

# Detailed Clinical and Psychological Phenotype of the X-linked *HNRNPH2*-Related Neurodevelopmental Disorder

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## Abstract

### Objective

To expand the clinical phenotype of the X-linked *HNRNPH2*-related neurodevelopmental disorder in 33 individuals.

### Methods

Participants were diagnosed with pathogenic or likely pathogenic variants in *HNRNPH2* using American College of Medical Genetics and Genomics/Association of Molecular Pathology criteria, largely identified via clinical exome sequencing. Genetic reports were reviewed. Clinical data were collected by retrospective chart review and caregiver report including standardized parent report measures.

### Results

We expand our clinical characterization of *HNRNPH2*-related disorders to include 33 individuals, aged 2–38 years, both females and males, with 11 different de novo missense variants, most within the nuclear localization signal. The major features of the phenotype include developmental delay/intellectual disability, severe language impairment, motor problems, growth, and musculoskeletal disturbances. Minor features include dysmorphic features, epilepsy, neuropsychiatric diagnoses such as autism spectrum disorder, and cortical visual impairment. Although rare, we report early stroke and premature death with this condition.

### Conclusions

The spectrum of X-linked *HNRNPH2*-related disorders continues to expand as the allelic spectrum and identification of affected males increases.

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## Glossary

**ABC** = Adaptive Behavior Composite; **ADHD** = attention-deficit hyperactivity disorder; **ASD** = autism spectrum disorder; **BASC-3** = Behavior Assessment System for Children, third edition; **NDD** = neurodevelopmental disorder; **NLS** = nuclear localization sequence; **OFC** = occipital frontal circumference; **PC** = principal component; **PCA** = PC analysis; **PDD** = pervasive developmental disorder; **PEDI-CAT** = Pediatric Evaluation of Disability Inventory Computer Adaptive Test; **RBP** = RNA-binding protein; **SCQ** = Social Communication Questionnaire; **SP2** = Sensory Profile 2; **SRS** = Social Responsiveness Scale; **SSP2** = Short SP2; **VABS-III** = Vineland Adaptive Behavior Scales, third edition.

Neurodevelopmental disorders (NDDs) are a complex, heterogeneous group of disorders with shared phenomenology associated with significant lifelong burdens. Up to 30% of these conditions currently have an identifiable genetic basis.<sup>1–3</sup> X-linked genes are a frequent cause of NDDs, including intellectual disability and autism spectrum disorder (ASD).<sup>4–7</sup> One X-linked gene, *HNRNPH2*, encodes the hnRNP H2 protein, a member of the heterogeneous ribonucleoprotein family.<sup>8,9</sup> We previously described 3 missense variants in the nuclear localization sequence (NLS) in *HNRNPH2* in 6 unrelated females with a common neurodevelopmental phenotype including developmental delay/intellectual disability, ASD, tone abnormalities, and seizures (OMIM 300986, Mental retardation, X-linked, syndromic, Bain type).<sup>10</sup> Since our initial report, there have been additional reports of males with variants in *HNRNPH2* and another family with presumed germline mosaicism with 2 affected siblings.<sup>7,11,12</sup> Herein, we describe an expanded genotypic and phenotypic spectrum of individuals with variants in the X-linked *HNRNPH2* gene. We hypothesize that those individuals who carry a pathogenic variant located within the NLS are more severely affected than those with variants outside the NLS.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

Participants were referred to this study (ClinicalTrials.gov NCT03492060) if they were diagnosed with pathogenic or likely pathogenic variants in *HNRNPH2* using American College of Medical Genetics and Genomics/Association of Molecular Pathology criteria, largely identified via clinical exome sequencing. The study was approved by the Columbia University Institutional Review Board, and informed consent was obtained from all caregivers or legal guardians.

### Retrospective Chart Review

Genetic reports were reviewed to confirm the diagnosis. Information was provided by the primary caregiver by phone interview and online questionnaires and verified with clinician report when available. Cognitive, behavioral, and other psychological testing was collected on participants or clinical providers when available. Photographs were collected from families and taken during family conferences. Brain MRI reports were reviewed, and when available, images were reviewed by a board-certified pediatric neuroradiologist. A heuristic

clinical severity score was developed based on the most common phenotypic variables such as presence of ASD, anxiety, vision problems, seizures, and tone anomalies. We performed a principal component analysis (PCA) of participants using the same set of clinical features. Missing values were imputed using the mean value of the corresponding clinical feature in the cohort. The PCA was conducted using an R package “pcaMethods.”

### Prospective Data Collection

Once enrolled in the natural history study, parents and caregivers provided responses about the individuals’ medical history from birth to present. Of note, some participants, based on their older age, may have previously been diagnosed using earlier version of the *Diagnostic and Statistical Manual, Fourth Edition*, and for accuracy purpose, we report the diagnosis that was given at that time to the parents, such as pervasive developmental disorder (PDD)-not otherwise specified. Parents and caregivers also completed standardized measures of functioning using various online platforms. Adaptive functioning was measured using the online Vineland Adaptive Behavior Scales, third edition (VABS-III).<sup>13,14</sup> Vineland normed scores were standardized with a mean of 100 and an SD of 15. Social communication skills were measured by completion of the Social Communication Questionnaire (SCQ)<sup>15</sup> and Social Responsiveness Scale (SRS), Second Edition.<sup>16</sup> Sensory processing was evaluated to assess the participants’ ability to create a balance between high and low threshold stimuli, using the Sensory Profile 2 (SP2).<sup>17</sup> The Short SP2 (SSP2) is a valid standardized parent report measure that defines and illustrates responses to sensory stimuli.<sup>17–19</sup> The measure is organized using a 5-point Likert scale with possible responses ranging from “never” to “always.” Interpretation of scores is based on normative data.<sup>17,18</sup> Six sensory domains of the SP2 were performed: auditory processing, visual processing, touch processing, movement processing, oral processing, and behavioral and then calculated into the 4 quadrants Avoiding, Seeking, Sensitivity, and Registration.<sup>17,18</sup> The SSP2 scoring scale is segmented into lower and high levels comprised of “much less than others (more than 2 SD below the mean), “less than others” (1–2 SD below the mean), “just like the majority of others” ( $\pm 1$  SD from the mean), “more than others” (between 1 SD and 2 SD above the mean), and “much more than others” (2+ SD above the mean).<sup>17,18,20</sup> Behavioral and emotional concerns were measured using the Behavior Assessment System for Children, third edition (BASC-3), for ages 2 through 22 years.<sup>21</sup> The Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) is designed for use with

children and youth (birth through 20 years of age) with a variety of physical and/or behavioral conditions and measures functions across 4 domains (i.e., daily activities, mobility, social-cognitive, and responsibility).<sup>22</sup>

### Data Availability

Anonymized data will be shared by request from any qualified investigator. For those participants who have consented to research with Simons Searchlight, data are available through SFARIbase (base.sfari.org/).

## Results

We describe 33 participants with 11 different de novo missense variants in *HNRNPH2*, including 2 recurrent variants

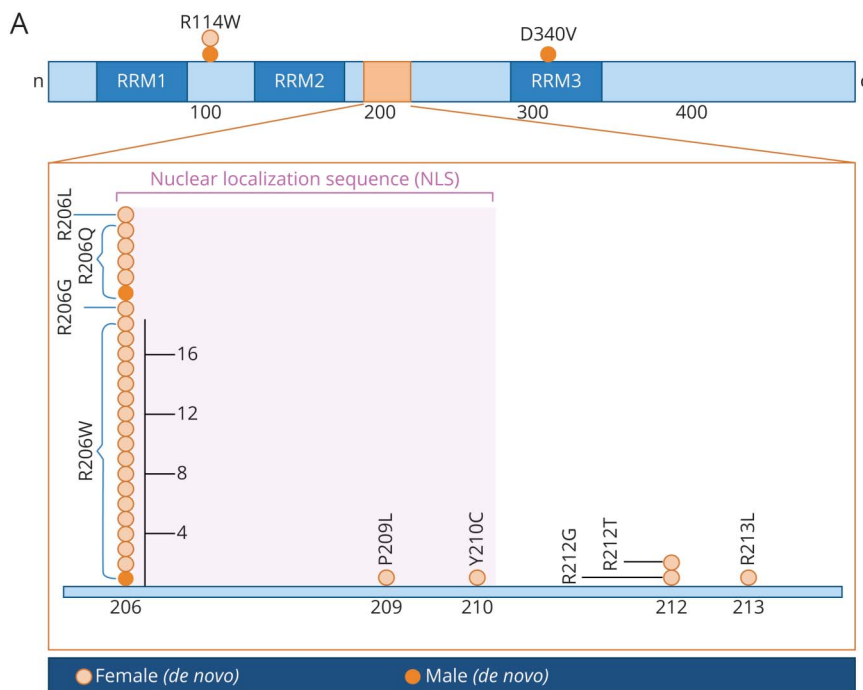
p.R206W (n = 18) and p.R206G (n = 5) (figure 1, table 1). All variants are predicted pathogenic based on at least 2 algorithms, and none of the variants are observed in Genome Aggregation Database (figure 1).

Probands ranged from age 2–38 years and included 29 females and 4 males (average 15 years, median 11 years). One participant died in her sleep at age 23 years. Of note, her genetic diagnosis was returned postmortem, and an autopsy was not performed. The summary below is the medical history reported for 32 individuals in the natural history study with 1 lost to follow up (table e-2, links.lww.com/NXG/A362).

### Prenatal and Birth Complications

All participants were conceived naturally, to mothers ranging from 19 to 39 years of age and fathers ranging from 18 to 42

**Figure 1** Participant Genotypes and Predicted Pathogenicity



**B**

Variant		CADD Phred
c.1019A>T	p.D340V	24.7
c.638C>T	p.P213L	25.1
c.635G>C	p.R212T	24.4
c.634A>G	p.R212G	24.5
c.629A>G	p.Y210C	15.2
c.626C>T	p.P209L	27.1
c.617G>T	p.R206L	23.9
c.617G>A	p.R206Q	22.8
c.616C>G	p.R206G	25.2
c.616C>T	p.R206W	22.6
c.340C>T	p.R114W	22

Regions of *HNRNPH2* gene with plot of all the variants (A) and predicted pathogenicity and allele frequencies of *HNRNPH2* variants (B).

**Table 1** Clinical Phenotypes of Individuals With *HNRNPH2* Variants

Subject ID	Inheritance	cDNA	Sex	Age, y	Alive	DD/ID	Regression	ASD, PDD-NOS, SCD, CDD, and RETT	Anxiety	ADHD	Psychiatric meds	Tone abnormalities	Seizure type	Current seizure medications (prior)	Ambulatory	Movement disorder	Sleep problems	Orthopedic	Ophthalmologic	FTT or growth issues	OFC SD	Z score BMI	Z score weight	Z score height	Abnormal brain MRI	
1	De novo	c.340C>T	M	2	Y	Y	Y	N/A	N	N	Gabapentin	↓	N/A	None	N	Tics	N	N	N	CVI	N	Unk	2.26	0.2	-2.1	Y
2	De novo	c.340C>T	F	4	Y	Y	Y	ASD	Unk	Unk	—	↓	N/A	None	N	None	N	Unk	N	Unk	Y	-1.76	Unk	Unk	Unk	Unk
3	De novo	c.616C>T	F	19	Y	Y	N	N/A	Y	N	—	↓	N/A	None	Y	None	N	N	Y	Strabismus	Y <sup>a</sup>	-2.17	-1.4	-2.76	-2	N
4	De novo	c.616C>T	F	8	Y	Y <sup>b</sup>	N	ASD <sup>b</sup>	Y	Y	—	↓	N/A	None	Y	None	N	N	N	CVI and strabismus	Y <sup>a</sup>	-0.9	-4.41	-2.57	-3	N
5	De novo	c.616C>T	F	3	Y	Y <sup>b</sup>	N	N/A	N	N	—	↓	Febrile	None	N	None	N	N	Y	CVI and strabismus	Y	-1.33	-1.69	-3.55	-2.7	Y
6	De novo	c.616C>T	M	17	Y	Y	N	N/A	Y	Y	Quetiapine and buspirone	↓ (b)	Tonic-clonic, absence, and spasms (R)	OXC and LVT	N	Tics	N	N	Y	CVI, nystagmus, and strabismus	Y	-1.18	-0.67	-1.77	-2.1	Y
7	De novo	c.616C>T	F	38	Y	Y	N	PDD-NOS <sup>c</sup>	Y	Y	Aripiprazole, MPH, BZD, and naltrexone	↓	Febrile, clonic (R)	None	Y	Tremor	Y	N	Y	Strabismus	Y	-3.13	-0.84	-1.89	-1.7	N
8	De novo	c.616C>T	F	11	Y	Y	Y	ASD	Y	Y	—	↓	Abnormal EEG	LVT	N	None	N	N	N	Poor vision and strabismus	Y <sup>a</sup>	-4.08	-5.93	-8.3	-4.9	N
9	De novo	c.616C>T	F	18	Y	Y	N	N/A	N	N	—	↓	Absence and clonic	LVT and VPA	N	None	N	Y	Y	CVI and strabismus	Y <sup>a</sup>	-0.28	-2.02	-0.5	1.84	Y
10	De novo	c.616C>T	F	6	Y	Y	Y	N/A	Y	N	—	↓	Abnormal EEG	LVT	Y	None	Y	N	Y	CVI and myopia	Y	-1.3	-3.96	-7.13	-4.6	N
11	De novo	c.616C>T	F	13	Y	Y	N	N/A	Y	Y	—	↓	N/A	None	N	Tics	N	N	Y	None	Y	-0.85	-5.05	-3.52	-0.9	N
12	De novo	c.616C>T	F	10	Y	Y	N	N/A	N	N	—	↓	N/A	None	N	None	N	N	N	Strabismus	Y	-0.55	-1.57	-2.33	-1.8	N
13	De novo	c.616C>T	F	27	N	Y	Y	ASD	Y	Y	—	↓	N/A	None	N	Tics	N	Y	N	CVI	Y	-2.91	-0.52	-0.85	-0.7	N
14	De novo	c.616C>T	F	3	Y	Y	N	N/A	Y	N	—	↓	N/A	None	N	None	N	N	Y	Abnormal Structure	Y	0.24	0.68	-1.91	-3	Y
15	De novo	c.616C>T	F	8	Y	Y	Y	ASD	Y	N	Risperidone	↓	Tonic, tonic-clonic, and absence	VPA	N	None	N	Y	N	Unk	Y	-1.69	0.16	-0.62	-1.4	Y
16	De novo	c.616C>T	F	17	Y	Y <sup>b</sup>	N	ASD	Y	N	Escitalopram	↓	Absence	LVT	Y	None	Y	N	Y	Poor vision	Y	-0.28	-5	-4.32	-0.3	N
17	De novo	c.616C>T	F	23	Y	Y	Y	ASD	Y	Y	Sertraline	↓	N/A	None	Y	None	Y	N	N	Myopia	N	1.97	-1.43	-0.17	1.82	N
18	De novo	c.616C>T	F	24	Y	Y	N	RETT	N	N	—	↓	Abnormal EEG	PIR	Y	None	Y	N	N	Myopia	N	-0.29	-1.78	-1.57	-0.1	N
19	De novo	c.616C>T	F	28	Y	Y <sup>b</sup>	N	ASD	Y	Y	Olanzapine, quetiapine, and fluoxetine	↓	Febrile, tonic-clonic, and myoclonic	VPA	Y	None	N	Y	Y	CVI and strabismus	N	-2.82	0.94	1.69	2.63	N
20	De novo	c.616C>T	F	6	Y	Y	N	N/A	Y	N	—	↓	N/A	None	Y	None	Y	N	Y	Strabismus	N	Unk	-1.82	-1.27	-0.4	N
21	De novo	c.616C>G	F	20	Y	Y	N	N/A	N	N	—	↓	Tonic-clonic	VPA	N	None	N	N	Y	None	Y	-3.11	-4.8	-5.84	-2.1	Y
22	De novo	c.617G>A	F	36	Y	Y	N	RETT	Y	N	Olanzapine and fluoxetine	↓	Tonic, absence	VPA	N	None	N	N	Y	Unk	Y	-1.52	-3.18	-4.98	-2.5	Y

Continued

**Table 1** Clinical Phenotypes of Individuals With *HNRNP2* Variants (continued)

Subject ID	Inheritance	cDNA	Sex	Age, y	Alive	DD/ID	Regression	ASD, PDD-NOS, SCD, CDD, and RETT	Anxiety	ADHD	Psychiatric meds	Tone abnormalities	Seizure type	Current seizure medications (prior)	Ambulatory	Movement disorder	Verbal	Sleep problems	Orthopedic	Ophthalmologic	FTT or growth issues	OFC SD	Z score BMI	Z score weight	Z score height	Abnormal brain MRI	
23	De novo	c.617G>A	F	8	Y	Y <sup>b</sup>	Y	ASD <sup>b</sup>	Y	Y	—	↓	N/A	None	Y	None	N	Y	N	Strabismus	Y	-0.65	-5.24	-2.11	0.61	N	
24	De novo	c.617G>A	M	17	Y	Y	N	N/A	Y	Y	Guanfacine and aripiprazole	↓	N/A	None	N	None	N	N	Y	CVI	Y	-3.6	-5.73	-6.74	-3.3	N	
25	De novo	c.617G>A	F	17	Y	Y	Y	ASD and RETT	Y	N	CBD	↑↓	Single symptomatic	None	N	Dystonia and tremor	N	Y	Y	Unk	Y	-2.63	-2.69	-3.84	-1.6	Y	
26	De novo	c.617G>A	F	11	Y	Y	N	Unk	N	N	—	↓	Abnormal EEG	Unk	Y	None	N	N	Y	Right eye Brown syndrome	Y	-0.49	-5.2	-3.65	-1	N	
27	De novo	c.617G>T	F	36	Y	Y <sup>b</sup>	Y	PDD-NOS <sup>c</sup> , and RETT	Y	N	—	↑↓	N/A	None	N	Dystonia and tremor	N	Y	Y	Poor vision	Y	-1.71	-3.5	-3.17	-0.5	Y	
28	De novo	c.626C>T	F	10	Y	Y	N	N/A	Y	N	—	↓	Tonic-clonic, absence, and febrile	LVT	N	None	N	Y	Y	Unk	Y	-4.08	-2.9	-5.21	-3.8	N	
29	De novo	c.629A>G	F	5	Y	Y	Y	N/A	N	N	—	↑↓	N/A	None	N	None	N	Y	Y	Strabismus	Y	-2.33	1.61	-2.76	-5.5	N	
30	De novo	c.634A>G	F	5	Y	Y	Y	CDD <sup>c</sup>	Y	Y	—	↑↓	Tonic, absence, and spasms	SUL	N	Tremor	N	Y	N	Strabismus, myopia, and ptosis	Y	-2.02	-3.5	-4.51	-2.9	N	
31	De novo	c.635G>C	F	8	Y	Y	N	N/A	N	N	—	↓	Tonic-clonic	LVT	N	None	N	N	N	Strabismus	N	-0.32	-3.2	-3.05	-1.8	N	
32	De novo	c.638C>T	F	20	Y	Y <sup>b</sup>	N	PDD-NOS <sup>c</sup> and SCD <sup>b</sup>	Y	Y	—	Normal	N/A	None	Y	Akathisia	Y	N	Y	None	N	1.4	2.36	2.82	0.27	N	
33	De novo	c.1019A>T	M	8	Y	Y <sup>b</sup>	N	ASD <sup>b</sup>	N	Y	—	↓	Abnormal EEG	Unk	Y	None	Y	Y	Y	Astigmatism	N	1.45	0.95	-0.56	-2.2	Y	
Harmsen et al., 2019 <sup>11</sup>	De novo	c.617G>A	M	Unk	Unk	Y	Unk	Unk	Unk	Unk	Unk	↓	Unk	Unk	N	Unk	N	Unk	Y	Unk	Unk	Unk	Unk	Unk	Unk	Unk	N
Jepsen et al., 2019 (patient A) <sup>23</sup>	De novo	c.616C>T	M	5	Unk	Y	N	Unk	Unk	Unk	Unk	↓	Unk	Unk	N	Unk	N	Unk	Unk	Unk	Unk	Y	Unk	Unk	Unk	Unk	Y
Jepsen et al., 2019 (patient B) <sup>23</sup>	De novo	c.340C>T	M	8	Unk	Y	Unk	Unk	Unk	Unk	Unk	—	Medically refractory epilepsy	Unk	Unk	Athetosis and dyskinesia	Unk	Unk	Unk	Unk	Unk	Y	Unk	Unk	Unk	Unk	Unk
Somashekar et al., 2020 (P1) <sup>7</sup>	Mosaic?	c.616C>T	M	8	Unk	Y	Y	Unk	Unk	Unk	Unk	↓	Tonic-clonic	Unk	Unk	Hand flapping and tremors	N	Unk	Unk	Unk	Unk	Unk	-2	N/A	-3	-3	N
Somashekar et al., 2020 (P2) <sup>7</sup>	Mosaic?	c.616C>T	F	5	Unk	Y	Y	Unk	Unk	Unk	Unk	↓	N/A	Unk	Unk	Involuntary movement of hands	N	Unk	N	Unk	Unk	Unk	-2	N/A	-2	-2	N
<b>Total, n</b>							33	38	37	32	32	32	36	35	36	38	32	33	29								
<b>Average</b>							97% alive	100% DD/ID	38% regression	44% ASD	69% anxiety	40% ADHD	36% epilepsy	38% ambulatory	33% movement disorder	20% verbal	35% sleep problems	70% ortho	86% vision problems								

Abbreviations: ADHD = attention-deficit hyperactivity disorder; ASD = autism spectrum disorder; C = complementary DNA coding; BZD = benzodiazepine; CBD = cannabidiol; CDD = childhood disintegrative disorder; CVI = cortical visual impairment; DD = developmental delay; ID = intellectual disability; LVT = levetiracetam; MPH = methylphenidate; N = no; N/A = not applicable; OXC = oxcarbazepine; PDD-NOS = pervasive developmental disorder—not otherwise specified; PIR = piracetam; SCD = social communication disorder; SUL = sulthiamine; Unk = unknown; VPA = valproic acid; Y = yes.

<sup>a</sup> G-tube placement.

<sup>b</sup> Additional cognitive information provided in table e-1 ([links.lww.com/NXG/A361](https://links.lww.com/NXG/A361)).

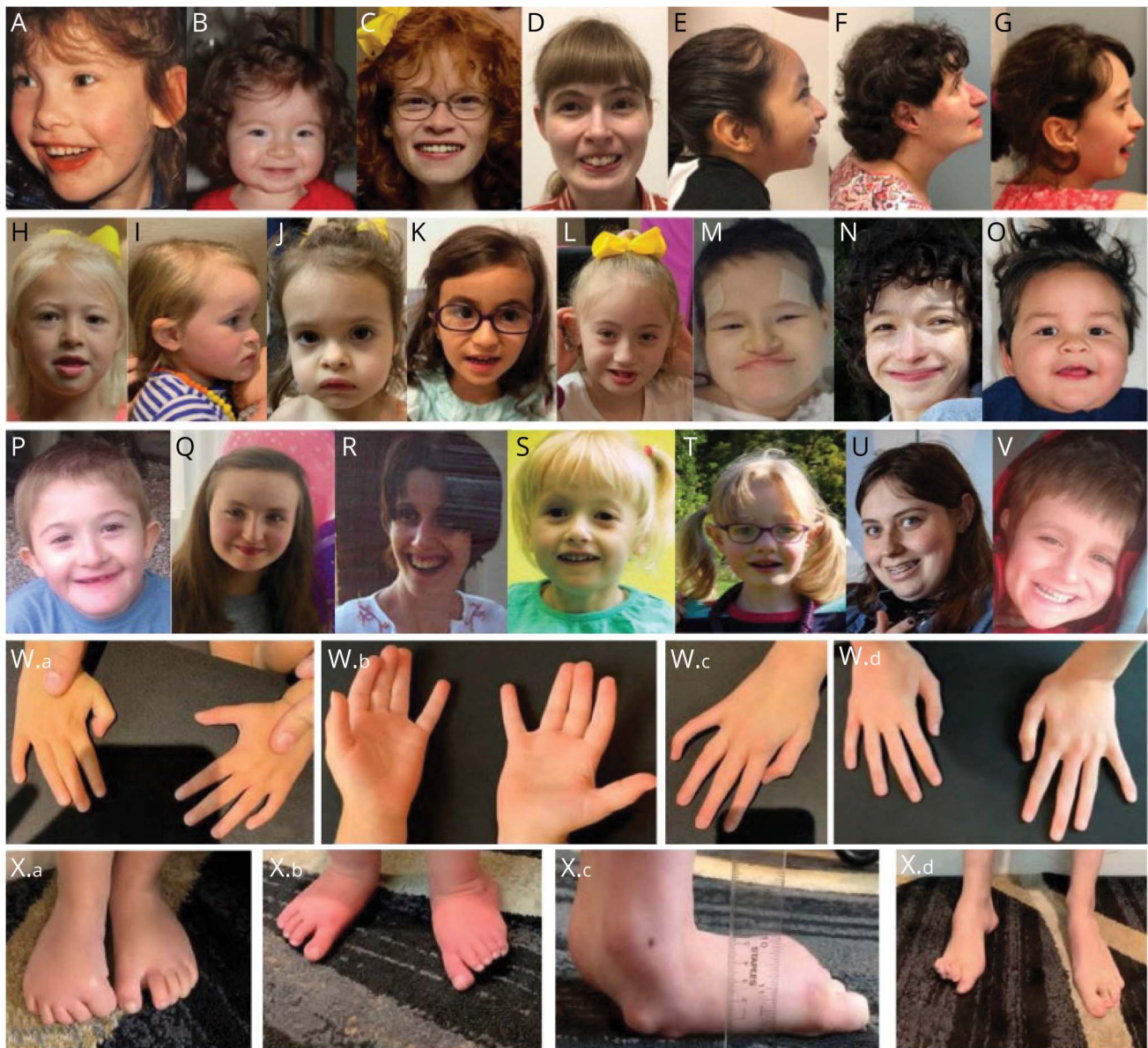


years old. Aside from 1 fraternal twin birth, all others were singleton births. Four parents reported intrauterine growth restriction, and 24% of mothers recalled having decreased fetal movements or periods of stillness. All were born full term, although 39% were induced. Five required intensive care admission, ranging from 3 hours to 6 days. One participant (#24) briefly required ventilator support, but most others had normal Apgar scores. All 5 participants who were admitted to the neonatal intensive care unit had subsequent

brain imaging. One had delayed myelination, but all others did not reveal any concern for hypoxic-ischemic, anoxic, or white matter abnormalities suggestive of fetal or neonatal distress. No birth defects were noted, although common facial features are seen (figure 2).

The average birth weight was 3.32 kg (range 2.34–5.97 kg, SD = 0.70). The average birth length was 50.5 cm (range 45.7–54.6 cm, SD = 2.3). The average occipital frontal

**Figure 2** Participant Face and Extremity Findings



Participant 1 at 5 years (A), participant 2 at 4 years (B), participant 3 at 17 years (C), participant 4 at 21 years (D), participant 5 at 10 years (E), participant 6 at 37 years (F), participant 7 at 11 years (G), participant 8 at 5 years (H), participant 9 at 3 years (I), participant 10 at 3 years (J), participant 11 at 4 years (K), participant 12 at 7 years (L), participant 13 at 13 years (M), participant 14 at 18 years (N), participant 15 at 2 years (O), participant 17 at 8 years (P), participant 18 at 16 years (Q), participant 19 at 23 years (R), participant 20 at 4 years (S), participant 21 at 6 years (T), participant 22 at 19 years (U), and participant 23 at 9 years (V). (W.a) Dorsal view of thumb hypoplasia in participant 5 at 3 years. (W.b) Palmar view of thumb hypoplasia in participant 20 at 5 years. (W.c) Dorsal view of arachnodactyly in participant 16 at 17 years. (W.d) Curvature of the fifth finger toward the adjacent fourth finger (clinodactyly) in participant 11 at 12 years. (X.a) Frontal view; sandal gap left hallux; right foot clubbing in participant 5 at 2 years. (X.b) Bilateral brachydactyly in participant 29 at 3 years. (X.c) Medial view of calcaneal adduction with navicular bone drop in participant 9 at 18 years. (X.d) Frontal view of sandal gap (right) with varus deviation in participant 17 at 21 years.

circumference (OFC) was normocephalic at 33.7 cm (range 33–35 cm, SD = 1.07), although birth OFC was not available for most participants.

Most mothers reported difficulties with feeding (67%), and half of probands had difficulty gaining weight (55%) as infants. Although 3 parents reported initial concerns immediately after birth, most parents reported concerns about their child's development before age 12 months. All probands have developmental delay or intellectual disability (table e-2, [links.lww.com/NXG/A362](https://links.lww.com/NXG/A362)). Six caregivers report regression or loss of skills during an intercurrent illness, which were regained afterward. Most individuals are nonverbal or minimally verbal (76%). Those who acquired speech did so between 1 and 5 years of age. In addition, most report speech articulation difficulties or speech or oral motor apraxia.

### Neurologic Issues

More than half of the participants had EEG or magnetoencephalography. Abnormal EEG monitoring included paroxysmal activity in the right temporal lobe and left posterior and midline epileptiform discharges as well as diffuse background slowing. Nearly half of the cohort had a clinical seizure (42%), and 3 more reported an abnormal EEG without clinical seizures (10%). Clinical seizure semiologies were varied, including febrile (23%), staring (69%), tonic (38%), tonic-clonic (43%), spasms (23%), myoclonic (15%), and clonic (15%). One participant had a generalized tonic-clonic seizure at age 6 years after head injury but did not have any further episodes and did not take any antiepileptic medication. The average age of first seizure was 8.7 years. Of the participants who reported seizures, 9 (64%) participants had taken a seizure medication, but many stopped taking the medication due to being ineffective (15%), side effects (23%), or cessation of seizures (15%). Participants currently on levetiracetam and valproic acid report good seizure control (table 1). One participant had a first-time seizure (tonic-absence) at age 34 years. The same participant had a stroke 3 weeks following the seizure.

OFCs were obtained from those available, and 30% have microcephaly (defined as more than 2 SDs below the mean OFC), mostly acquired microcephaly. Other neurologic diagnoses include hypotonia (97%), difficulty with coordination (70%), balance (70%), gait (48%), whole-body apraxia (motor planning difficulties) (52%), muscle rigidity/spasticity (33%), tics (15%), dizziness (12%), tremor (9%), headaches (9%), dystonia (6%), and akathisia (3%). Weakness is reported in 24%, while 15% of individuals have been given the diagnosis of cerebral palsy by clinical providers. Ninety-four and 90% either currently or previously have received physical therapy and occupational therapy, respectively.

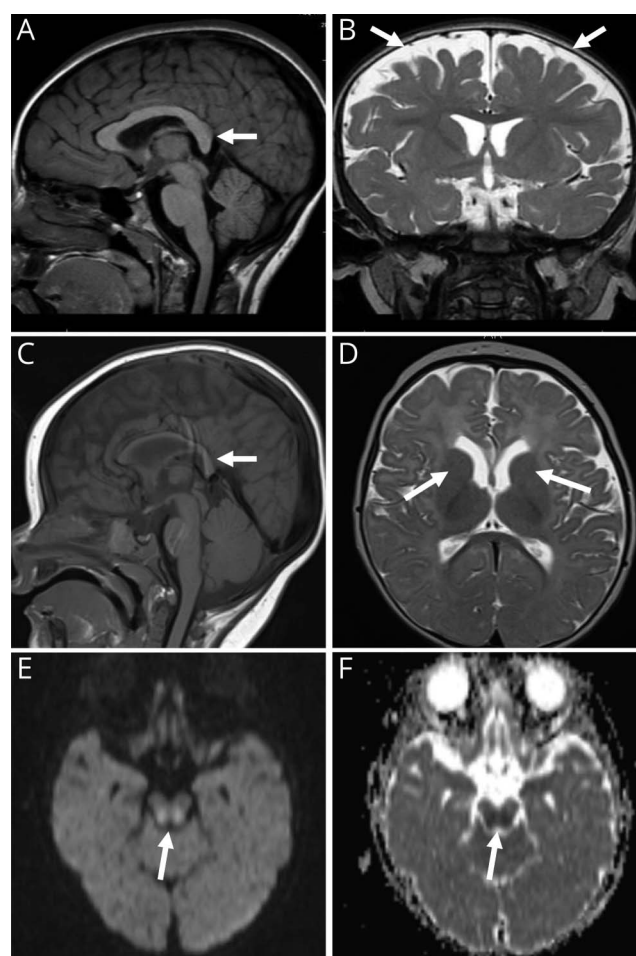
### Sleep

Six participants (18%) reported severe sleep disturbance associated with difficulty falling and staying asleep. Of the

participants who reported sleep disturbance, half reported melatonin as an effective remedy.

Sensory issues are reported in many, including both hypo- and hyper-sensitivity to pain, temperature, and touch. Sensory processing issues were stratified using the SSP2, which was completed by caregivers of 11 female participants, including 2 toddlers, 5 children, 1 adolescent, and 3 adults, aged 2–39 years (figure 4, A–C). Of the 1 toddlers who were evaluated, both exhibited distinctive diminished sensory processing with more than 2 SDs above the mean in the domains of visual processing and auditory processing. They also both showed increased sensory processing in areas of general processing and oral sensory processing, scores at least 1 SD above the mean. For the children who had SSP2 completed, all except 1 participant with an ASD diagnosis were found to have distinct

**Figure 3** Remarkable Brain MRIs



Sagittal T1-weighted image demonstrates a vertical configuration of the posterior body/splenium of the corpus callosum (A and C, arrows) as well as thinning of the corpus callosum (C) (participant 27). Coronal T2-weighted image demonstrates prominence of the extra-axial spaces (arrows) in this child age 1 year 5 months (B) (participant 14). Axial T2-weighted image demonstrates delayed myelination of the anterior limbs of the internal capsule (arrow) in this patient age 10.5 months (D) (participant 1). Axial diffusion-weighted (E) and apparent diffusion coefficient (F) images demonstrate restricted diffusion involving the tegmental tracts (arrows, participant 1).



diminished sensory processing in the area of body positioning, each of which was more than 2 SDs above the mean. Disturbances in modulation were also noted in movement processing, all except 1 participant with an ASD diagnosis exhibited 1–2+ SD above the mean. The majority of the child cohort presented with typical modulation of sensory input affecting emotional responses, within 1 SD above the mean. Within the adult cohort evaluated, 2 participants exhibited distinct diminished sensory processing in touch processing and body movement processing, scoring at least 2 SD above the mean. The third participant in the adult cohort responded to multiple questions in the same areas, with “almost always.”

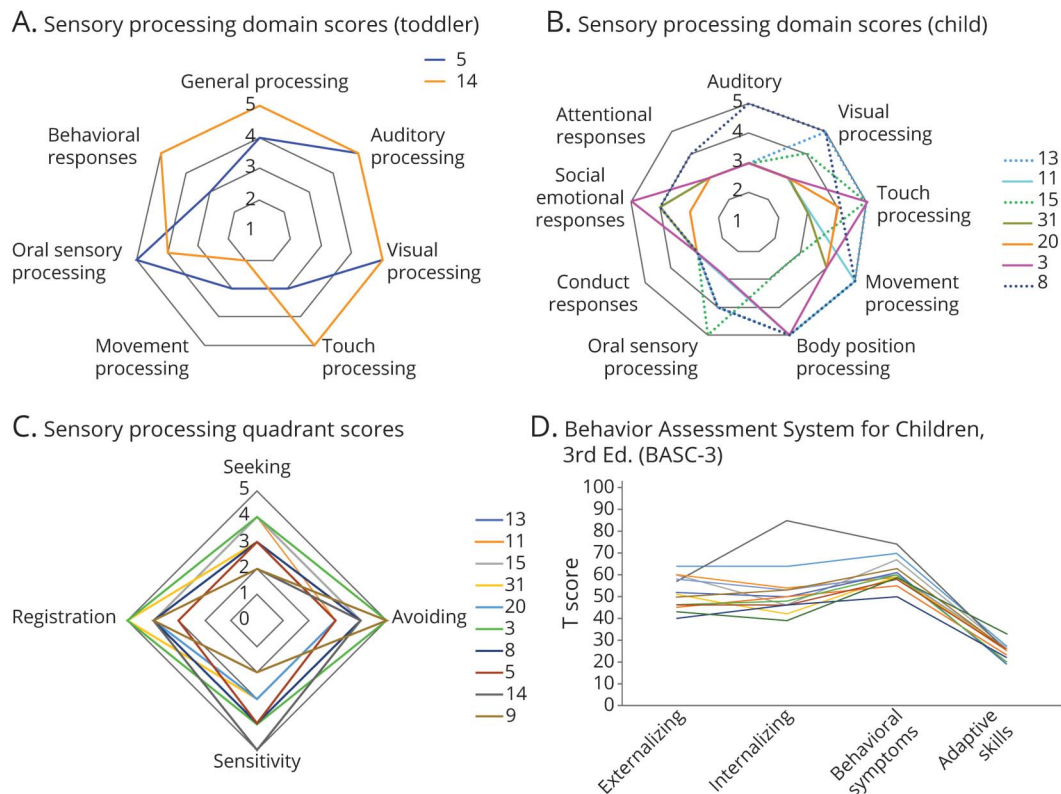
Most individuals have had brain imaging, most commonly MRI, and general findings include vertical configuration of the splenium of the corpus callosum, delayed myelination, and decreased cerebellar volume (figure 3, table e-2, links.lww.com/NXG/A362). In addition, 1 male participant (#1) had restricted diffusion of the tegmental tracts at age 10 months (figure 3, E and F). Two participants had MR spectroscopy, one was normal and the other showed lactate peaks in the bilateral basal ganglia.

Five participants had muscle biopsies during their diagnostic evaluation for hypotonia and global developmental delay. Muscle biopsies were mixed, with 3 normal results (table e-2, links.lww.com/NXG/A362) and 2 abnormal. One result showed mild type II fiber atrophy by muscle enzyme histochemistry with mild increase in morphologically normal glycogen and mitochondria (participant 8 at age 10 months), and another showed reduced activity complex II and III of the respiratory chain enzymes (participant 30 at age 1 month). One participant had an EMG/nerve conduction study with normal amplitude, distal latency, and conduction velocity of the peroneal nerve. Needle EMG of selected muscles showed evidence of chronic denervation with decreased recruitment of high amplitude long duration motor units in the extensor digitorum brevis and abductor hallucis muscles with normal gastrocnemius and tibialis anterior (#18).

### Psychiatric Diagnoses and Concerns

Caregivers reported a high frequency of psychiatric or other behavioral concerns, and these were often corroborated by formal testing (table e-1, links.lww.com/NXG/A361).

**Figure 4** Parent-Reported Sensory Processing of Participants Carrying Variants in *HNRNP2*



(A) Radar plot depicting sensory processing domains of Toddler Sensory Profile 2, where scores of 1 represent much less than others, 2 represents less than others, 3 represents just like the majority of others, 4 represents more than others, and 5 represents much more than others (n = 2). (B) Radar plot depicting sensory processing domains of Child Sensory Profile 2, where scores of 1 represent much less than others, 2 represents less than others, 3 represents just like the majority of others, 4 represents more than others, and 5 represents much more than others. Dotted lines represent participants with a parent reported ASD diagnosis (n = 7). (C) Radar plot depicting sensory processing quadrants for all Toddler, Child and Adolescent Sensory Profile 2, where scores of 1 represent much less than others, 2 represents less than others, 3 represents just like the majority of others, 4 represents more than others, and 5 represents much more than others. Dotted lines represent participants with an ASD diagnosis (n = 10). (D) Domain scores behavioral and emotional concerns were measured using the Behavior Assessment System for Children, third edition. ASD = autism spectrum disorder.



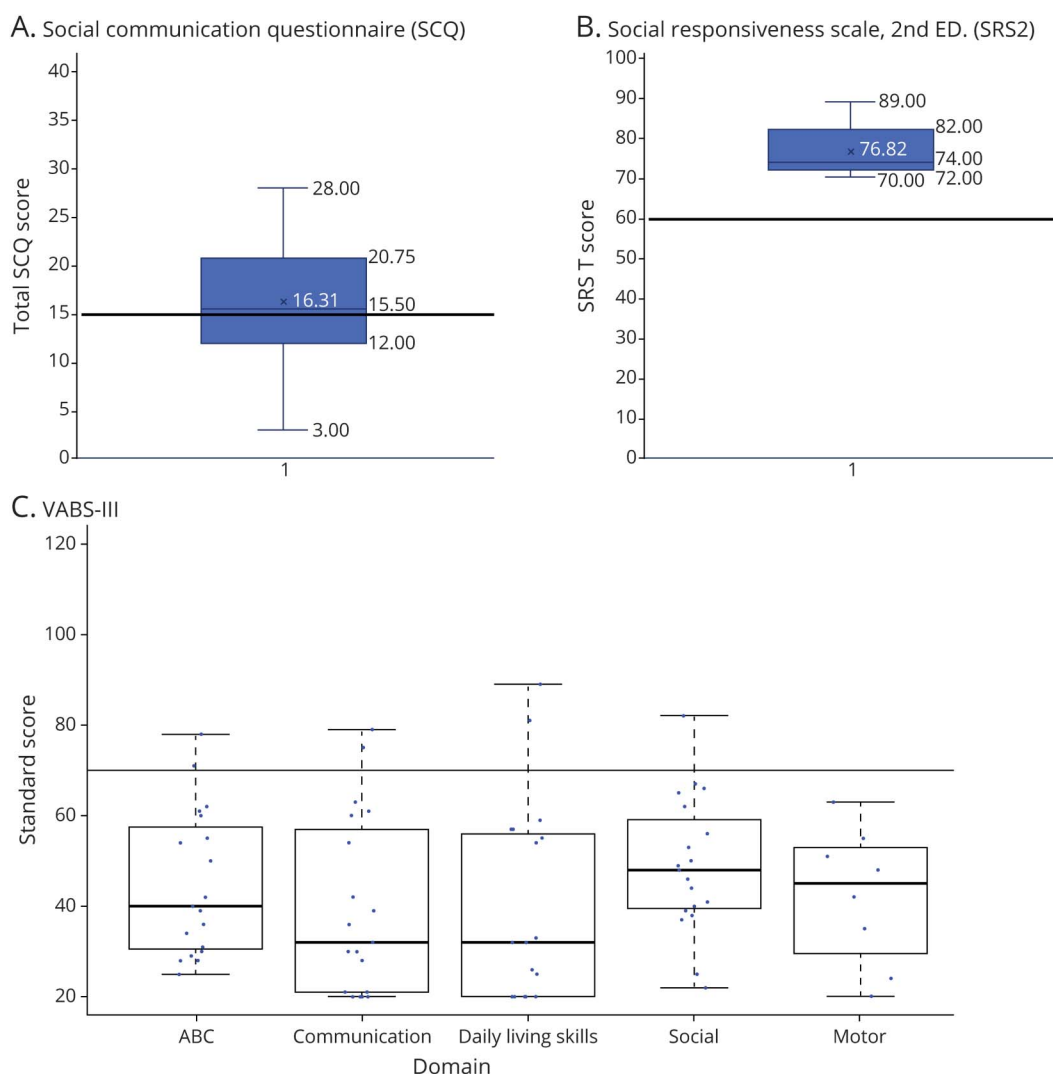
Diagnoses in this group include ASD (34%), PDD (17%), (atypical) Rett syndrome (10%), social communication disorder (3%), and childhood disintegrative disorder (3%), with a total of 47% overall with one of these diagnoses. Although parent report revealed just under half with an ASD clinical diagnosis (inclusive of PDD in older individuals), most individuals had elevated scores suggestive of ASD on both the SCQ and the SRS (figure 5, A and B). Many individuals reported clinically notable elevated scores for externalizing, internalizing, and overall behavioral symptoms with lower adaptive skillset (figure 4D). Only 15% had a clinical diagnosis of attention deficit hyperactivity disorder (ADHD), but many caregivers reported concerns with attention (33%), distractibility (24%), and hyperactivity (14%). Many report anxiety

(67%), self-injurious behaviors (38%), panic attacks (10%), depression (5%), and hallucinations (5%). Twenty-three percent of participants have taken psychiatric medications, including antipsychotics, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, psychostimulants, beta blockers, benzodiazepines, alpha-2-agonists, and opioid antagonists (table 1).

### Gastrointestinal Issues

Feeding and gastrointestinal issues are present in nearly all participants: any feeding concern (97%), chronic constipation (60%), poor appetite (34%), difficulty with swallowing (34%), gastroesophageal reflux (28%), diarrhea (9%), pica (9%), overeating (6%), chronic abdominal bloating (3%), and

**Figure 5** Parent-Reported Standardized Social, Adaptive, and Motor Skills Testing of Participants Carrying Variants in *HNRNP2*



(A) Social Communication Questionnaire (SCQ) with elevated scores more than 15 suggestive of autism spectrum disorder (ASD) diagnosis. (B) Social Responsiveness Scale (SRS) with elevated T scores more than 60 suggestive of ASD diagnosis. (C) Standard scores for 19 affected individuals are shown for the Vineland Adaptive Behavior Scale, third edition (VABS-III), Parent or Caregiver form. Scores include the overall Adaptive Behavior Composite (ABC) Score as well as individual scores for each domain (communication, daily living skills, socialization, and motor skills). The motor skills domain is only calculated for individuals aged 9 years or younger ( $n = 8$ ). Scores are norm-referenced to individual of the same age, with normed scores standardized with a mean of 100 and a SD of 15. The horizontal line at 70 represents 2 SDs below the mean.

severe abdominal pain (3%). Four participants use a gastrostomy tube for feeding (13%).

### Endocrine, Growth Issues

Approximately half of caregivers report significant weight abnormalities (47%) and history of failure to thrive (36%). Twelve gained weight too slowly, whereas 2 gained too much weight. Six were short for age (19%). One had precocious puberty (3%) and 3 with delayed sexual development (9%).

### Orthopedic Issues

Seventy-five percent have an orthopedic issue, including scoliosis (33%), hip dysplasia (21%), kyphosis (4%), lordosis (4%), arthritis (4%), and missing spinous process (5%). Common surgeries include scoliosis, hip dysplasia or dislocated hips, or ankle/foot repairs.

Of the 24 participants with a reported orthopedic issue, 29% report muscle, bone, or joint pain, whereas 13% had stiffness. Half of individuals wear supportive braces (50%), including ankle foot orthotics (44%), orthotic inserts (19%), supra-malleolar orthotics (13%), and dynamic ankle orthotics (13%). Most children and adults were noted to have similar extremity deformities such as pes planus, calcaneal adduction with navicular bone drop, with finger arachnodactyly (figure 2).

### Vision

Many children (73%) have visual defects. Of these, 54% report strabismus. Other findings include cortical visual impairment (33%), poor vision (13%), myopia (17%), and congenital ptosis (4%).

### Hearing

About one-fourth of individuals report hearing deficits (28%), including recurrent infections (22%) and tinnitus (11%).

### Cardiovascular Issue

Two individuals had mitral valve prolapse (6%), 1 individual had aortic dilation (3%), and 1 participant had atrial septal defect (3%).

### Pulmonary Issues

Three participants reported occasional hyperventilation associated with breath-holding, one with silent aspiration, and another with reactive airway disease.

A heuristic severity score was developed by applying a weighted sum of common symptoms within the cohort, including developmental delay/intellectual disability, developmental regression, microcephaly, cortical vision impairment, tone problems, seizures, movement disorder, growth problems, and other neuropsychiatric diagnoses such as ASD, anxiety, and ADHD.

PCA shows that principal component (PC) 1 is highly correlated with the heuristic severity scores with Pearson correlation coefficient of  $-0.72$ . The top contributing features for PC1 and

contributing to severity include ASD, PDD, social communication disorder, childhood disintegrative disorder, Rett syndrome, anxiety, and regression. PC2 is attributed mostly to sex and sex-differentiated features. Boys in this cohort are more likely to have cortical visual impairment and abnormal brain MRI, and more girls experienced anxiety. PC3 distinguishes age of the participants. Older children were diagnosed with attention-deficit/hyperactivity disorder more often. Younger children often had sleep problems, developmental regression, or microcephaly. The first 3 PCs explain 17.8%, 14.7%, and 11.4%, respectively, of the variance in the data.

A subset of caregivers ( $n = 19$ ) provided information about their child's adaptive daily living functioning using the VABS-III (figure 5C). Scores include the overall Adaptive Behavior Composite (ABC) Score as well as individual scores for each domain (communication, daily living skills, socialization, and motor skills). All individuals had relatively higher scores for socialization compared with other domains, although the overall values were low to below average. Most individuals were grossly delayed across all domains, which was reflected in the overall composite score (ABC score). The motor skills domain, which is only calculated for individuals aged 9 years or younger ( $n = 8$ ), also showed gross delays. Few participants had higher scores in some domains and among these outliers were individuals with the genotypes p.R212G ( $n = 1$ ) and p.P213L ( $n = 1$ ).

## Discussion

Variants in the X-linked gene *HNRNPH2* cause a neurodevelopmental syndrome with an expanding phenotype with the identification of additional variants and a small number of males.<sup>10–12,23</sup> Here, we describe the largest descriptive study of 33 individuals, with 11 different de novo missense variants in *HNRNPH2*, most located within or adjacent to the NLS. The 2 recurrent missense variants, p.R206W ( $n = 18$ ) and p.R206Q ( $n = 5$ ), remain the most common missense variants. There are 2 additional missense variants at this same amino acid residue (p.R206G and p.R206L), suggesting that this amino acid is functionally important. Furthermore, there are other nearby missense variants at amino acids 209, 210, 212, and 213, all within or adjacent the NLS (figure 1) supporting an earlier hypothesis that the NLS is critical for gene function. Two additional predicted pathogenic de novo variants were also identified farther away from this region at residues 114 and 340.

This study also includes 4 males whose average heuristic severity score is elevated (more severe) than females. Moreover, the 2 males harboring variants within the NLS appear to have a much more severe phenotype than the 2 outside the NLS. These findings along with previously reported males with *HNRNPH2*-related disorder refute the previous hypothesis that variants in males are always embryonic lethal.

The major features of the *HNRNPH2*-related disorder phenotype include developmental delay/intellectual disability,

severe language impairment, motor problems, growth, and musculoskeletal disturbances. Minor features include dysmorphic features, epilepsy, neuropsychiatric diagnoses such as ASD, and cortical visual impairment. A third of the cohort reports short-term regression in times of illness or after clinical seizures, followed by regaining previously acquired skills in most individuals. Importantly, microcephaly is reported in about half of the individuals, mostly acquired, but there is no association between microcephaly and developmental regression or seizures. The most severely affected individuals have severe intellectual disability, are nonambulatory, and nonverbal. The least affected individual in this group is a 17-year-old girl with the p.R212T variant with developmental delay and ASD who is verbal, ambulatory, and in secondary education. Based on this larger study, the clinical course appears to be static and not progressive or degenerative through early adulthood. Although rare, we report early stroke and premature death with this condition, although it is unclear whether these are comorbid conditions or whether *HNRNPH2*-related disorder is causative of these neurologic outcomes.

Although most participants were born without any specific findings, caregivers had early concerns usually before 12 months of age, such as poor feeding with failure to thrive in infancy. There are no associated congenital anomalies, but distinct physical features are often seen including almond-shaped eyes, short palpebral fissures, a short philtrum, full lower lip and micrognathia with associated extremity findings such as arachnodactyly, curled toes, pes planus, calcaneal adduction, and navicular bone drop.

Most individuals with *HNRNPH2*-related disorder have low cognitive profiles. We sought to better understand the adaptive functioning of this group, as they may also better reflect the overall functioning of individuals compared with cognitive measures, given challenges with the administration and interpretation of standardized cognitive tests in severely disabled individuals, anxiety, and avoidance affecting test performances. Overall skillsets were low across several measures of adaptive functioning (VABS-III, BASC-3, and PEDI-CAT). Communication is severely affected, as 76% of individuals are nonverbal or minimally verbal, and others have apraxia of speech or articulation difficulties. Psychiatric comorbidities are also high in this group, notably anxiety, ADHD, and self-injurious behaviors.

The motor system is particularly involved in *HNRNPH2*-related disorders, with early motor concerns in both fine and gross motor skills. Tone abnormalities are common, with weakness and decreased muscle bulk with nonspecific muscle biopsy findings (table e-1, [links.lww.com/NXG/A361](https://links.lww.com/NXG/A361)) and 1 participant with EMG finding of selective lower extremity denervation. Orthopedic and musculoskeletal issues are common in this group, and many have required surgical procedures of the hips and feet. Sensory issues are commonly reported across the lifespan present with elevated modulation disturbances in touch, body movement, auditory, visual, and oral sensory

processing. These sensory issues were markedly exaggerated in all 4 quadrants in children with ASD compared with those without ASD diagnosis, similar to other ASD cohorts.<sup>20</sup> Of interest, individuals in this group also shared similar findings to children with cerebral palsy with sensory processing deficits on body positioning and movement that impede their motor system.<sup>24</sup> More detailed phenotyping of these sensory anomalies will be important to describe and quantify as these appear to be significant impact on daily activities.

Seizures have been reported as early as 3 years and as late as 34 years of age; however, 23% had reported seizures in the setting of a fever so it is unclear whether some of these are benign febrile seizures. The oldest participant had the seizure preceding a stroke. Altogether, 60% of participants have either clinical seizures or seizure activity on EEG. There is no specific seizure type, and different medications have been used, with both levetiracetam and valproic acid reported as effective.

All participants share a common developmental phenotype with developmental delays, neuropsychiatric diagnoses, and low adaptive function across all domains. Although there does not appear to be a strict genotype-phenotype correlation, this is limited by the distribution of cases across genotypes, with the majority of individuals with p.R206W and p.R206Q. There is heterogeneity even within the 2 most common genotypes, perhaps due to differences in X inactivation. However, boys are generally more severely affected than girls. *HNRNPH2* amino acids between 194 and 220, including the highly conserved region at 205–210, are responsible for the nuclear import activity of the GYR domain, and even variants outside this region are also associated with disease and pathogenic.<sup>25–27</sup> Our cohort with 31 of 33 individuals carrying pathogenic variants between residues 205 and 213 suggests that this is a critical region for protein function. We continue to propose a change in function mechanism in the pathogenesis of *HNRNPH2*-related disorder, possibly through mis-localization of the protein due to the disruption of the NLS and other non-NLS residues; however, there does not appear to be any toxic accumulation with several unrevealing muscle biopsies in this study.

Importantly, *HNRNPH1* is a highly conserved autosomal paralogue of *HNRNPH2* with over 95% sequence homology. Heterozygous missense variants in *HNRNPH1* are associated with an overlapping clinical phenotype with *HNRNPH2*-related disorder, and these variations occur at residue 206 in *HNRNPH1*, further suggesting the importance of this region.<sup>28,29</sup> Assuming that *HNRNPH1* is fully functional in individuals with *HNRNPH2*-related disorder and that these 2 proteins function similarly, functional *HNRNPH1* may be able to partially compensate for disrupted *HNRNPH2*. Assessing the functional consequences of each these de novo variants will be important to better understand the pathophysiology and identify possible therapeutic interventions for these disorders.

Although RNA splicing factors including *hnRNPs A1, A2, A1/B2, H, K, and M* have been implicated in various cancers, other

RNA-binding proteins (RBPs) are increasingly implicated in neurologic disorders.<sup>25,26,30,31</sup> Various mechanisms of altered RNA homeostasis are implicated in neurologic disorders such as spinal muscular atrophy, ALS, ASD, and other neurodegenerative disorders with altered RBP expression, RBP aggregation, and RNA-mediated toxicity.<sup>31</sup> Specifically, *HNRNP* genes are an emerging class of genes associated with neurologic disorders including limb-girdle muscular dystrophy associated with *HNRNPDL*,<sup>7,32</sup> *HNRNPR*-related NDD,<sup>33</sup> and epileptic encephalopathies associated with *HNRNPU* loss-of-function variants.<sup>34</sup> This study broadens the clinical spectrum of *HNRNP2*-related disorder and may provide insight to a newly emerging group of NDDs associated with the group of RBPs called hnRNPs.

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<b>Olivia Thornburg, BA</b>	Columbia University Irving Medical Center, New York, NY	Major role in the acquisition of data and analysis or interpretation of data
<b>Cheryl Pan</b>	Columbia University, New York, NY	Major role in the acquisition of data
<b>Donnielle Rome-Martin, MS, OTR/L, ATR</b>	Columbia University Irving Medical Center, New York, NY	Major role in the acquisition of data and analysis or interpretation of data
<b>Xiao Fan, PhD</b>	Columbia University Irving Medical Center, New York, NY	Major role in the acquisition of data
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## Appendix (continued)

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<b>Wendy K. Chung, MD, PhD</b>	Columbia University Irving Medical Center, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design

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# Neurology<sup>®</sup> Genetics

## **Detailed Clinical and Psychological Phenotype of the X-linked *HNRNPH2*-Related Neurodevelopmental Disorder**

Jennifer M. Bain, Olivia Thornburg, Cheryl Pan, et al.

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