HNRNPH1-related syndromic intellectual disability: Seven additional cases suggestive of a distinct syndromic neurodevelopmental syndrome

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Abstract
Pathogenic variants in HNRNPH1 were first reported in 2018. The reported individual, a 13 year old boy with a c.616C>T (p.R206W) variant in the HNRNPH1 gene, was noted to have overlapping symptoms with those observed in HNRNPH2-related X-linked intellectual disability, Bain type (MRXSB), specifically intellectual disability and dysmorphic features. While HNRNPH1 variants were initially proposed to represent an autosomal cause of MRXSB, we report an additional seven cases which identify phenotypic differences from MRXSB. Patients with HNRNPH1 pathogenic variants diagnosed via WES were identified using clinical networks and GeneMatcher. Features unique to individuals with HNRNPH1 variants include distinctive dysmorphic facial features; an increased incidence of congenital anomalies including cranial and brain abnormalities, genitourinary malformations, and palate abnormalities; increased incidence of ophthalmologic abnormalities; and a decreased incidence of epilepsy and
1 | INTRODUCTION

The \textit{HNRNPH1} [MIM 601035] and \textit{HNRNPH2} [MIM 300986] genes produce the hnRNP H and hnRNP H’ (also called hnRNP H2) proteins, respectively. These proteins belong to the heterogeneous nuclear ribonucleoprotein (hnRNP) family of RNA binding proteins which bind to pre-mRNA transcripts and assist in stabilizing, transporting, and targeting transcripts between the nucleus and cytoplasm for processing and alternative splicing prior to becoming mature mRNAs. More than 20 hnRNP have been identified, and hnRNP H and hnRNP H’ share 96% homology. Both genes are ubiquitously expressed across multiple tissue types including the brain, eye, smooth muscle, small intestine, and stomach. The functions of hnRNP H and H’ on pre-mRNA processing include capping, splicing, polyadenylation, export, and translation and are mainly exerted within the nucleus.

Given their central role in cellular function, it is not surprising that pathogenic variants affecting genes that code for hnRNPs are an emerging cause of disease. Altered expression of hnRNPs has been linked to tumorigenesis and germline variants in genes encoding hnRNPs have been implicated as a potential causes of adult-onset neurodegenerative conditions including frontotemporal dementia/amyotrophic lateral sclerosis, inclusion body myopathy with frontotemporal dementia (IBMPFIM [MIM: 615424]), and Alzheimer disease. Whole exome sequencing (WES) has identified multiple \textit{HNRNP} genes as novel causes of early-onset syndromic intellectual disability.

In 2016, pathogenic variants in \textit{HNRNPH2} were reported as a novel cause for an X-linked intellectual disability syndrome in females. This new syndrome, \textit{HNRNPH2}-related X-linked intellectual disability, Bain type, (MRXSB [MIM: 300986]), was characterized by intellectual disability, dysmorphic features, feeding difficulties, seizures, and hypotonia. While originally thought that pathogenic variants would be lethal in males, three groups have reported four males with pathogenic variants in \textit{HNRNPH2} and symptoms consistent with MRXSB. Among the 11 cases of MRXSB reported to date, seven have a common c.616C>T (p.R206W) variant, while another two have c.617G>A (p.R206Q) variants. The remaining two male cases carry c.626C>T (p.P209L) and c.340C>T (p.R114W) variants.

The first pathogenic variant in \textit{HNRNPH1} was reported by Pilch et al in 2018. In the reported individual, a 13-year-old boy, a de novo c.616C>T (p.R206W) variant in \textit{HNRNPH1} was identified by WES. His phenotype included dysmorphic facial features, microcephaly, hypermobile joints, hypotonia, non-verbal intellectual disability, and feeding difficulties. Given the similar phenotypes, the conserved amino acid sequences at position 206 of hnRNP H and H’, and the overall homology between these proteins, it was postulated that variants in \textit{HNRNPH1} may represent an autosomal cause of MRXSB. However, some features reported by Pilch et al were not observed in the MRXSB cohort, including arched eyebrows, blepharophimosis, congenital microcephaly, and hip dislocations.

Here, we present an additional seven cases of de novo pathogenic variants in \textit{HNRNPH1} to further characterize and expand the phenotype initially described by Pilch et al.

2 | MATERIALS AND METHODS

Seven individuals with \textit{HNRNPH1} pathogenic variants were identified using GeneMatcher and clinical networks. One individual resides in the United States, the remaining in the European Union. DNA extracted form peripheral blood was analyzed by WES on all individuals using standard technologies. Details on case specific WES can be found in Supporting Materials. This series was reviewed by the VCU Health IRB and not found to meet the definitions of human subjects research, and thus did not require IRB review or approval. Written informed consent was obtained for individuals whose photographs are included within this report. We characterized their phenotype retrospectively and contrasted them with features reported previously by Pilch et al as well as with individuals with MRXSB.

3 | RESULTS

The seven individuals range in age from a fetus at 30w4d to a 23-year-old. The five surviving cases have intellectual disability, ranging from moderate to severe. Congenital anomalies were observed in this cohort, with 7/7 having abnormalities identified on brain MRI, 4/7 having palate abnormalities, and 3/7 having genitourinary malformations. Other notable features observed include ophthalmological abnormalities (6/7), short stature (5/7), microcephaly (5/7), and hypotonia (4/7). Developmental regression is not observed in this cohort. 4/6 surviving individuals are non-verbal or have very limited speech. A complete phenotypic review can be found in Table 1. Dysmorphic features were also observed within our cohort, including medial...
| Table 1 | Clinical characteristics of Individuals with HNRNPH1 variants (NM 005520.2) in comparison with individuals with HNRNPH2-related X-linked intellectual disability, Bain type (MRXSB) |
|-----------------|-------------------------------------------------------------------------------------------------|
| **Variant**     | MRXSB (n = 11)                                                                                   | Pilch et al 11 | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | HNRNPH1 (n = 8) |
|                 | c.616C>T (p.R206W)                                                                               | c.616C>T       | c.616C>T | c.618dupG | c.617G>A (p.R206Q) | c.1116_1175del (p.Glu373-Tyr392del) | c.1240_1243dup (p.Q415fs) | c.616C>T |
|                 | n = 7, c.617G>A (p.R206Q) n = 2, c.626C>T (p.R206Q) n = 1, c.340C>T (p.R114W) n = 1               |               |        |        |       |       |       |       |       |
| **Sex**         | 7F, 4M                                                                                           | M              | M       | M       | M       | M       | F       | F       | M       | 2F, 6M |
| **Age**         | 13y                                                                                              | 14y            | 11y     | 14y     | 30w3d (d) | 5 years | 23 years | 10.5 m (d) | 30w3d–14y |
| **Intellectual disability** | + (11/11)                                                                                        | +              | +       | +       | +       | +       | +       | +       | + global developmental delay |
| **Verbal skills** | Variable: nonverbal to short sentences                                                              | Non-verbal    | Non-verbal | Non-verbal | Minimal | Minimal |   | 3/8 nonverbal; 2/8 minimal verbal skills |
| **Abnormalities of the cerebellar vermis** | + (2/11)                                                                                        | +              | –       | +       | +       | +       | –       | +       | 5/8 |
| **Other Brain Abnormalities** | + (1/11) Lipoma in the corpus callosum region; (1/11) white matter abnormalities | Anomaly of clivus and atlantoaxial joint | Tethered Cord, Anomaly of clivus and atlantoaxial joint | T2 periventricular white matter hyperintensities with cysts | Foramen magnum stenosis | White Matter Abnormalities | Dysmorphic midbrain, delayed myelination |
| **Joint laxity** | + (3/11)                                                                                        | +              | +       | +       | –       | –       | +       | 4/8 |
| **Short stature** | + (4/11)                                                                                        | +              | +       | +       | +       | + (IUGR) | –       | +       | 6/8 |
| **Skeletal Issues** | + (4/11) Scoliosis; (1/11) Pectus carinatum; (2/11) Pes Planus | Pectus carinatum, Scoliosis/Lordosis, contractures | Scoliosis/Lordosis | Bilateral clubfoot, camptodactyly | Clenched fists, elbows and wrists flexed, toe walking | Prognathism | Bilateral Hip Dysplasia |
| **Gastrointestinal abnormalities** | + (8/11) FTT, GERD, constipation, feeding difficulties | GERD | FTT, G-tube dependent, Hiatal hema, constipation | Feeding difficulties, G-tube, GERD, constipation | – | – | Feeding difficulties, G-tube | 4/8 (Continues) |
|                      | MRXSB (n = 11) | Pich et al \(^{11}\) | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | HNRNPH1 (n = 8) |
|----------------------|----------------|----------------------|--------|--------|--------|--------|--------|--------|--------|----------------|
| Tone Abnormalities   | + (11/11)      | + Hypotonia           | + Hypotonia | + Hypotonia | + Hypertonia | + Hypotonia | + Hypotonia | + Hypotonia | + Hypotonia | 6/8 |
| Genitourinary anomalies | −              | Hypospadia           | Horseshoe kidney, hypospadia | − | Posterior urethral valves, Cryptorchidism | − | − | Cryptorchidism | 4/8 |
| Ophthalmologic findings | + (1/11) exotropia, cortical visual impairment | Strabismus | Strabismus, Myopic astigmatism | Motility issue, retinal dystrophy/ RP? | Strabismus, nystagmus Optic disk pallor | Left Squint | Hypermetropia, strabismus | Retinopathy of prematurity | 7/8 |
| Movement disorder    | + (1/11) gait disturbance; (1/11) ataxia; (1/11) athetoid movements; (1/11) involuntary movements; (1/11) dystonic posturing | Non-ambulatory | Non-ambulatory | Non-ambulatory | Ataxia, tremor, wide-based gait, Dystonia | Dystonia | Dystonia | 3/8 dystonia | 1/8 ataxia |
| Epilepsy             | + (5/11)       | −                    | −      | −      | −      | +      | +      | −      | −      | 2/8 |

Abbreviations: d, deceased; FTT, failure to thrive; GERD, gastroesophageal reflux disease; (−), not present; (+), present; (+/−), mild.
arched eyebrows (4/7), blepharophimosis (3/7), ptosis (3/7), and hypotelorism (3/7). (Figure 1, Table S1). These features are similar to what was reported by Pilch et al. Additional clinical history can be found in Supporting Materials.

Overlapping features with MRXSB include intellectual disability, microcephaly, and gastrointestinal abnormalities. However, our cohort has other anomalies not consistently reported among individuals with MRXSB. These include cerebellar anomalies, palate abnormalities, genitourinary abnormalities, micrognathia, and short stature. 3/7 individuals in this cohort were noted to have dystonia, vs 1/11 individuals with MRXSB. Individuals in this cohort were also more frequently observed to have ophthalmological abnormalities, most often strabismus. Epilepsy, reported in 5/11 individuals with MRXSB, was only observed in 2/7 individuals within our cohort. The constellation of dysmorphic features observed in this cohort also suggests a distinct phenotype when compared with MRXSB. Congenital microcephaly, blepharophimosis, ptosis, hypotelorism, posteriorly rotated hypoplastic ears, medial arched eyebrows, open bite, and syndactyly/cinodactyly are features observed in individuals with HNRNPH1 pathogenic variants but not widely reported in MRXSB.

Six variants were identified in this cohort including two missense variants, two frameshift variants, an in-frame deletion, and an entire gene duplication (Figure 2). One variant, c.616C>T (p.R206W) identified in Cases 1 and 7, was previously described by Pilch et al. Another, c.617G>A (p.R206Q) was identified in Case 4 and is analogous to the HNRNPH2 variant described by Bain et al. The remaining four variants have not been described in either HNRNPH1 or HNRNPH2 to date. These include two small duplications, c.618dupG (p.Pro207fs) and c.1240_1243dup (p.Q415fs) and one in-frame deletion, c.1116_1175del (p.Glu373-Tyr392del). The final variant is a large duplication encompassing both the HNRNPH1 and RUFY1 [MIM 610327] genes.

4 | DISCUSSION

The seven individuals reported in this series suggest a unique, but variable, phenotype due to pathogenic HNRNPH1 variants. We hypothesize that much of the clinical variability observed among our cohort may be due to genotype/phenotype correlations. The hnRNP H and H’ proteins have three highly homologous RNA recognition motifs that allow them to specifically bind to G-rich RNA. In addition, they also have two glycine-rich domains, designated GYR and GY. A non-classical nuclear localization sequence (NLS) has been identified within the GYR region between amino acids 194 and 220 with amino acids 205 to 213 being highly conserved and required for nuclear transport. In vitro studies introducing point mutations into this NLS resulted in failure of these hnRNPs to shuttle from the cytoplasm to the nucleus, which is expected to compromise function.

Individuals with missense variants affecting amino acids 206 to 208 appear to have a more severe clinical phenotype. This is probably because these variants are predicted to disrupt the NLS, thus...
impacting the overall function on the hnRNP H protein.\textsuperscript{6,11} Individuals observed with the recurrent c.616C>T and c.617G>A variants (Cases 1, 7, and 4) presented immediately following birth or prenatally with issues including microcephaly, respiratory distress, hypotonia, and congenital anomalies. This early-onset severe presentation further highlights the importance of the NLS sequence in the hnRNP H protein and suggests that disruption of this sequence has severe clinical consequences.

The two frameshift variants reported in this cohort, c.618dupG (p.P207fs) and c.1240_1243dup (c.Q415fs), are expected to result in either an abnormal, truncated protein or loss of protein from nonsense mediated mRNA decay. c.618dupG falls within the NLS and c.1240_1243dup in the GY domain. The discordant phenotypes of these two individuals with frameshift mutations may reflect the severity of the frameshift on the overall protein structure. As c.618dupG (p.P207fs) lies within the NLS, it is predicted to produce a protein with a malfunctioning NLS. This supports the above suggestion that disruption of the NLS results in severe clinical consequences, as Case 2, found to have c.618dupG (p.P207fs), presented with hypotonia, respiratory distress, and congenital anomalies, similar to those with missense variants in the NLS. In contrast, Case 6, found to have c.1240_1243dup (p.Q415fs), has a less severe phenotype compared to cases 1, 2, 4, and 7. Case 6 did not come to medical attention in the neonatal period, is not noted to have microcephaly, and does not have palate abnormalities, short stature, or clinodactyly/syndactyly. Case 6 also has milder intellectual disability compared to other cases. Because c.1240_1243dup lies within the GY domain, it is predicted to impact the protein after the NLS, possibly resulting in an abnormal

| Variant (NC_000059.9, NM_001257293.1, hg19) | Mutational Consequence | CADD | SIFT | Mutation Assessor | Provean | PolyPhen-2 |
|---------------------------------------------|------------------------|------|------|-------------------|---------|-----------|
| Cases 1 and 7 c.616C>T p.Arg206Try chr5:g.179045245G>A | Missense              | Deleterious (25.2) | Damaging (0.024) | 2.02 (medium) | Deleterious (-4.63) | Benign (0.028) |
| Case 2 c.618dupG p.Pro207Alafs*5 chr5:g.179045243dupC | Frameshift             | NA | NA | NA | NA | NA |
| Case 3 NA chr5:178977572-179050134dup | Partial Gene Duplication | NA | NA | NA | NA | NA |
| Case 4 c.617G>A p.Arg206Gln chr5:g.179045244C>T | Missense              | Deleterious (24.0) | Damaging (0.025) | 1.42 (low) | Neutral (-1.95) | Benign (0.051) |
| Case 5 c.1116_1175del152 p.Glu373_Ser392del chr5:g.17904302_179044053del | In-Frame Deletion | NA | NA | NA | NA | NA |
| Case 6 c.1240_1243dup p.Gln415Profs*30 chr5:g.179043193_179043196dup | Frameshift             | NA | NA | NA | NA | NA |

FIGURE 2 Characteristics of HNRNPH1 pathogenic variants. A. Location of HNRNPH1 pathogenic variants in the HNRNP H protein. B. Predicted pathogenicity and mutational consequence of HNRNPH1 pathogenic variants [Colour figure can be viewed at wileyonlinelibrary.com]
protein that may have a functional NLS region, which may ameliorate the severity of the observed phenotype.

Of the remaining HNRNPH1 variants, one falls in the GY domain, c.1116_1175del (p.Glu373-Tyr392del) (Case 5), and is expected to remove 19 amino acids. The function of the GY domain is not as well understood as the GYR domain, however it is thought to be important for protein-protein interactions and splicing. Thus, these pathogenic variants may have functional implications on protein/protein or protein/RNA interactions however it is difficult to say without additional functional studies. Case 5 has a less severe phenotype compared to those with pathogenic variants within the NLS, similar to Case 6 with a normal neonatal period, milder intellectual disability, and no microcephaly.

The final variant reported is an entire gene duplication of HNRNPH1 and RUFY1 (Case 3). This de novo 100.1 kb duplication was consistently identified by WES and whole genome sequencing (WGS) independently, with coordinates identified by three different CNV identification tools, ExomeDepth v1.1.10, XHMM and Conifer v0.2.2 (Figure S1). To confirm this duplication, a qPCR assay was run on fibroblasts from the proband and parents to confirm the de novo duplication (Figure S1). The RUFY1 gene encodes the RUN and FYVE domain containing 1 protein, and is thought to be involved in early endosomal trafficking. To date, no human disease has been associated with the RUFY1 gene. The impact of this HNRNPH1 gene duplication on protein function is unclear, however given the overlap of features observed in other individuals with missense, frameshift, and small deletions within HNRNPH1, it is probably that it would result in abnormal hnRNP H function. It is also worth considering that a small rearrangement within the duplicated region cannot be ruled out, as it would go undetected by short read WES or WGS. Further functional studies are required to better understand the implications of this duplication on protein function. The clinical features of Case 3 are not as severe as those with pathogenic variants impacting the NLS, however they are more severe than those with pathogenic variants in the GY glycine rich domain. Specifically, Case 3 was found to have white matter and cerebellar abnormalities, dysmorphic features, short stature, genitourinary abnormalities, and microcephaly along with dysmorphic traits present in other reported cases. However, he has moderate intellectual disability, is verbal, and is ambulatory.

While limited due to a small number of individuals, these findings provide additional evidence that pathogenic variants in HNRNPH1 cause a related, but unique syndrome from MRXSB. Given the observations presented in this report, genotype/phenotype correlation does appear to exist, because individuals with variants impacting the NLS have a more severe phenotype. Given the absence of predicted loss of function variants in healthy controls, haploinsufficiency is a probably pathogenic mechanism for variants in HNRNPH1. Future endeavors focusing on functional studies will provide insights into the pathological mechanisms of HNRNPH1 variants.

Our findings suggest that pathogenic variants in HNRNPH1 represent a related, but distinct, syndrome from MRXSB with unique dysmorphic features, increased incidence of congenital anomalies, and an increased incidence of ophthalmological abnormalities. Importantly, identification of additional individuals with pathogenic HNRNPH1 variants will continue to shape the observed phenotype and provide further insights into the potential genotype/phenotype correlation. While this represents a rare form of syndromic intellectual disability, given the severity observed in individuals with variants impacting the NLS, consideration of rapid-WES in critically ill newborns with microcephaly, congenital anomalies, and respiratory distress may identify pathogenic variants in HNRNPH1. Common features reported among the majority of individuals with HNRNPH1 variants include short stature, microcephaly, intellectual disability, congenital anomalies, and dysmorphic features, specifically blepharophimosis, ptosis, hypotelorism, medial arched eyebrows, and micrognathia. We therefore propose that individuals with HNRNPH1 pathogenic variants be described as having HNRNPH1-related syndromic intellectual disability.

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CONFLICTS OF INTEREST
There are no conflicts of interest to disclose among the authors included in the preparation and publication of this manuscript.

DATA AVAILABILITY STATEMENT
There are no other data associated with this manuscript.

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REFERENCES
1. Han SP, Tang YH, Smith R. Functional diversity of the hnRNPs: past, present and perspectives. Biochem J. 2010;430(3):379-392.
2. Honore B, Rasmussen HH, Vorum H, et al. Heterogeneous nuclear ribonucleoproteins H, H', and F are members of a ubiquitously expressed subfamily of related but distinct proteins encoded by genes mapping to different chromosomes. J Biol Chem. 1995;270(48):28780-28789.
3. Van Dusen CM, Yee L, McNally LM, McNally MT. A glycine-rich domain of hnRNP H/F promotes nucleocytoplasmic shuttling and nuclear import through an interaction with Transportin 1. Mol Cell Biol. 2010;30(10):2552-2562.
4. Geuens T, Bouhy D, Timmerman V. The hnRNP family: insights into their role in health and disease. Hum Genet. 2016;135(8):851-867.
5. Au PYB, You J, Caluseriu O, et al. GeneMatcher aids in the identification of a new malformation syndrome with intellectual disability,
unique facial Dysmorphisms, and skeletal and connective tissue abnormalities caused by De novo variants in HNRNPK. *Hum Mutat.* 2015;36(10):1009-1014.

6. Bain Jennifer M, Cho Megan T, Telegrafi A, et al. Variants in HNRNPH2 on the X chromosome are associated with a neurodevelopmental disorder in females. *Am J Hum Genet.* 2016;99(3):728-734.

7. Bramswig NC, Lüdecke H-J, Hamdan FF, et al. Heterozygous HNRNPU variants cause early onset epilepsy and severe intellectual disability. *Hum Genet.* 2017;136(7):821-834.

8. Harmsen S, Buchert R, Mayatepek E, Haack TB, Distelmaier F. Bain type of X-linked syndromic mental retardation in boys. *Clin Genet.* 2019;95(6):734-735.

9. Jepsen WM, Ramsey K, Szelinger S, et al. Two additional males with X-linked, syndromic mental retardation carry de novo mutations in HNRNPH2. *Clin Genet.* 2019;96(2):183-185.

10. Somashekar PH, Narayanan DL, Jagadeesh S, et al. Bain type of X-linked syndromic mental retardation in a male with a pathogenic variant in HNRNPH2. *Am J Med Genet A.* 2020;182(1):183-188.

11. Pilch J, Koppolu AA, Walczak A, et al. Evidence for HNRNPH1 being another gene for Bain type syndromic mental retardation. *Clin Genet.* 2018;94(3–4):381-385.

12. 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(10):928-930.

13. Yang J, Kim O, Wu J, Qiu Y. Interaction between tyrosine kinase Etk and a RUN domain- and FYVE domain-containing protein RUFY1: a possible role of Etk in regulation of vesicle trafficking. *J Biol Chem.* 2002;277(33):30219-30226.

**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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