(15):2658–2670. doi: 10.1093/hmg/ddy174

[217] Niaki AG, Sarkar J, Cai X, et al. Loss of dynamic RNA interaction and aberrant phase separation induced by two distinct types of ALS/FTD-Linked FUS mutations. Mol Cell. 2020;77(1):82–94 e84. doi: 10.1016/j.molcel.2019.09.022

[218] Gonzalez A, Mannen T, Çağatay T, et al. Mechanism of karyopherin-β2 binding and nuclear import of ALS variants FUS(P525L) and FUS(R495X). Sci Rep. 2021;11(1):3754. doi: 10.1038/s41598-021-83196-y

[219] Conte A, Lattante S, Zollino M, et al. P525L FUS mutation is consistently associated with a severe form of juvenile amyotrophic lateral sclerosis. Neuromuscul Disord. 2012;22(1):73–75. doi: 10.1016/j.nmd.2011.08.003

[220] Sharma A, Lyashchenko AK, Lu L, et al. ALS-associated mutant FUS induces selective motor neuron degeneration through toxic gain of function. Nat Commun. 2016;7(1):10465. doi: 10.1038/ncomms10465

[221] Corcia P, Danel V, Lacour A, et al. A novel mutation of the C-terminal amino acid of FUS (Y526C) strengthens FUS gene as the most frequent genetic factor in aggressive juvenile ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3–4):298–301. doi: 10.1080/21678421.2016.1265564

[222] Zhou B, Wang H, Cai Y, et al. FUS P525L mutation causing amyotrophic lateral sclerosis and movement disorders. Brain Behav. 2020;10(6):e01625. doi: 10.1002/brb3.1625

[223] Rothstein JD, Warlick C, Coyne AN. Highly variable molecular signatures of TDP-43 loss of function are associated with nuclear pore complex injury in a population study of sporadic ALS patient iPsns. bioRxiv. 2023.

[224] Megat S, Mora N, Sanogo J, et al. Integrative genetic analysis illuminates ALS heritability and identifies risk genes. Nat Commun. 2023;14(1):342. doi: 10.1038/s41467-022-35724-1

[225] Kaneb HM, Folkmann AW, Belzil VV, et al. Deleterious mutations in the essential mRNA metabolism factor, hGle1, in amyotrophic lateral sclerosis. Hum Mol Genet. 2015;24(5):1363–1373. doi: 10.1093/hmg/ddu545

[226] van Rheenen W, van der Spek RAA, Bakker MK, et al. Common and rare variant association analyses in amyotrophic lateral sclerosis identify 15 risk loci with distinct genetic architectures and neuron-specific biology. Nat Genet. 2021;53(12):1636–1648. doi: 10.1038/s41588-021-00973-1

[227] Workman MJ, Lim RG, Wu J, et al. Large-scale differentiation of iPSC-derived motor neurons from ALS and control subjects. Neuron. 2023;111(8):1191–1204.e1195. doi: 10.1016/j.neuron.2023.01.010

[228] Wu CH, Fallini C, Ticozzi N, et al. Mutations in the profilin 1 gene cause familial amyotrophic lateral sclerosis. Nature. 2012;488(7412):499–503. doi: 10.1038/nature11280

[229] Smith BN, Ticozzi N, Fallini C, et al. Exome-wide rare variant analysis identifies TUBA4A mutations associated with familial ALS. Neuron. 2014;84(2):324–331. doi: 10.1016/j.neuron.2014.09.027

[230] Nicolas A, Kenna KP, Renton AE, et al. Genome-wide analyses identify KIF5A as a novel ALS gene. Neuron. 2018;97(6):1268–1283.e6. doi: 10.1016/j.neuron.2018.02.027

[231] Baron DM, Fenton AR, Saez-Atienzar S, et al. ALS-associated KIF5A mutations abolish autoinhibition resulting in a toxic gain of function. Cell Rep. 2022;39(1):110598. doi: 10.1016/j.celrep.2022.110598

[232] Tran D, Chalhoub A, Schooley A, et al. A mutation in VAPB that causes amyotrophic lateral sclerosis also causes a nuclear envelope defect. J Cell Sci. 2012;125:2831–2836. doi:10.1242/jcs.102111

[233] James C, Müller M, Goldberg MW, et al. Proteomic mapping by rapamycin-dependent targeting of APEX2 identifies binding partners of VAPB at the inner nuclear membrane. J Biol Chem. 2019;294(44):16241–16254. doi: 10.1074/jbc.RA118.007283

[234] Tullio-Pelet A, Salomon R, Hadj-Rabia S, et al. Mutant WD-repeat protein in triple-A syndrome. Nat Genet. 2000;26(3):332–335. doi: 10.1038/81642

[235] Handschug K, Sperling S, Yoon SJ, et al. Triple a syndrome is caused by mutations in AAAS, a new WD-repeat protein gene. Hum Mol Genet. 2001;10(3):283–290. doi: 10.1093/hmg/10.3.283

[236] Huebner A, Kaindl AM, Knobeloch KP, et al. The triple a syndrome is due to mutations in ALADIN, a novel member of the nuclear pore complex. Endocr Res. 2004;30(4):891–899. doi: 10.1081/ERC-200044138

[237] Cronshaw JM, Matunis MJ. The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. Proc Natl Acad Sci U S A. 2003;100(10):5823–5827. doi: 10.1073/pnas.1031047100

[238] Nousiainen HO, Kestilä M, Pakkasjärvi N, et al. Mutations in mRNA export mediator GLE1 result in a fetal motoneuron disease. Nat Genet. 2008;40(2):155–157. doi: 10.1038/ng.2007.65

[239] Paakkola T, Vuopala K, Kokkonen H, et al. A homozygous I684T in GLE1 as a novel cause of arthrogryposis and motor neuron loss. Clin Genet. 2018;93(1):173–177. doi: 10.1111/cge.13086

[240] Smith C, Parboosingh JS, Boycott KM, et al. Expansion of the GLE1-associated arthrogryposis multiplex congenita clinical spectrum. Clin Genet. 2017;91(3):426–430. doi: 10.1111/cge.12876

[241] Bonnin E, Cabochette P, Filosa A, et al. Biallelic mutations in nucleoporin NUP88 cause lethal fetal akinesia deformation sequence. PLoS Genet. 2018;14(12):e1007845. doi: 10.1371/journal.pgen.1007845

[242] Shamseldin HE, Makhseed N, Ibrahim N, et al. NUP214 deficiency causes severe encephalopathy and microcephaly in humans. Hum Genet. 2019;138(3):221–229. doi: 10.1007/s00439-019-01979-w

[243] Fichtman B, Harel T, Biran N, et al. Pathogenic variants in NUP214 cause "plugged" nuclear pore channels and acute febrile encephalopathy. Am J Hum Genet. 2019;105(1):48–64. doi: 10.1016/j.ajhg.2019.05.003

[244] Farooqui S, Narayanan DL, Mascarenhas S, et al. c.202_204del in NUP214 causes late onset form of febrile encephalopathy. Am J Med Genet A. 2024. doi:10.1002/ajmg.a.63529.

[245] Neilson DE, Adams MD, Orr CMD, et al. Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. Am J Hum Genet. 2009;84(1):44–51. doi: 10.1016/j.ajhg.2008.12.009

[246] Shibata A, Kasai M, Hoshino A, et al. RANBP2 mutation causing autosomal dominant acute necrotizing encephalopathy attenuates its interaction with COX11. Neurosci Lett. 2021;763:136173. doi:10.1016/j.neulet.2021.136173

[247] Deshmukh P, Singh A, Khuperkar D, et al. Acute necrotizing encephalopathy-linked mutations in Nup358 impair interaction of Nup358 with TNRC6/GW182 and miRNA function. Biochem Biophys Res Commun. 2021;559:230–237. doi:10.1016/j.bbrc.2021.04.027

[248] Braun DA, Lovric S, Schapiro D, et al. Mutations in multiple components of the nuclear pore complex cause nephrotic syndrome. J Clin Invest. 2018;128(10):4313–4328. doi: 10.1172/JCI98688

[249] Miyake N, Tsukaguchi H, Koshimizu E, et al. Biallelic mutations in nuclear pore complex subunit nup107 cause early-childhood-onset steroid-resistant nephrotic syndrome. Am J Hum Genet. 2015;97(4):555–566. doi: 10.1016/j.ajhg.2015.08.013

[250] Rosti RO, Sotak BN, Bielas SL, et al. Homozygous mutation in *NUP107* leads to microcephaly with steroid-resistant nephrotic condition similar to Galloway-Mowat syndrome. J Med Genet. 2017;54(6):399–403. doi: 10.1136/jmedgenet-2016-104237

[251] Zhao F, Zhu J-Y, Richman A, et al. Mutations in *NUP160* Are Implicated in Steroid-Resistant Nephrotic Syndrome. J Am Soc Nephrol. 2019;30 (5):840–853. doi: 10.1681/ASN.2018080786

[252] Braun DA, Sadowski CE, Kohl S, et al. Mutations in nuclear pore genes NUP93, NUP205 and XPO5 cause steroid-resistant nephrotic syndrome. Nat Genet. 2016;48(4):457–465. doi: 10.1038/ng.3512

[253] Zhang X, Chen S, Yoo S, et al. Mutation in nuclear pore component NUP155 leads to atrial fibrillation and early sudden cardiac death. Cell. 2008;135 (6):1017–1027. doi: 10.1016/j.cell.2008.10.022

[254] Sandestig A, Engström K, Pepler A, et al. Biallelic loss of function may underlie a new syndrome: nucleoporin 188 insufficiency syndrome? Mol Syndromol. 2020;10 (6):313–319. doi: 10.1159/000504818

[255] Muir AM, Cohen JL, Sheppard SE, et al. Bi-allelic loss-of-function variants in NUP188 cause a recognizable syndrome characterized by neurologic, ocular, and cardiac abnormalities. Am J Hum Genet. 2020;106 (5):623–631. doi: 10.1016/j.ajhg.2020.03.009

[256] Harrer P, Schalk A, Shimura M, et al. Recessive NUP54 variants underlie early-onset dystonia with striatal lesions. Ann Neurol. 2023;93(2):330–335. doi: 10.1002/ana.26544

[257] Basel-Vanagaite L, Muncher L, Straussberg R, et al. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. Ann Neurol. 2006;60 (2):214–222. doi: 10.1002/ana.20902

[258] Van Bergen NJ, Bell KM, Carey K, et al. Pathogenic variants in nucleoporin TPR (translocated promoter region, nuclear basket protein) cause severe intellectual disability in humans. Hum Mol Genet. 2022;31 (3):362–375. doi: 10.1093/hmg/ddab248

[259] Strauss M, Koehler K, Krumbholz M, et al. Triple a syndrome mimicking ALS. Amyotroph Lateral Scler. 2008;9(5):315–317. doi: 10.1080/17482960802259016

[260] Vallet AE, Verschueren A, Petiot P, et al. Neurological features in adult Triple-A (Allgrove) syndrome. J Neurol. 2012;259(1):39–46. doi: 10.1007/s00415-011-6115-9

[261] Vigano' M, Mantero V, Basilico P, et al. Don't forget Allgrove syndrome in adult patients as a bulbar-ALS mimicker. Neurol Sci. 2023;44:3703–3705. doi: 10.1007/s10072-023-06961-z.

[262] Strauss KA, Gonzaga-Jauregui C, Brigatti KW, et al. Genomic diagnostics within a medically underserved population: efficacy and implications. Genet Med. 2018;20(1):31–41. doi: 10.1038/gim.2017.76

[263] Consortium U, Martin M-J, Orchard S. UniProt: the Universal Protein Knowledgebase in 2023. Nucleic Acids Res. 2023;51(D1):D523–D531. doi: 10.1093/nar/gkac1052

[264] Tarazón E, Rivera M, Roselló-Lletí E, et al. Heart failure induces significant changes in nuclear pore complex of human cardiomyocytes. PLoS One. 2012;7(11): e48957. doi: 10.1371/journal.pone.0048957

[265] Lai TH, Wu Y-Y, Wang Y-Y, et al. SEPT12–NDC1 Complexes Are Required for Mammalian Spermiogenesis. Int J Mol Sci. 2016;17(11):1911. doi: 10.3390/ijms17111911

[266] Cipollini M, Luisi S, Piomboni P, et al. Functional polymorphism within NUP210 encoding for nucleoporin GP210 is associated with the risk of endometriosis. Fertil Steril. 2019;112(2):343–352.e341. doi: 10.1016/j.fertnstert.2019.04.011

[267] Qiao W, Han Y, Jin W, et al. Overexpression and biological function of TMEM48 in non-small cell lung carcinoma. Tumour Biol. 2016;37(2):2575–2586. doi: 10.1007/s13277-015-4014-x

[268] Rodriguez-Bravo V, Pippa R, Song W-M, et al. Nuclear pores promote lethal prostate cancer by increasing POM121-driven E2F1, MYC, and AR nuclear import. Cell. 2018;174(5):1200–1215.e1220. doi: 10.1016/j.cell.2018.07.015

[269] Gu Q, Hou W, Liu H, et al. NUP210 and MicroRNA-22 modulate fas to elicit HeLa cell cycle arrest. Yonsei Med J. 2020;61(5):371–381. doi: 10.3349/ymj.2020.61.5.371

[270] Guan L, Zhang L, Wang T, et al. POM121 promotes proliferation and metastasis in non-small-cell lung cancer through TGF-β/SMAD and PI3K/AKT pathways. Cancer Biomark. 2021;32(3):293–302. doi: 10.3233/CBM-210001

[271] Hong SH, Son KH, Ha SY, et al. Nucleoporin 210 serves a key scaffold for SMARCB1 in liver cancer. Cancer Res. 2021;81(2):356–370. doi: 10.1158/0008-5472.CAN-20-0568

[272] Bindra D, Mishra RK. In pursuit of distinctiveness: transmembrane nucleoporins and their disease associations. Front Oncol. 2021;11:784319. doi:10.3389/fonc.2021.784319

[273] Wong X, Stewart CL. The laminopathies and the insights they provide into the structural and functional organization of the nucleus. Annu Rev Genom Hum Genet. 2020;21(1):263–288. doi: 10.1146/annurev-genom-121219-083616

[274] Han M, Zhao M, Cheng C, et al. Lamin a mutation impairs interaction with nucleoporin NUP155 and disrupts nucleocytoplasmic transport in atrial fibrillation. Hum Mutat. 2019;40(3):310–325. doi: 10.1002/humu.23691

[275] Lussi YC, Hügi I, Laurell E, et al. The nucleoporin Nup88 is interacting with nuclear lamin A. Mol Biol Cell. 2011;22(7):1080–1090. doi: 10.1091/mbc.e10-05-0463

[276] Bechert K, Lagos-Quintana M, Harborth J, et al. Effects of expressing lamin A mutant protein causing Emery-Dreifuss muscular dystrophy and familial partial lipodystrophy in HeLa cells. Exp Cell Res. 2003;286 (1):75–86. doi: 10.1016/S0014-4827(03)00104-6

[277] Dutta S, Das JK, Maganti L, et al. Skeletal muscle dystrophy mutant of lamin A alters the structure and

dynamics of the Ig fold domain. Sci Rep. 2018;8 (1):13793. doi: 10.1038/s41598-018-32227-2

[278] Méjat A, Misteli T. LINC complexes in health and disease. Nucleus. 2010;1(1):40–52. doi: 10.4161/nucl.1.1.10530

[279] Liu Q, Pante N, Misteli T, et al. Functional association of Sun1 with nuclear pore complexes. J Cell Bio. 2007;178(5):785–798. doi: 10.1083/jcb.200704108

[280] Smith MA, Blankman E, Jensen CC, et al. Nuclear pore complexes concentrate on Actin/LINC/Lamin nuclear lines in response to mechanical stress in a SUN1 dependent manner. Heliyon. 2022;8(12):e12147. doi: 10.1016/j.heliyon.2022.e12147

[281] Meinke P, Mattioli E, Haque F, et al. Muscular dystrophy-associated SUN1 and SUN2 variants disrupt nuclear-cytoskeletal connections and myonuclear organization. PLoS Genet. 2014;10(9):e1004605. doi: 10.1371/journal.pgen.1004605

[282] Li P, Meinke P, Huong LT, et al. Contribution of SUN1 mutations to the pathomechanism in muscular dystrophies. Hum Mutat. 2014;35(4):452–461. doi: 10.1002/humu.22504

[283] Chen CY, Chi Y-H, Mutalif R, et al. Accumulation of the inner nuclear envelope protein Sun1 is pathogenic in progeric and dystrophic laminopathies. Cell. 2012;149(3):565–577. doi: 10.1016/j.cell.2012.01.059

[284] Arii J, Maeda F, Maruzuru Y, et al. ESCRT-III controls nuclear envelope deformation induced by progerin. Sci Rep. 2020;10(1):18877. doi: 10.1038/s41598-020-75852-6

[285] Shankar R, Lettman MM, Whisler W, et al. The ESCRT machinery directs quality control over inner nuclear membrane architecture. Cell Rep. 2022;38(3):110263. doi: 10.1016/j.celrep.2021.110263

[286] Wu X, Kasper LH, Mantcheva RT, et al. Disruption of the FG nucleoporin NUP98 causes selective changes in nuclear pore complex stoichiometry and function. Proc Natl Acad Sci U S A. 2001;98(6):3191–3196. doi: 10.1073/pnas.051631598

[287] Jevtić P, Schibler AC, Wesley CC, et al. The nucleoporin ELYS regulates nuclear size by controlling NPC number and nuclear import capacity. EMBO Rep. 2019;20(6). doi: 10.15252/embr.201847283

[288] Sakuma S, Zhu EY, Raices M, et al. Loss of Nup210 results in muscle repair delays and age-associated alterations in muscle integrity. Life Sci Alliance. 2022;5(3):e202101216. doi: 10.26508/lsa.202101216

[289] Cho KI, Yoon D, Qiu S, et al. Loss of Ranbp2 in motoneurons causes disruption of nucleocytoplasmic and chemokine signaling, proteostasis of hnRNPH3 and Mmp28, and development of amyotrophic lateral sclerosis-like syndromes. Dis Model Mech. 2017;10 (5):559–579. doi: 10.1242/dmm.027730

[290] Zimmerli CE, Allegretti M, Rantos V, et al. Nuclear pores dilate and constrict in cellulo. Science. 2021;374 (6573):eabd9776. doi: 10.1126/science.abd9776

[291] Xu S, Zhang X, Liu C, et al. Role of mitochondria in neurodegenerative diseases: from an epigenetic perspective. Front Cell Dev Biol. 2021;9:688789. doi: 10.3389/fcell.2021.688789

[292] Panagaki D, Croft JT, Keuenhof K, et al. Nuclear envelope budding is a response to cellular stress. *Proc Natl Acad Sci, USA*. 2021;118(30). doi: 10.1073/pnas.2020997118

[293] Donnaloja F, Jacchetti E, Soncini M, et al. Mechanosensing at the nuclear envelope by nuclear pore complex stretch activation and its effect in physiology and pathology. Front Physiol. 2019;10:896. doi:10.3389/fphys.2019.00896

[294] Hoffman LM, Smith MA, Jensen CC, et al. Mechanical stress triggers nuclear remodeling and the formation of transmembrane actin nuclear lines with associated nuclear pore complexes. Mol Biol Cell. 2020;31 (16):1774–1787. doi: 10.1091/mbc.E19-01-0027

[295] Goelzer M, Goelzer J, Ferguson ML, et al. Nuclear envelope mechanobiology: linking the nuclear structure and function. Nucleus. 2021;12(1):90–114. doi: 10.1080/19491034.2021.1962610

[296] Hocquemiller M, Giersch L, Audrain M, et al. Adeno-associated virus-based gene therapy for CNS diseases. Hum Gene Ther. 2016;27(7):478–496. doi: 10.1089/hum.2016.087

[297] Au HKE, Isalan M, Mielcarek M. Gene therapy advances: a meta-analysis of AAV usage in clinical settings. Front Med. 2021;8:809118. doi:10.3389/fmed.2021.809118

[298] Kuzmin DA, Shutova MV, Johnston NR, et al. The clinical landscape for AAV gene therapies. Nat Rev Drug Discov. 2021;20(3):173–174. doi: 10.1038/d41573-021-00017-7

[299] Mendell JR, Al-Zaidy SA, Rodino-Klapac LR, et al. Current clinical applications of in vivo gene therapy with AAVs. Mol Ther. 2021;29(2):464–488. doi: 10.1016/j.ymthe.2020.12.007

[300] Dominguez E, Marais T, Chatauret N, et al. Intravenous scAAV9 delivery of a codon-optimized SMN1 sequence rescues SMA mice. Hum Mol Genet. 2011;20(4):681–693. doi: 10.1093/hmg/ddq514

[301] Stevens D, Claborn MK, Gildon BL, et al. Onasemnogene Abeparvovec-xioi: gene therapy for spinal muscular atrophy. Ann Pharmacother. 2020;54 (10):1001–1009. doi: 10.1177/1060028020914274

[302] Huang Q, Chen AT, Chan KY, et al. Targeting AAV vectors to the central nervous system by engineering capsid–receptor interactions that enable crossing of the blood–brain barrier. PLoS Biol. 2023;21(7):e3002112. doi: 10.1371/journal.pbio.3002112

[303] Bastos R, Lin A, Enarson M, et al. Targeting and function in mRNA export of nuclear pore complex protein Nup153. J Cell Bio. 1996;134(5):1141–1156. doi: 10.1083/jcb.134.5.1141

[304] Boer J, Bonten-Surtel J, Grosveld G. Overexpression of the nucleoporin CAN/NUP214 induces growth arrest, nucleocytoplasmic transport defects, and apoptosis. Mol Cell Biol. 1998;18(3):1236–1247. doi: 10.1128/MCB.18.3.1236

[305] Wu Z, Yang H, Colosi P. Effect of genome size on AAV vector packaging. Mol Ther. 2010;18(1):80–86. doi: 10.1038/mt.2009.255

[306] Marrone L, Marchi PM, Azzouz M. Circumventing the packaging limit of AAV-mediated gene replacement therapy for neurological disorders. Expert Opin Biol Ther. 2022;22(9):1–14. doi: 10.1080/14712598.2022.2012148

[307] Nofrini V, Di Giacomo D, Mecucci C. Nucleoporin genes in human diseases. Eur J Hum Genet. 2016;24(10):1388–1395. doi: 10.1038/ejhg.2016.25

[308] Talap J, Zhao J, Shen M, et al. Recent advances in therapeutic nucleic acids and their analytical methods. J Pharm Biomed Anal. 2021;206:114368. doi: 10.1016/j.jpba.2021.114368

[309] Ori A, Banterle N, Iskar M, et al. Cell type-specific nuclear pores: a case in point for context-dependent stoichiometry of molecular machines. Mol Syst Biol. 2013;9(1):648. doi: 10.1038/msb.2013.4

[310] Fare CM, Shorter J. (Dis)Solving the problem of aberrant protein states. Dis Model Mech. 2021;14(5). doi: 10.1242/dmm.048983

[311] Shorter J. Hsp104: a weapon to combat diverse neurodegenerative disorders. Neurosignals. 2008;16(1):63–74. doi: 10.1159/000109760

[312] Hartl FU, Bracher A, Hayer-Hartl M. Molecular chaperones in protein folding and proteostasis. Nature. 2011;475(7356):324–332. doi: 10.1038/nature10317

[313] Ciechanover A, Kwon YT. Protein quality control by molecular chaperones in neurodegeneration. Front Neurosci. 2017;11:185. doi:10.3389/fnins.2017.00185

[314] Mann JR, Gleixner AM, Mauna JC, et al. RNA binding antagonizes neurotoxic phase transitions of TDP-43. Neuron. 2019;102(2):321–338 e328. doi: 10.1016/j.neuron.2019.01.048

[315] Takeuchi T, Maeta K, Ding X, et al. Sustained therapeutic benefits by transient reduction of TDP-43 using ENA-modified antisense oligonucleotides in ALS/FTD mice. Mol Ther Nucleic Acids. 2023;31:353–366. doi: 10.1016/j.omtn.2023.01.006

[316] McCampbell A, Cole T, Wegener AJ, et al. Antisense oligonucleotides extend survival and reverse decrement in muscle response in ALS models. J Clin Invest. 2018;128(8):3558–3567. doi: 10.1172/JCI99081

[317] Miller TM, Cudkowicz ME, Genge A, et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med. 2022;387(12):1099–1110. doi: 10.1056/NEJMoa2204705

[318] Odeh HM, Fare CM, Shorter J. Nuclear-import receptors counter deleterious phase transitions in neurodegenerative disease. J Mol Biol. 2022;434(1):167220. doi: 10.1016/j.jmb.2021.167220

[319] Guo L, Fare CM, Shorter J. Therapeutic dissolution of aberrant phases by nuclear-import receptors. Trends Cell Biol. 2019;29(4):308–322. doi: 10.1016/j.tcb.2018.12.004

[320] Robinson E, Shorter J, Guo L. Karyopherin-β2 inhibits and reverses aggregation and liquid-liquid phase separation of the ALS/FTD-Associated protein FUS. Bio Protoc. 2020;10(16):e3725. doi: 10.21769/BioProtoc.3725

[321] Mizuguchi-Hata C, Ogawa Y, Oka M, et al. Quantitative regulation of nuclear pore complex proteins by O-GlcNAcylation. Biochim Biophys Acta. 2013;1833(12):2682–2689. doi: 10.1016/j.bbamcr.2013.06.008

[322] Ruba A, Yang W. O-GlcNAc-ylation in the nuclear pore complex. Cell Mol Bioeng. 2016;9(2):227–233. doi: 10.1007/s12195-016-0440-0

[323] Zhu Y, Liu T-W, Madden Z, et al. Post-translational O-GlcNAcylation is essential for nuclear pore integrity and maintenance of the pore selectivity filter. J Mol Cell Biol. 2016;8(1):2–16. doi: 10.1093/jmcb/mjv033

[324] Yoo TY, Mitchison TJ. O-GlcNAc modification of nuclear pore complexes accelerates bidirectional transport. J Cell Bio. 2021;220(7). doi: 10.1083/jcb.202010141

[325] Kitchen DB, Decornez H, Furr JR, et al. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004;3(11):935–949. doi: 10.1038/nrd1549

[326] Leman JK, Weitzner BD, Lewis SM, et al. Macromolecular modeling and design in Rosetta: recent methods and frameworks. Nat Methods. 2020;17(7):665–680. doi: 10.1038/s41592-020-0848-2

[327] Coyne AN, Rothstein JD. The ESCRT-III protein VPS4, but not CHMP4B or CHMP2B, is pathologically increased in familial and sporadic ALS neuronal nuclei. Acta Neuropathol Commun. 2021;9(1):127. doi: 10.1186/s40478-021-01228-0

[328] Parkinson N, Ince PG, Smith MO, et al. ALS phenotypes with mutations in CHMP2B (charged multivesicular body protein 2B). Neurology. 2006;67(6):1074–1077. doi: 10.1212/01.wnl.0000231510.89311.8b

[329] van der Zee J, Urwin H, Engelborghs S, et al. CHMP2B C-truncating mutations in frontotemporal lobar degeneration are associated with an aberrant endosomal phenotype in vitro. Hum Mol Genet. 2008;17(2):313–322. doi: 10.1093/hmg/ddm309

[330] Cox LE, Ferraiuolo L, Goodall EF, et al. Mutations in CHMP2B in lower motor neuron predominant amyotrophic lateral sclerosis (ALS). PLoS One. 2010;5(3):e9872. doi: 10.1371/journal.pone.0009872

[331] Isaacs AM, Johannsen P, Holm I, et al. Frontotemporal dementia caused by CHMP2B mutations. Curr Alzheimer Res. 2011;8(3):246–251. doi: 10.2174/156720511795563764

[332] Clayton EL, Bonnycastle K, Isaacs AM, et al. A novel synaptopathy-defective synaptic vesicle protein trafficking in the mutant CHMP2B mouse model of

frontotemporal dementia. J Neurochem. 2022;160 (3):412–425. doi: 10.1111/jnc.15551

[333] van Blitterswijk M, Vlam L, van Es MA, et al. Genetic overlap between apparently sporadic motor neuron diseases. PloS One. 2012;7(11):e48983. doi: 10.1371/journal.pone.0048983

[334] Narain P, Pandey A, Gupta S, et al. Targeted next-generation sequencing reveals novel and rare variants in Indian patients with amyotrophic lateral sclerosis. Neurobiol Aging. 2018;71:.e265.269–.e265.214. doi: 10.1016/j.neurobiolaging.2018.05.012

[335] Urwin H, Authier A, Nielsen JE, et al. Disruption of endocytic trafficking in frontotemporal dementia with CHMP2B mutations. Hum Mol Genet. 2010;19 (11):2228–2238. doi: 10.1093/hmg/ddq100

[336] Ghazi-Noori S, Froud KE, Mizielinska S, et al. Progressive neuronal inclusion formation and axonal degeneration in CHMP2B mutant transgenic mice. Brain. 2012;135(3):819–832. doi: 10.1093/brain/aws006

[337] Clayton EL, Mizielinska S, Edgar JR, et al. Frontotemporal dementia caused by CHMP2B mutation is characterised by neuronal lysosomal storage pathology. Acta Neuropathol. 2015;130(4):511–523. doi: 10.1007/s00401-015-1475-3

[338] Clayton EL, Milioto C, Muralidharan B, et al. Frontotemporal dementia causative CHMP2B impairs neuronal endolysosomal traffic-rescue by TMEM106B knockdown. Brain. 2018;141(12):3428–3442. doi: 10.1093/brain/awy284

[339] Prissette M, Fury W, Koss M, et al. Disruption of nuclear envelope integrity as a possible initiating event in tauopathies. Cell Rep. 2022;40(8):111249. doi: 10.1016/j.celrep.2022.111249

[340] Gu M, LaJoie D, Chen OS, et al. LEM2 recruits CHMP7 for ESCRT-mediated nuclear envelope closure in fission yeast and human cells. Proc Natl Acad Sci U S A. 2017;114(11):E2166–E2175. doi: 10.1073/pnas.1613916114

[341] Nim S, O'Hara DM, Corbi-Verge C, et al. Disrupting the α-synuclein-ESCRT interaction with a peptide inhibitor mitigates neurodegeneration in preclinical models of Parkinson's disease. Nat Commun. 2023;14 (1):2150. doi: 10.1038/s41467-023-37464-2

[342] Baron O, Boudi A, Dias C, et al. Stall in canonical autophagy-lysosome pathways prompts nucleophagy-based nuclear breakdown in neurodegeneration. Curr Biol. 2017;27(23):3626–3642. e3626. doi: 10.1016/j.cub.2017.10.054

[343] Malik BR, Maddison DC, Smith GA, et al. Autophagic and endo-lysosomal dysfunction in neurodegenerative disease. Mol Brain. 2019;12(1):100. doi: 10.1186/s13041-019-0504-x

[344] Cunningham KM, Maulding K, Ruan K, et al. TFEB/Mitf links impaired nuclear import to autophagolysosomal dysfunction in C9-ALS. Elife. 2020;9. doi: 10.7554/eLife.59419

[345] Lin C, Wu H, Weng E, et al. Fluvoxamine restores TFEB-mediated autophagy through sigma-1R-controlled POM121 expression. Res Square. 2023 doi: 10.1007/s12035-023-03885-9

[346] Lee PT, Liévens J-C, Wang S-M, et al. Sigma-1 receptor chaperones rescue nucleocytoplasmic transport deficit seen in cellular and Drosophila ALS/FTD models. Nat Commun. 2020;11(1):5580. doi: 10.1038/s41467-020-19396-3

[347] Estévez-Silva HM, et al. Pridopidine promotes synaptogenesis and reduces spatial memory deficits in the Alzheimer's disease APP/PS1 mouse model. Neurotherapeutics. 2022;19:1566–1587. doi: 10.1007/s13311-022-01280-1

[348] Francardo V, et al. Pridopidine induces functional neurorestoration via the sigma-1 receptor in a mouse model of Parkinson's disease. Neurotherapeutics. 2019;16:465–479. doi: 10.1007/s13311-018-00699-9

[349] Eddings CR, Arbez N, Akimov S, et al. Pridopidine protects neurons from mutant-huntingtin toxicity via the sigma-1 receptor. Neurobiol Dis. 2019;129:118–129. doi: 10.1016/j.nbd.2019.05.009

[350] Madeira F, Pearce M, Tivey ARN, et al. Search and sequence analysis tools services from EMBL-EBI in 2022. Nucleic Acids Res. 2022;50(W1):W276–W279. doi: 10.1093/nar/gkac240

[351] Makałowski W, Zhang J, Boguski MS. Comparative analysis of 1196 orthologous mouse and human full-length mRNA and protein sequences. Genome Res. 1996;6(9):846–857. doi: 10.1101/gr.6.9.846

[352] Grenier K, Kao J, Diamandis P. Three-dimensional modeling of human neurodegeneration: brain organoids coming of age. Mol Psychiatry. 2020;25 (2):254–274. doi: 10.1038/s41380-019-0500-7

[353] Mohamed MS, Hazawa M, Kobayashi A, et al. Spatiotemporally tracking of nano-biofilaments inside the nuclear pore complex core. Biomaterials. 2020;256:120198. doi: 10.1016/j.biomaterials.2020.120198

[354] Venkataraman L, Fair SR, McElroy CA, et al. Modeling neurodegenerative diseases with cerebral organoids and other three-dimensional culture systems: focus on Alzheimer's disease. Stem Cell Rev And Rep. 2022;18 (2):696–717. doi: 10.1007/s12015-020-10068-9