






# Recessive *NUP54* Variants Underlie Early-Onset Dystonia with Striatal Lesions

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Infantile striatonigral degeneration is caused by a homozygous variant of the nuclear-pore complex (NPC) gene *NUP62*, involved in nucleo-cytoplasmic trafficking. By querying sequencing-datasets of patients with dystonia and/or Leigh(-like) syndromes, we identified 3 unrelated individuals with biallelic variants in *NUP54*. All variants clustered in the C-terminal protein region that interacts with *NUP62*. Associated phenotypes were similar to those of *NUP62*-related disease, including early-onset dystonia with dysphagia, choreoathetosis, and T2-hyperintense lesions in striatum. In silico and protein-biochemical studies gave further evidence for the argument that the variants were pathogenic. We expand the spectrum of NPC component-associated dystonic conditions with localized basal-ganglia abnormalities.

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## Introduction

In eukaryotes, protection of genome integrity and maintenance of the nuclear-transport machinery are mediated by

the nuclear envelope, a physical-barrier system composed of the nuclear membranes and the nuclear-pore complexes (NPCs).<sup>1</sup> NPCs, formed by multiprotein assemblies that control trafficking between the nucleus and the cytoplasm, exhibit a strong degree of compositional conservation, and their functions are essential for tissue development and homeostasis.<sup>2</sup> Although the clinical importance of variants in most nuclear-envelope components remains unknown, those that have been implicated in Mendelian diseases frequently involve nervous-system pathology.<sup>2, 3</sup> Among the associated disorders, 2 produce movement disorder-predominant phenotypes: a dominantly inherited deletion-variant of the nuclear envelope-associated protein torsinA causes *TOR1A*-related dystonia, a childhood-onset dystonic syndrome with normal neuroimaging findings<sup>3</sup>; moreover, a missense variant in the gene encoding the NPC nucleoporin (NUP) protein *NUP62* (*NUP62*) has been reported in

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autosomal-recessive infantile striatonigral degeneration,<sup>4</sup> a multisymptomatic condition characterized by choreoathetosis, dystonia, and abnormal high T2-weighted MRI signals in the striatum. Here, we describe 3 families where biallelic variants in the gene encoding NUP62's direct interaction partner in the NPC,<sup>1</sup> *NUP54*, segregated with clinical presentations that showed striking similarities to *NUP62*-related disease.<sup>4</sup> Our study adds to the evidence that defects of nuclear-envelope components are associated with dystonia.<sup>3</sup>

## Subjects and Methods

### Case Identification

In 708 families with dystonia, we recently demonstrated that a disease-causing gene defect remains elusive in ~80% of cases.<sup>5</sup> With the goal of gene discovery, we reanalyzed genetic data from our cohort<sup>5</sup> resulting in identification of a *NUP54* candidate variant (family-A). A search for additional patients was undertaken using matchmaking nodes, which identified family-B in GeneMatcher<sup>6</sup> and family-C within the GENOMIT-project of individuals with suspected mitochondrial disorders including Leigh(-like) phenotypes. All families were enrolled in ethics review board-approved research protocols with informed consent. Families A-C were clinically evaluated in Munich, Germany; Strasbourg, France; and Tokyo, Japan.

### Genetic Investigations

Whole-exome sequencing was performed on patient-parent trios using published procedures.<sup>5, 7</sup> Rare-variant interrogation was first done with virtual panels containing genes with described association with monogenic disorders to exclude known disease etiologies.<sup>5, 7</sup> New candidates were ranked based on established criteria.<sup>5, 7</sup> Sanger-verification and *in-silico* modeling<sup>8, 9</sup> were performed for *NUP54* variants; the structure of vertebrate NPC channel-NUP hetero-trimer NUP54-NUP62-NUP58 was utilized<sup>10</sup> (PDB:5C3L) and a human model of NUP54-NUP62-NUP58-NUP93 complex<sup>11</sup> was built using AlphaFold (<https://alphafold.ebi.ac.uk/>) from available templates (PDB:5CWS).

### Western Blotting and Immunostaining

The following antibodies were used for Western-blot and/or immunocytochemistry experiments: anti-NUP54 (ab220890/HPA035929); anti-NUP62 (ab96134); anti-NUP58/NUP45 (HPA039360); and anti-NPC proteins/NUP98/NUP153 (mAb414).

## Results

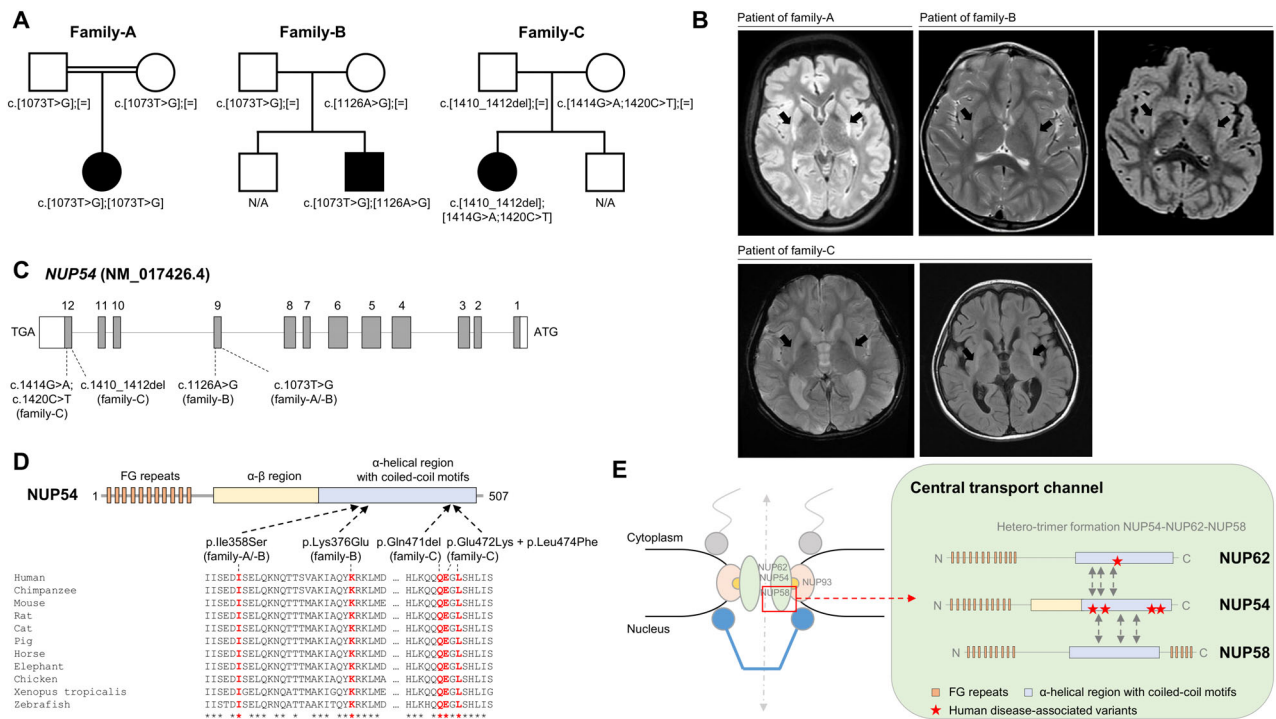
### Clinical Cases

Phenotypic manifestations of 3 patients from 3 unrelated families (Fig 1A) are compared in Table; these individuals presented with shared features of progressive neurological deterioration, suggestive of underlying mixed neurodevelopmental-neurodegenerative pathologies. Findings common to all subjects were movement disorders with dystonia, which dominated the disease courses (Videos S1 and S2). Dystonic symptoms started in the legs between

12 months-5 years of age, followed by rapid involvement of craniocervical, trunk, and 4-limb muscles. Involuntary oro-bulbar spasms resulted in dysarthria and inability to swallow with need for tube feeding. Accompanying limb-choreoathetoid and/or ataxic movements were also seen in all patients. Neurodevelopmental symptoms, mainly motor delay and hypotonia, were documented, but only one patient had intellectual disability. Brain MRIs performed for patients of family-A (age 17 years) and family-B (age 5 years) revealed T2/FLAIR hyperintensities in the dorsal parts of both putamina (Fig 1B). In family-C's patient, MRI findings (age 7 years) were thought to resemble Leigh-syndrome, with symmetrical T2/FLAIR-hyperintense basal-ganglia lesions affecting the putamina (Fig 1B).

### NUP54 Variants

The patients had homozygous or compound-heterozygous missense and in-frame deletion variants in *NUP54*, all located in close proximity toward the C-terminal end of the protein (Fig 1C; Table). An identical c.1073T > G (p.Ile358Ser) variant was identified in families A and B; the variant was homozygous in family-A's patient and carried in compound-heterozygosity with c.1126A > G (p.Lys376Glu) by family-B's patient. Family-C's patient harbored another set of compound-heterozygous alleles, a multi-nucleotide variation inducing 2 missense changes (c.1414G > A, p.Glu472Lys; c.1420C > T, p.Leu474Phe) and a c.1410\_1412del (p.Gln471del) 1-amino acid deletion. The variants were extremely rare and predicted by CADD to be deleterious (Table). Additionally, all variants clustered at invariant residues within the evolutionarily conserved coiled-coil domains of NUP54<sup>8, 9</sup> (Fig 1D); these motifs are crucial for protein-protein interactions in the central NPC channel, supporting NUP54's complex formation with NUP62 and NUP58 and anchorage of the resultant triple-subcomplex to the NPC scaffold<sup>8, 9, 11</sup> (Fig 1E). Among these NPC-channel NUPs, NUP54 is the most critical for providing plasticity to multimeric assemblies of NUP54, NUP62, and NUP58<sup>9</sup> (Suppl Fig 1). Hence, mutational defects of NUP54 could result in destabilization of the interactions between functionally related NUPs and (partial) disassembly of the channel-forming triple-subcomplex. To test this hypothesis, we performed protein-modeling analyses revealing that indeed all variants were expected to perturb integrity of the NUP54-NUP62-NUP58 hetero-trimer and/or the structural stability of this complex in relation to the neighboring NPC scaffold-protein NUP93<sup>8, 9, 11</sup> (Fig 2A). Since destabilized protein-complexes, including those affecting correct NPC assembly, are often subject to cellular clearance mechanisms,<sup>12</sup> we investigated steady-state levels of different NUPs in patient-derived fibroblasts (families-B/C). We found significantly reduced amounts of NUP54,



**FIGURE 1: Domain-specific *NUP54* variants in 3 unrelated patients. (A) Pedigrees of studied families and segregation of *NUP54* variants supporting autosomal-recessive inheritance. N/A, no genotyping available. (B) MR axial images showing abnormally high signals (arrows) in the dorsal parts of both putamina (patient of family-A at 17 years; patient of family-B at 5 years; patient of family-C at 7 years). In addition, the patient from family-C had global loss of cerebral volume. (C) Schematic drawing of *NUP54* (canonical isoform: NM\_017426.4) with location of the patient variants in the C-terminal exons. Intron-exon structure not drawn to exact scale. (D) Location of the variants on the *NUP54* protein, mapping within the coiled-coil motif region and nearby residues. All affected amino-acid positions are highly conserved (fully conserved positions are highlighted with asterisks [\*]). (E) Cartoon of the nuclear-pore complex (NPC; adapted from Guglielmi et al., 2020)<sup>2</sup> with the nucleoporins *NUP54*, *NUP62*, and *NUP58* at its center (green). The coiled-coil motifs in α-helical regions of these nucleoporins are required to form triple-subcomplexes (indicated by double arrows) and maintain the structure of the central channel; the disease-associated variants in *NUP54* (this study) and *NUP62* (Basel-Vanagaite et al., 2006)<sup>4</sup> fall into this protein–protein interaction region. The central-channel hetero-trimer of *NUP54*-*NUP62*-*NUP58* is anchored on the NPC via the scaffold protein *NUP93* (yellow).**

*NUP62*, and *NUP58* in association to variants identified in this study (Fig 2B; Suppl Fig 2); by contrast, the non-associated NPC components *NUP98* and *NUP153* were intact (Fig 2B; Suppl Fig 3). Using immunofluorescent stainings, we were able to demonstrate that mutant *NUP54*-proteins were still localized at the nuclear envelope in affected fibroblasts (Fig 2C).

## Discussion

We describe 3 independent patients with overlapping severe neurological phenotypes for whom trio-based whole-exome sequencing identified inherited variants of the nuclear-pore protein 54-encoding gene *NUP54* but no other pathogenic/or likely pathogenic gene-variations.

*NUP54* belongs to the class of central-channel NUPs that represent integral components of the innermost layer of the NPC, controlling the transport of proteins, mRNAs, and other macromolecules into and out of the nucleus.<sup>1</sup> Channel NUPs are organized into 2 basic domain-structures<sup>2</sup>: (1) a phenylalanine-glycine-rich repeat region, located at the

N-terminus in *NUP54*, which binds directly to transport receptors of particular cargoes and mediates their nucleocytoplasmic exchange; and (2) a coiled-coil-motif segment in the C-terminal α-helical region, which is critically required for subcomplex formation with other NUPs, thereby maintaining the overall structural architecture of the central transport channel of the NPC. *NUP54* and other transport-channel NUPs are highly expressed in the developing and adult brain,<sup>13, 14</sup> consistent with the key roles of the NPC in neurogenesis and promotion of neural maintenance.<sup>2</sup>

Collectively, we provide strong evidence that biallelic *NUP54* variants can cause a pediatric syndrome comprising progressive hyperkinetic movement abnormalities, striatal lesions, and variable neurodevelopmental disturbances. First, the identified variants, transmitted from asymptomatic carrier parents, segregated as expected for autosomal-recessive disease traits. No homozygous *NUP54* loss-of-function variants were represented in gnomAD, and we could neither find homozygous missense/in-frame deletion variants in the coiled-coil domain-encoding sequence of *NUP54* in gnomAD nor

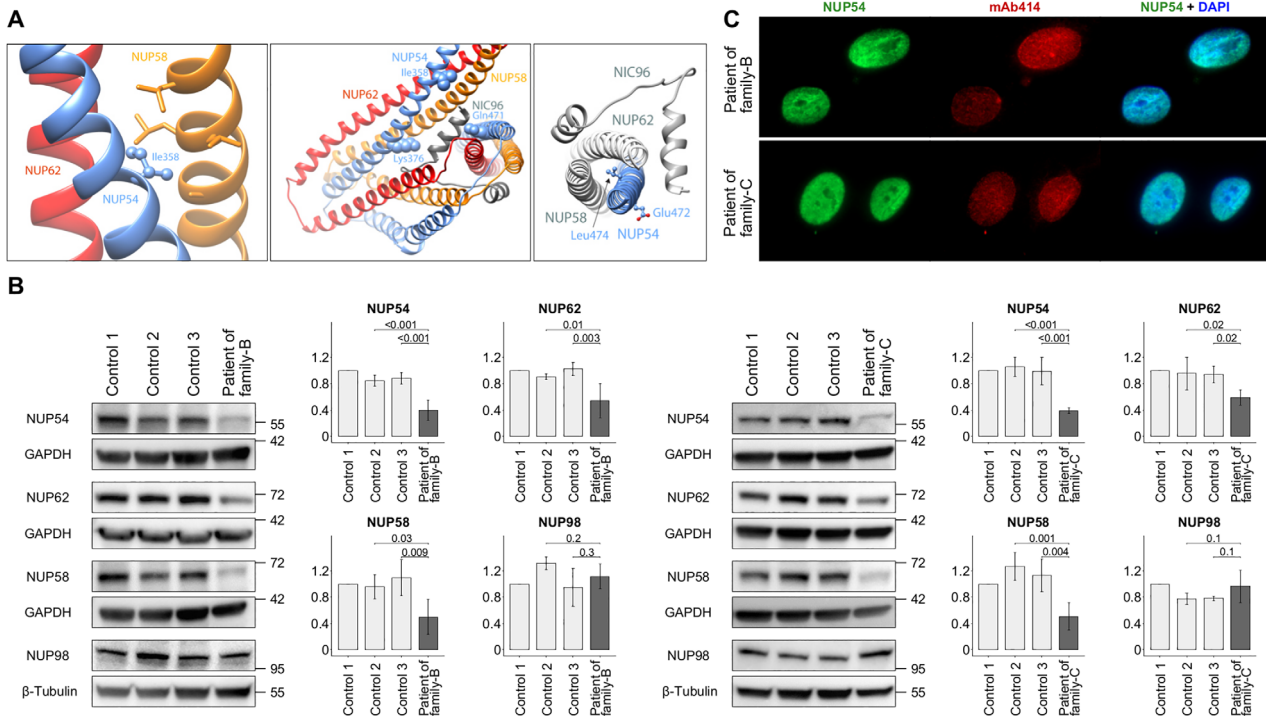
**TABLE. Molecular and Clinical Features of Patients with Biallelic *NUP54* Variants**

	Patient of Family-A	Patient of Family-B	Patient of Family-C
Variant(s) (NM_017426.4)	c.1073T > G (p.Ile358Ser), homozygous	c.1073T > G (p.Ile358Ser); c.1126A > G (p.Lys376Glu), compound heterozygous	c.1410_1412del (p.Gln471del); c.1414G > A (p.Glu472Lys) + c.1420C > T (p.Leu474Phe), compound heterozygous
Variant frequency (gnomAD), CADD score	2/244430 (no homozygotes), 32	2/244430 (no homozygotes); not found, 32; 28	2/238818 (no homozygotes); not found + not found, 23; 24 + 27
ACMG classification (pathogenicity criteria)	pathogenic (PS3, PM1, PM2, PP3, PP4)	pathogenic (PS3, PM1, PM2, PP3, PP4); pathogenic (PS3, PM1, PM2, PP3, PP4)	pathogenic (PS3, PM1, PM2, PP3, PP4); pathogenic (PS3, PM1, PM2, PP3, PP4)
Gender, current age, geographical origin (ethnicity)	F, 22 yr, Germany (European)	M, 6 yr, France (European)	F, 18 yr, Japan (Asian)
Movement disorder(s); gross motor skills (last assessment)	Progressive generalized dystonia (onset 13 mo), dysarthria, dysphagia (PEG tube), choreoathetoid movements, ataxia; wheelchair use	Progressive, predominantly lower-limb dystonia (onset 5 yr), dysarthria, dysphagia (PEG tube), chorea, ataxia; wheelchair bound	Progressive generalized dystonia (onset 12 mo), dysarthria, dysphagia (PEG tube), ataxia; bedridden
Neurodevelopmental and other comorbidities	DD, hypotonia, microcephaly	Hypotonia, oculomotor apraxia, sleep apnea	DD, ID, aspiration pneumonia, congenital cataract, hypoparathyroidism, chronic nephritis
MRI	Symmetrical T2/FLAIR hyperintensities in dorsal putamina (age 17 yr)	Symmetrical T2/FLAIR hyperintensities in dorsal putamina (age 5 yr)	Symmetrical T2/FLAIR hyperintensities in dorsal putamina, progressive atrophy of the basal ganglia, global cerebral atrophy (age 7 yr)

Abbreviations: ACMG, American College of Medical Genetics and Genomics; CADD, combined annotation dependent depletion; DD, developmental delay; F, female; FLAIR, fluid-attenuated inversion recovery; ID, intellectual disability; M, male; MRI, magnetic resonance imaging; PEG, percutaneous endoscopic gastrostomy.

biallelic rare protein-altering *NUP54* variants in >25,000 clinical exomes of individuals with nonrelated conditions within our local databases. Bioinformatics analyses including frequency assessment, deleteriousness prediction, amino acid-conservation evaluation, and structural modeling demonstrated that the variants were ultra-rare and likely disruptive. Accordingly, all variants qualified as pathogenic alterations<sup>15</sup> (Table ). Second, the observed C-terminal clustering of variants detected in different families was remarkable; in the 2 compound-heterozygous individuals, variants occurred on nearby residues within the same exons, a pattern that might reflect a pathophysiological mechanism. Notably, a homozygous p.Gln391Pro variant in the coiled-coil domain of *NUP62* that directly interacts with *NUP54*'s

coiled-coils has been shown to interfere with channel-NUP subcomplex assembly,<sup>8</sup> suggesting a deleterious impact on NPC structure.<sup>8</sup> The functional importance of the coiled-coil motifs of channel NUPs has also been studied during *Drosophila* development, where C-terminal truncation of *NUP54* was shown to produce neural-circuit architecture defects.<sup>16</sup> Given the locations of herein and previously reported<sup>4</sup> variants, in conjunction with support from the literature highlighting the role of *NUP54*'s C-terminus in neurotypical development,<sup>16</sup> it seems plausible to hypothesize that perturbation of subcomplex interaction-domain residues of different channel NUPs could represent a general pathomechanism leading to related (neurodevelopmental) phenotypes. Similar to patients with *NUP62* variants,<sup>4</sup> our



**FIGURE 2:** In silico and protein-biochemical studies of *NUP54* variants. (A) Structural analysis of mutated *NUP54* residues within the *NUP54*-*NUP62*-*NUP58* subcomplex. Left panel: Schematic representation of wild-type “knob” *NUP54* residue Ile358 (in stick-and-ball representation) that fits into hole formed by non-polar Ala and Leu side chains in *NUP58* (in stick representation). The Ile358Ser variant has apparently a deleterious effect on *NUP54*-*NUP62*-*NUP58* trimerization processes as the polar Ser moiety is likely to destabilize the knob-into-hole contact between  $\alpha$ -helices. The analyzed structure represents the partial vertebrate *Xenopus laevis* *NUP54*-*NUP62*-*NUP58*<sup>10</sup> (PDB:5C3L). The residues indicated are identical in the human *NUP54* sequence and human Ile358 corresponds to Ile386 in *Xenopus laevis* *NUP54*. *NUP54*, *NUP62*, and *NUP58* are depicted in blue, red, and orange, respectively. Middle panel: Visualization of *NUP54* Ile358, Lys376, and Gln471 (in sphere representation) within human hetero-trimeric *NUP54*-*NUP62*-*NUP58* in complex with NIC96, a fungal homologue of the human NPC scaffold protein *NUP93*. A human model of fungal *NUP54*-*NUP62*-*NUP58* in complex with NIC96<sup>11</sup> was built using AlphaFold (<https://alphafold.ebi.ac.uk/>) from an available structure (PDB:5CWS). Lys376 and Gln471 of *NUP54* are surface residues in close vicinity of invaginated NIC96  $\alpha$ -helix and likely a part of the interacting surface. Identified variants at these residues seem to affect the attachment of the heterotrimeric subcomplex to NIC96. In addition, the deletion of Gln471 would change the register of buried non-polar residues in the amphipathic *NUP54* helix leading to gross changes in the stability of the C-terminal *NUP54*-*NUP62*-*NUP58* coiled-coil region. Right panel: modeling of residues affected by the missense changes *in cis* suggests that substitution of buried residue Leu474 to “bulkier” Phe most likely alters the packing of non-polar residues within the heterotrimeric *NUP54*-*NUP62*-*NUP58* subcomplex. Glu472 is a surface residue, and the modelled human *NUP54*-*NUP62*-*NUP58* with an interacting domain of NIC96 (*NUP93*) indicates that the variant Glu472Lys may perturb bridging interactions that anchor *NUP54*-*NUP62*-*NUP58* to the NPC. (B) Western blots showing reduced expression of *NUP54* and its interaction partners *NUP62*/*NUP58* in patient fibroblasts. Quantitative analyses of relative *NUP* protein levels are shown next to the Western blots; the intensities of total protein signals were normalized to GAPDH (G8795) or  $\beta$ -tubulin (11–13,002). Bars indicate the mean  $\pm$  SD in lysates of separate fibroblast cultures. (C) Indirect immunofluorescent staining on fibroblasts of affected individuals. Expression of mutant *NUP54* (green) is confined to the nucleus/nuclear envelope, similar to other NPC components (mAb414 staining; red). Nuclei were counterstained with DAPI (blue).

cases manifested early-onset dystonic and choreoathetoid movements with gradual progression, leading to significant impairments (1/3) or loss (2/3) of independent ambulation. Another important overlap was seen with regard to presence of marked oro-lingual-buccal dystonia with dysphagia and dysarthria, a clue that often points to strategic basal-ganglia lesions. Furthermore, patients with both *NUP54* and *NUP62* variants displayed distinctive neuroanatomical alterations with MRI abnormalities consisting primarily of a signal increase on T2/FLAIR-weighted images in the striatum. Third, we observed decreased amounts of *NUP54* and its immediate subcomplex partner proteins in skin-fibroblasts

harboring the variants of our patients. Although this remains to be directly confirmed, the clustered variants are expected to induce expression changes of *NUP54* and *NUP62*/*NUP58* by impairing protein–protein interactions and multimerization processes, as has been shown for other *NUP* variant-alleles implicated in human disorders.<sup>17</sup> We speculate that mutant and/or mal-assembled patient proteins might be degraded by quality-control systems for NPC integrity; this would be consistent with studies in yeast and human cells demonstrating proteosomal clearance of defective NPC-assembly intermediates, e.g. via *VPS4*/*VPS4A*,<sup>12</sup> variants of which have also been associated with dystonia.<sup>18</sup> Absence of

biallelic *NUP54* loss-of-function variants in our series and controls, as well as detectable levels of residual NUP54-protein in studied cells suggest that the identified variants are hypomorphic (i.e., partial loss-of-function) alleles; complete loss of NUP54 might be incompatible with life. Our immunocytochemistry analyses showing that patient fibroblasts had predominant localization of mutant NUP54 at the nuclear envelope indicate that the variants may exert their pathogenicity via disruption of nuclear pore-linked mechanisms such as macromolecular traffic-control. In line with this, an *in vitro* study of NUP-depleted cells identified significant alterations in nuclear-transport kinetics in association to a 50 to 75% decrease in total cellular amounts of NUP54.<sup>19</sup> However, a wide array of transport-independent or only indirectly transport-associated functions has been described for NPCs and nuclear pore-related factors including NUP54, ranging from regulation of chromatin states (similar to the dystonia-linked gene *KMT2B*)<sup>2</sup> to transposon silencing.<sup>20</sup> Future studies optimally involving iPSC-derived neuronal models are required to more precisely elucidate the impact of the NUP54 C-terminal variants on the channel-NUP subcomplex and their downstream effects in the context of dystonia pathogenesis.

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## Author Contributions

P.H., A.S., M.S., J.W., and M.Z. contributed to study concept and design. All authors contributed to data acquisition and analysis. P.H., I.M., and M.Z. contributed to drafting the manuscript and figures.

## Potential Conflicts of Interest

None of the authors has any relevant conflict of interest to declare.

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