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Prominent Movement Disorders in RNU2-2-Related Spliceosomopathy

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ABSTRACT

Pediatric movement disorders often overlap with neurodevelopmental diseases, suggesting shared molecular mechanisms. Variants in small nuclear RNA (snRNA) genes encoding spliceosome components have recently been associated with neurodevelopmental disorders, termed "RNUopathies." We analyzed genome sequencing data from 14 patients with undiagnosed pediatric movement disorders for pathogenic variants in snRNA genes. We identified recurrent *de novo RNU2-2* variants (n.35A > G and n.4G > A) in two patients with intellectual disability, epilepsy, and hyperkinetic movement disorders. RNA sequencing of fibroblasts in one patient showed no characteristic transcriptomic signature. Spliceosomopathies should be considered in neurodevelopmental disorders and developmental and epileptic encephalopathies with hyperkinetic features.

1 | Introduction

Pediatric movement disorders (PMDs) are a heterogeneous group of neurological diseases with diverse clinical presentations and etiologies. The implementation of next-generation sequencing has significantly increased the rate of genetic findings in PMDs [1]. Moreover, combining multiomics approaches has improved variant interpretation and diagnostic yield in unsolved cases [2, 3]. Nevertheless, despite extensive genetic investigations, more than half of individuals with a presumed hereditary movement disorder still do not receive a molecular diagnosis [2, 4].

To date, most studies across various genetic diseases have used exome sequencing (ES), which typically does not analyze non-coding regions, particularly those located far from protein-coding genes [5]. Importantly, growing evidence supports a contribution of the non-coding genome to penetrant monogenic diseases [6]. Most recently, several genes encoding small nuclear RNAs (snRNAs), a subclass of non-coding RNAs that form the spliceosome, have been linked to dominant and recessive neurodevelopmental disorders (NDDs) [5, 7–14].

The spliceosome is a large RNA–protein complex that recognizes intronic splice sites and removes introns from precursor messenger RNA. The major spliceosome, which catalyzes the splicing of over 99% of introns in the human genome, consists of five snRNAs (U1, U2, U4, U5, and U6), each associated with a range of other proteins [15]. Spliceosomopathies arise from pathogenic variants in genes encoding snRNAs or spliceosomal proteins, leading to splicing defects. The associated phenotypes are diverse and include retinitis pigmentosa, myelodysplastic syndromes, mandibulofacial dysostosis, NDDs, cerebellar ataxia, and epilepsy [15–19].

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In 2024, *de novo* variants in *RNU4-2* were shown to cause one of the most prevalent known NDDs—ReNU syndrome [5, 7]. Subsequently, in 2025, variants in another major spliceosome gene, *RNU2-2*, were reported to cause a distinct developmental and epileptic encephalopathy [8, 9]. Notably, initial studies primarily focused on neurodevelopmental and epileptic phenotypes, whereas motor symptoms have not been systematically examined. Given the substantial overlap between NDDs and movement disorders, we aimed to investigate the contribution of snRNA-related spliceosomopathies to undiagnosed PMDs.

2 | Patients and Methods

We analyzed genome sequencing results from 14 Polish and Ukrainian patients with complex PMDs for pathogenic variants in snRNA genes linked to neurodevelopmental and movement disorders, namely *RNU4-2*, *RNU2-2*, *RNU12*, *RNU5B-1*, and *RNU5A-1*. The families were recruited from the Developmental Neurology Department at the Medical University of Gdansk (MUG, Poland). The cohort included seven females and seven males, with a mean age of 11.1 years (range: 2–28 years). Dystonia was present in 11 patients, chorea in four, ataxia in four, and pyramidal signs in five. Motor delay and/or regression were reported in all patients; eight individuals were nonverbal or minimally verbal, nine were diagnosed with intellectual disability (ID), and five had epilepsy (Table S1). All patients underwent extensive prior diagnostic work-up, including magnetic resonance neuroimaging (MRI), electrophysiological studies, laboratory investigations, and exome sequencing (2/14) or trio exome sequencing (12/14), which yielded no diagnosis. Whole-genome sequencing was performed in short read mode as described recently [2]. Twelve cases underwent trio-WGS, and two patients underwent singleton WGS. Briefly, sequencing was carried out on an Illumina NovaSeq6000 and raw data were analyzed with a custom-built pipeline (Munich EVAdb, https://github.com/mri-ihg/EVAdb). We screened the sequences of snRNA genes in genomic data using hg19 annotations, considering known (likely) pathogenic entries for these genes in ClinVar. In addition, RNA sequencing was performed on cultured skin fibroblasts from one patient with an *RNU2-2* variant (P7). Transcriptome-wide analysis for aberrant splicing was conducted using FRASER2 within our established diagnostic framework [3]. Significant splicing outliers were defined according to thresholds described in Saparov *et* al. [3], with particular attention to targets of the U2 snRNA (major spliceosome). This work was performed as part of an ethics-approved study on dystonia genetics (TU Munich) and was approved by MUG Bioethics Committee.

3 | Results

We uncovered two recurrent *de novo* substitutions in *RNU2-2*, n.35A > G and n.4G > A, in patients 7 (P7) and 14 (P14), respectively (Figure 1A). Both variants were classified as pathogenic according to ACMG/AMP criteria [20]. The n.35A > G variant in P7 fulfilled criteria PS2 (confirmed *de novo*), PM2 (absent from population databases), PP3 (computational evidence of pathogenicity), and PS1 (previously reported pathogenic variant at the same position). The n.4G > A variant in P14 similarly fulfilled PS2, PM2, PP3, and PS1. No other pathogenic or likely pathogenic variants were identified in the investigated snRNA genes or in other established disease genes in the remaining cases. Therefore, these patients remained unsolved. To test whether the *RNU2-2* n.35A > G variant produced perturbation of downstream RNA targets, we ran a transcriptomics pipeline on cultured skin fibroblasts derived from P7. We did not identify significant splicing outliers—including in major spliceosome targets—consistent with previous findings from other *RNU2-2* cases [8, 12].

A seven-year-old female (P7) and an eleven-year-old male (P14) shared key clinical features, including global developmental delay, severe intellectual disability, and drug-resistant epilepsy. Both presented with neonatal hypotonia and feeding difficulties, followed by developmental regression and plateauing after seizure onset at 25 and 19 months of age, respectively. Multiple seizure types were observed, including tonic–clonic, focal clonic, focal impaired consciousness, tonic, myoclonic, atonic, and absence seizures, including episodes of status epilepticus. Electroencephalography showed multifocal and generalized epileptiform discharges (Figure 1B). According to the International League Against Epilepsy classification, epilepsy in both patients was consistent with Lennox–Gastaut syndrome [21]. Brain MRI, metabolic investigations, and extensive prior genetic testing were unremarkable. Detailed clinical information is provided in the Appendix S1.

In P7, mild involuntary movements were noted in the neonatal period and initially interpreted as restlessness. The movement disorder later showed marked fluctuations, with episodes of generalized hyperkinesia alternating with mild choreiform limb movements. At 7 years of age, the patient is nonverbal and gastrostomy-fed; she can sit unsupported but is unable to stand or walk. Neurological examination revealed facial dysmorphic features (a bulbous nose, low-set ears), strabismus, sialorrhea, generalized hypotonia, pyramidal signs in the lower limbs (hyperreflexia, ankle clonus, and Babinski sign), and generalized chorea (Figure 1C; Video S1). Involuntary movements were exacerbated by physical activity, emotional stress, and fatigue.

P14 began walking with assistance at 20 months. At 11 years, examination showed dysmorphic features (long palpebral fissures, long eyelashes, and a broad nasal root), a slender build, generalized hypotonia, joint laxity, an unstable walking pattern with flexed elbows, and almost continuous hand stereotypies (Figure 1D; Video S2). Episodes of hyperventilation occasionally preceded generalized tonic–clonic seizures. The patient is nonverbal and exhibits autistic features, including limited eye contact, repetitive movements, and intense preoccupation with specific objects.

4 | Discussion

De novo variants in *RNU2-2*, which encodes the U2 component of the major spliceosome, have been associated with a distinct form of syndromic NDD—developmental and epileptic encephalopathy (DEE) 119 (MIM#621304). DEE119 is characterized by global developmental delay with regression, drug-resistant epilepsy, severe to profound intellectual disability, hypotonia, hyperventilation, and dysmorphic features, as summarized by

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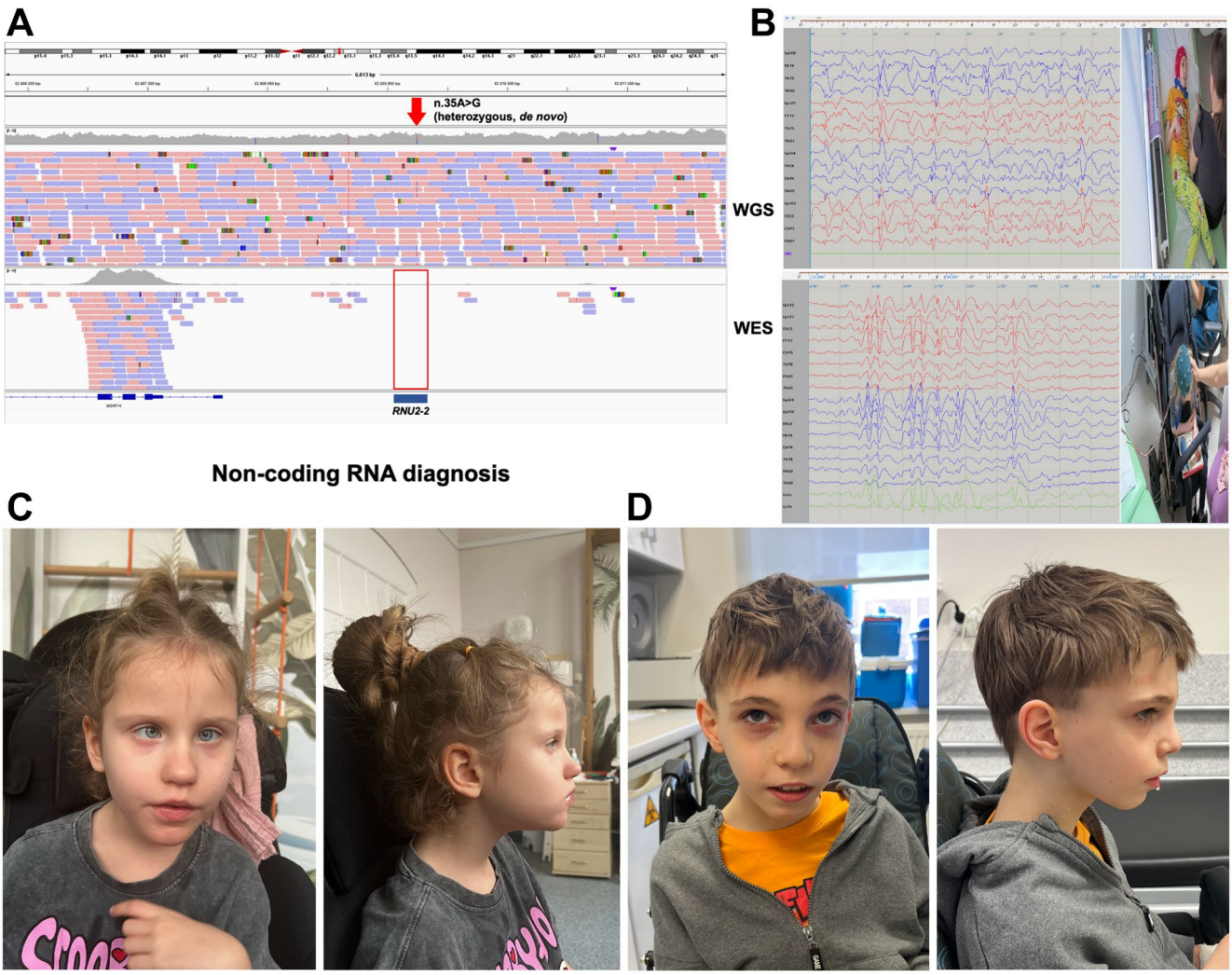

FIGURE 1 | *Molecular, electrophysiological, and dysmorphic features of patients with pathogenic dominant RNU2-2 variants.* (A) Molecular genetic findings in patient 7 (P7) showing the heterozygous *de novo RNU2-2* n.35A > G variant. The variant was not detected by whole-exome sequencing (WES) but was identified by whole-genome sequencing (WGS). (B) EEG recordings of patients 7 (P7, lower trace) and 14 (P14, upper trace) demonstrating generalized slow spike-and-wave complexes (1–2.5 Hz). (C) Facial dysmorphic features of P7 including strabismus, bulbous nose, and low-set ears. (D) Facial dysmorphic features of P14 including long palpebral fissures, long eyelashes, and a broad nasal root and tip.

Chiu *et* al. [22] Two recurrent *RNU2-2* substitutions, n.4G > A and n.35A > G, have been identified in most cases, but additional pathogenic variants continue to be discovered. Although initially considered a dominant disorder, recent studies have shown that *RNU2-2* variants cause both dominant and recessive NDDs, with the recessive form at least twice as common as the dominant form [11–13]. *RNU2-2*-related phenotypes span from DEE to mild learning disability without epilepsy, demonstrating a wide clinical spectrum of this spliceosomopathy, recently named "ReNU2" syndrome [12].

Movement disorders have repeatedly been described in patients with ReNU2 syndrome [8, 9, 11, 13]. In the initial studies, Jackson *et* al. reported a patient with stereotyped hand movements, while Greene *et* al. described individuals with hand stereotypies, tremor, dystonia, chorea, and ataxia [8, 9]. In a recent series of individuals with dominant and recessive *RNU2-2* variants, movement disorders were present in 29 out of 76 cases (38%) and occurred more frequently in biallelic than in monoallelic forms [13]. Although detailed motor phenotypes were not systematically described, available data suggest that RNU2-2 disruption leads to a complex movement disorder including chorea, dystonia, tremor, stereotypies, and ataxia. Preliminary data suggest a possible association between the n.35A > G variant and chorea, and between n.4G > A and motor stereotypies. However, these observations are based on a very small number of cases and require confirmation in larger cohorts before any genotype–phenotype inference can be drawn.

The exact mechanism by which *RNU2-2* variants affect splicing in humans remains unknown. U2 snRNA is essential at all stages of the splicing process, including spliceosome assembly, intron substrate recognition, and protein scaffolding [23]. In contrast to *RNU4-2* patients, who exhibited specific defects in alternative 5′ splice-site selection, investigation of blood and fibroblast transcriptomes has not revealed a distinct splicing signature among *RNU2-2* patients [8, 12]. This is consistent with our findings, as we did not detect significant aberrant splicing

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events in fibroblasts from P7 carrying the n.35A > G variant. It has been shown that *RNU2-2* variants cause subtle disruptions of alternative splicing without generating novel splice junctions detectable in blood [13]. Therefore, studies on neuronal stem cells and mouse models may be required to elucidate the molecular mechanisms of *RNU2-2* syndrome [8]. Supporting this, a global disruption of alternative splicing leading to neurodegeneration was demonstrated in the cerebellum of mice homozygous for a deletion in the U2 ortholog, *Rnu2-8* [24].

Given that recently described RNUopathies account for about 1.5% of previously unexplained NDDs [11], identifying two carriers in a group of 14 undiagnosed patients with complex PMDs suggests potential ascertainment bias. Our cohort was enriched for hyperkinetic movement disorders in the context of syndromic NDDs, rather than representing an unselected NDD population. The observed frequency (2/14, ~14%) exceeds expected background rates, supporting movement disorders as a genuine feature of *RNU2-2* syndrome rather than coincidental ascertainment. Studies on larger PMD cohorts will be required to formally quantify this enrichment.

Non-coding genes are increasingly being identified as causal for diverse monogenic disorders; however, their contribution to hereditary movement disorders is still poorly understood. Our findings highlight spliceosomopathies as emerging causes of PMDs. Although hyperkinetic features occur in a minority of cases (~35%–40%) [11, 13], their presence in the context of NDDs or DEE should prompt consideration of ReNU2 syndrome. Beyond *RNU2-2*, variants in other snRNA genes, especially *RNU4-2*, may explain additional cases, supporting systematic interrogation of pathogenic snRNA loci in WGS data for unsolved PMDs.

Author Contributions

M.K., M.Z.: conception, organization and execution of research project; writing of the first draft and review and critique of manuscript preparation. U.S., M.W., M.Z.A., A.L.: organization and execution of research project; review and critique of manuscript preparation. M.M.B.: conception and organization of research project; review and critique of manuscript preparation.

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Ethics Statement

This study was approved by the Ethics Committees of the Technical University of Munich and the Medical University of Gdansk. Written informed consent for the publication of genetic and clinical data, including videos, was obtained from the patient's parents. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Conflicts of Interest

This authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Patient case descriptions. **Video S1:** Generalized chorea with marked exacerbation of hyperkinesia during excitement in a patient with the n.35A > G *RNU2-2* variant (P7). **Video S2:** Motor stereotypies with hyperventilation and an abnormal, asymmetric, unstable gait in a patient with the n.4G > A *RNU2-2* variant (P14). **Table S1:** Clinical characteristics of the studied group.

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