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

Philip Harrer, MD,[1,2] Audrey Schalk, MD,[3] Masaru Shimura, MD, PhD,[1,4] Sarah Baer, MD,[5,6] Nadège Calmels, PharmD, PhD,[3,7] Marie Aude Spitz, MD,[5] Marie-Thérèse Abi Warde, MD,[5] Elise Schaefer, MD, PhD,[8] Volker M.Sc Kittke, MSc,[1,2] Yasemin Dincer, MSc,[9,10] Matias Wagner, MD,[1,2] Ivana Dzinovic, MSc,[1,2] Riccardo Berutti, PhD,[1,2] Tatsuharu Sato, MD,[11] Toshihiko Shirakawa, MD, PhD,[11] Yasushi Okazaki, MD, PhD,[12] Kei Murayama, MD, PhD,[4,12] Konrad Oexle, MD,[1,2] Holger Prokisch, PhD,[1,2] Volker Mall, MD,[9,13] Ivo Melčák, PhD,[14] Juliane Winkelmann, MD,[1,2,15,16] and Michael Zech, MD[1,2]

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.

ANN NEUROL 2023;93:330–335

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).[1] 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.[2] 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.[2, 3] 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[3]; moreover, a missense variant in the gene encoding the NPC nucleoporin (NUP) protein NUP62 (*NUP62*) has been reported in

From the [1]Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany; [2]Institute of Human Genetics, School of Medicine, Technical University of Munich, Munich, Germany; [3]Institut de génétique médicale d'Alsace (IGMA), Laboratoires de Diagnostic Génétique, Hôpitaux universitaires de Strasbourg, Strasbourg, France; [4]Center for Medical Genetics, Department of Metabolism, Chiba Children's Hospital, Chiba, Japan; [5]Department of Neuropediatrics, ERN EpiCare, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [6]Institute for Genetics and Molecular and Cellular Biology (IGBMC), Illkirch, France; [7]Laboratoire de Génétique Médicale, INSERM U1112, Institut de génétique médicale d'Alsace, CRBS, Strasbourg, France; [8]Service de Génétique Médicale, Institut de Génétique Médicale d'Alsace (IGMA), Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [9]Lehrstuhl für Sozialpädiatrie, Department of Pediatrics, Technische Universität München, Munich, Germany; [10]Zentrum für Humangenetik und Laboratoriumsdiagnostik (MVZ), Martinsried, Germany; [11]Department of Pediatrics, Nagasaki University Hospital, Nagasaki, Japan; [12]Diagnostics and Therapeutic of Intractable Diseases, Intractable Disease Research Center, Graduate School of Medicine, Juntendo University, Tokyo, Japan; [13]kbo-Kinderzentrum München, Munich, Germany; [14]Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory School of Medicine, Atlanta, Georgia, USA; [15]Lehrstuhl für Neurogenetik, Technische Universität München, Munich, Germany; and [16]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

Address correspondence to Dr Zech, Institute of Neurogenomics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany. E-mail: michael.zech@mri.tum.de

Additional supporting information can be found in the online version of this article.

Received Aug 1, 2022, and in revised form Oct 31, 2022. Accepted for publication Nov 3, 2022.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26544.

Philip Harrer, Audrey Schalk and Masaru Shimura contributed equally to this work as first authors.

Juliane Winkelmann and Michael Zech contributed equally to this work as last authors.

autosomal-recessive infantile striatonigral degeneration,[4] 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,[1] *NUP54*, segregated with clinical presentations that showed striking similarities to *NUP62*-related disease.[4] Our study adds to the evidence that defects of nuclear-envelope components are associated with dystonia.[3]

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.[5] With the goal of gene discovery, we reanalyzed genetic data from our cohort[5] 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[6] 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.[5, 7] Rare-variant interrogation was first done with virtual panels containing genes with described association with monogenic disorders to exclude known disease etiologies.[5, 7] New candidates were ranked based on established criteria.[5, 7] Sanger-verification and *in-silico* modeling[8, 9] were performed for *NUP54* variants; the structure of vertebrate NPC channel-NUP hetero-trimer NUP54-NUP62-NUP58 was utilized[10] (PDB:5C3L) and a human model of NUP54-NUP62-NUP58-NUP93 complex[11] 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[8, 9] (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[8, 9, 11] (Fig 1E). Among these NPC-channel NUPs, NUP54 is the most critical for providing plasticity to multimeric assemblies of NUP54, NUP62, and NUP58[9] (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[8, 9, 11] (Fig 2A). Since destabilized protein-complexes, including those affecting correct NPC assembly, are often subject to cellular clearance mechanisms,[12] we investigated steady-state levels of different NUPs in patient-derived fibroblasts (families-B/C). We found significantly reduced amounts of NUP54,

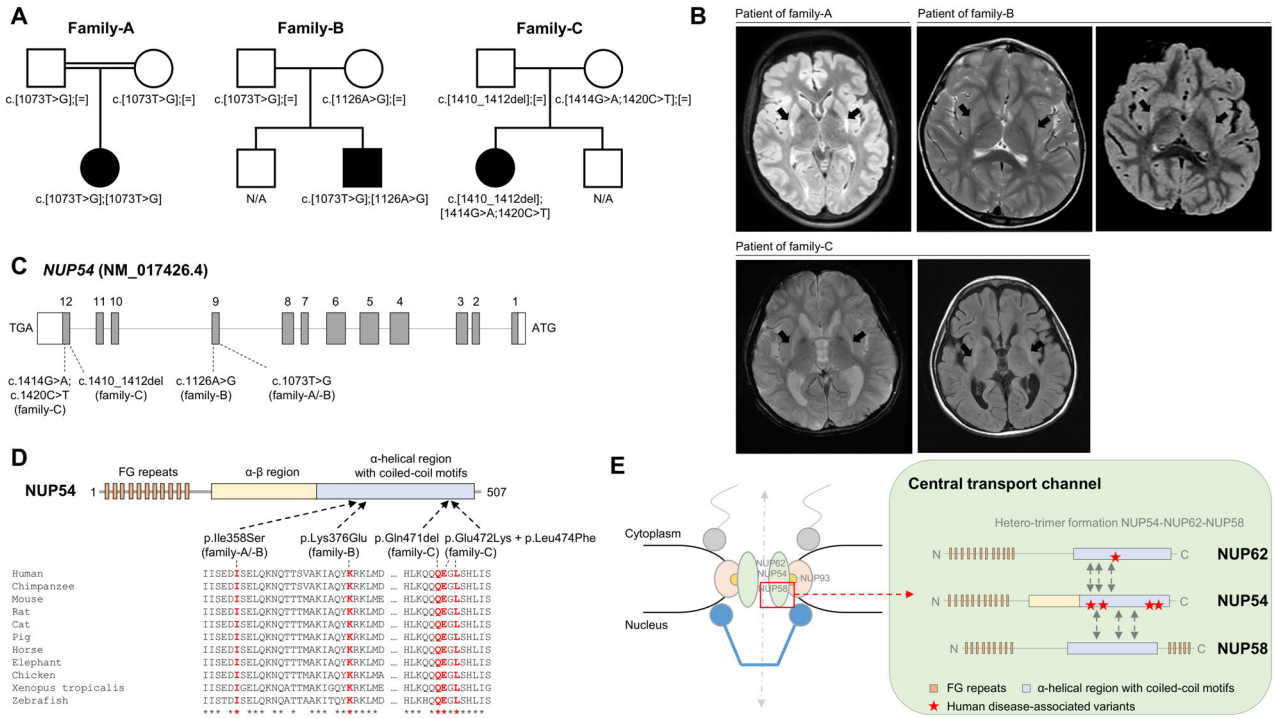

FIGURE 1: Domain-specific *NUP54* variants in 3 unrelated patients. (A) Pedigrees of studied families and segregation of *NUP54* variants supporting autosomal-recessive inheritance. N/A, no genotyping available. (B) MR axial images showing abnormally high signals (arrows) in the dorsal parts of both 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)[2] 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)[4] 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.[1] Channel NUPs are organized into 2 basic domain-structures[2]: (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 nucleo-cytoplasmic exchange; and (2) a coiled-coil-motif segment in the C-terminal alpha-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,[13, 14] consistent with the key roles of the NPC in neurogenesis and promotion of neural maintenance.[2]

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[15] (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 subomplex assembly,[8] suggesting a deleterious impact on NPC structure.[8] 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.[16] Given the locations of herein and previously reported[4] variants, in conjunction with support from the literature highlighting the role of NUP54's C-terminus in neurotypical development,[16] 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,[4] our

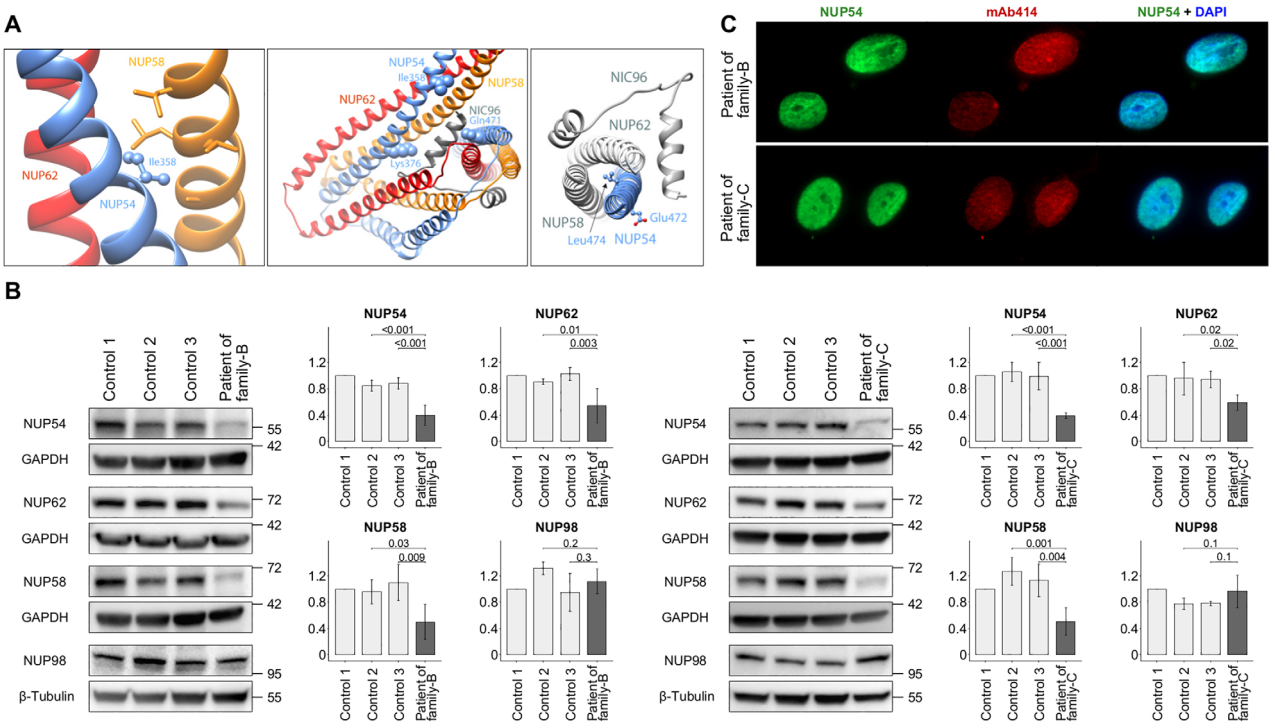

FIGURE 2: In silico and protein-biochemical studies of *NUP54* variants. (A) Structural analysis of mutated NUP54 residues within the NUP54-NUP62-NUP58 subcomplex. Left panel: Schematic representation of wild-type "knob"NUP54 residue Ile358 (in stick-and-ball representation) that fits into hole formed 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 α-helices. The analyzed structure represents the partial vertebrate Xenopus laevis NUP54-NUP62-NUP58[10] (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[11] 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 α-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 β-tubulin (11–13,002). Bars indicate the mean ± 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.[17] 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,[12] variants of which have also been associated with dystonia.[18] 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.[19] 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*)[2] to transposon silencing.[20] 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.

Acknowledgments

We thank the patients and their families who took part in our study. This study was funded in part by a research grant from the Else Kröner-Fresenius-Stiftung, the European Joint Programme on Rare Diseases (EJP RD) project GENOMIT (01GM1920A), as well as by in-house institutional funding from Technische Universität München, Munich, Germany, and Helmholtz Zentrum München, Munich, Germany. MZ and JW receive research support from the German Research Foundation (DFG 458949627; ZE 1213/2-1; WI 1820/14-1). MS acknowledges the research support from JSPS Overseas Research Fellowships. This work was supported in part by the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development, AMED (JP22ek0109468, JP22kk0305015). We gratefully thank Monika Zimmermann and Celestine Dutta (Institute of Neurogenomics, Helmholtz Center Munich, Munich, Germany) for their generous contribution with immunoblotting analyses. Open Access funding enabled and organized by Projekt DEAL.

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.

References

1. Strambio-De-Castillia C, Niepel M, Rout MP. The nuclear pore complex: bridging nuclear transport and gene regulation. Nat Rev Mol Cell Biol 2010;11:490–501.
2. Guglielmi V, Sakuma S, D'Angelo MA. Nuclear pore complexes in development and tissue homeostasis. Development 2020;147:dev183442.
3. Worman HJ, Dauer WT. The nuclear envelope: an intriguing focal point for neurogenetic disease. Neurotherapeutics 2014;11:764–772.
4. Basel-Vanagaite L, Muncher L, Straussberg R, et al. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. Ann Neurol 2006;60:214–222.
5. Zech M, Jech R, Boesch S, et al. Monogenic variants in dystonia: an exome-wide sequencing study. Lancet Neurol 2020;19:908–918.
6. Sobreira N, Schiettecatte F, Valle D, Hamosh A. GeneMatcher: a matching tool for connecting investigators with an interest in the same gene. Hum Mutat 2015;36:928–930.
7. Schalk A, Cousin MA, Dsouza NR, et al. De novo coding variants in the AGO1 gene cause a neurodevelopmental disorder with intellectual disability. J Med Genet 2022;59:965–975.
8. Solmaz SR, Chauhan R, Blobel G, Melcak I. Molecular architecture of the transport channel of the nuclear pore complex. Cell 2011;147:590–602.
9. Sharma A, Solmaz SR, Blobel G, Melcak I. Ordered regions of channel nucleoporins Nup62, Nup54, and Nup58 form dynamic complexes in solution. J Biol Chem 2015;290:18370–18378.
10. Chug H, Trakhanov S, Hulsmann BB, et al. Crystal structure of the metazoan Nup62*Nup58*Nup54 nucleoporin complex. Science 2015;350:106–110.
11. Stuwe T, Bley CJ, Thierbach K, et al. Architecture of the fungal nuclear pore inner ring complex. Science 2015;350:56–64.
12. Webster BM, Colombi P, Jager J, Lusk CP. Surveillance of nuclear pore complex assembly by ESCRT-III/Vps4. Cell 2014;159:388–401.
13. Thul PJ, Lindskog C. The human protein atlas: a spatial map of the human proteome. Protein Sci 2018;27:233–244.
14. Miller JA, Ding SL, Sunkin SM, et al. Transcriptional landscape of the prenatal human brain. Nature 2014;508:199–206.
15. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–424.
16. Nallasivan MP, Haussmann IU, Civetta A, Soller M. Channel nuclear pore protein 54 directs sexual differentiation and neuronal wiring of female reproductive behaviors in *Drosophila*. BMC Biol 2021;19:226.
17. 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;105:48–64.
18. Rodger C, Flex E, Allison RJ, et al. De novo VPS4A mutations cause multisystem disease with abnormal neurodevelopment. Am J Hum Genet 2020;107:1129–1148.
19. Yoo TY, Mitchison TJ. O-GlcNAc modification of nuclear pore complexes accelerates bidirectional transport. J Cell Biol 2021;220:e202010141.
20. Munafo M, Lawless VR, Passera A, et al. Channel nuclear pore complex subunits are required for transposon silencing in *Drosophila*. Elife 2021;10:e66321.