HNRNPH2-NDD

https://www.ncbi.nlm.nih.gov/books/NBK584018/

SummaryClinical characteristics.Most individuals with HNRNPH2-related neurodevelopmental disorder (HNRNPH2-NDD) have symptoms early in life, before age 12 months. The major features of HNRNPH2-NDD are developmental delay / intellectual disability, motor and language delays, behavioral and psychiatric disorders, and growth and musculoskeletal abnormalities. Minor features include dysmorphic facies, gastrointestinal disturbances, epilepsy, and visual defects. Although HNRNPH2-NDD is an X-linked condition, there is not enough information on affected females versus affected males to make any generalizations about phenotypic differences between the two sexes.Diagnosis/testing.The diagnosis of HNRNPH2-NDD is established in a proband with suggestive clinical findings and a heterozygous or hemizygous pathogenic (or likely pathogenic) variant in HNRNPH2 identified by molecular genetic testing.Management.Treatment of manifestations: Feeding therapy or gastrostomy tube placement for those with poor weight gain; standard treatment for developmental delay / intellectual disability, behavioral problems, epilepsy, movement disorders, abnormal tone, constipation, sleep apnea, cortical visual impairment, hearing loss, musculoskeletal anomalies, cardiac defects, and pubertal anomalies.Surveillance: At each visit: measurement of growth parameters; evaluation of nutritional status, feeding issues, and safety of oral intake; assessment of developmental progress and educational needs; behavioral assessment; assessment for new manifestations (seizures, change in tone, movement disorders, developmental regression); monitoring for evidence of sleep disturbance and signs/symptoms of sleep apnea; orthopedic assessment, including for scoliosis (until skeletal maturity or in older individuals who are nonambulatory). Assess for hip dysplasia in infancy or at each visit in individuals who are nonambulatory. At each visit in childhood and adolescence: assessment for signs/symptoms of puberty. At least annually or as clinically indicated: hearing evaluation (in childhood); ophthalmologic evaluation.Genetic counseling.HNRNPH2-NDD is inherited in an X-linked manner. Most affected individuals have the condition as the result of a de novo pathogenic

variant. If the mother of the proband has an HNRNPH2 pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%. Females who inherit the pathogenic variant are at high risk of being affected. Males who inherit the pathogenic variant have a variable phenotype ranging from severe manifestations to mild developmental delay with autistic features and psychiatric diagnoses. A male with a mosaic HNRNPH2 pathogenic variant that includes the germline may transmit the HNRNPH2 pathogenic variant to daughters but not to sons. Prenatal and preimplantation genetic testing are possible if the familial pathogenic variant has been identified.

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DiagnosisFor the purposes of this GeneReview, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth [Caughey et al 2021].No consensus clinical diagnostic criteria for HNRNPH2-related neurodevelopmental disorder (HNRNPH2-NDD) have been published.Suggestive FindingsHNRNPH2-NDD should be considered in both females and (less commonly) males with the following clinical features.

Clinical findings

Developmental delay / intellectual disability, most often characterized by significant motor abnormalities with severe expressive and receptive language impairmentANDAny of the following features in infancy or childhood:Developmental regressionGeneralized hypotonia of infancyInfant

feeding difficultiesAcquired microcephalyPoor growthMovement disorders, such as hand stereotypiesEpilepsy, of variable semiologyBehavioral problems and psychiatric issues including anxiety, attention-deficit/hyperactivity disorder, sensory issues, social communication disorder, or autism spectrum disorderNonspecific dysmorphic features (See Clinical Description.)Ophthalmologic involvement including strabismus and cortical visual impairmentFamily history. Because HNRNPH2-NDD is typically caused by a de novo pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with X-linked inheritance (e.g., no male-to-male transmission).Establishing the DiagnosisThe diagnosis of HNRNPH2-NDD is established in a proband with suggestive clinical findings and a heterozygous or hemizygous pathogenic (or likely pathogenic) variant in HNRNPH2 identified by molecular genetic testing (see Table 1).Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous HNRNPH2 variant of uncertain significance does not establish or rule out the diagnosis of this disorder.Because the phenotype of HNRNPH2-NDD is indistinguishable from many other inherited disorders with developmental delay / intellectual disability, recommended molecular genetic testing approaches include use of a multigene panel or comprehensive genomic testing.Note: Single-gene testing (sequence analysis of HNRNPH2, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.An intellectual disability / autism multigene panel that includes HNRNPH2 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview. (3) In some laboratories, panel options

may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Exome sequencing is most commonly used; genome sequencing is also possible.For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.Table 1. Molecular Genetic Testing Used in HNRNPH2-Related Neurodevelopmental DisorderView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

HNRNPH2

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Epilepsy, of variable semiology

Behavioral problems and psychiatric issues including anxiety, attention-deficit/hyperactivity disorder, sensory issues, social communication disorder, or autism spectrum disorder

Nonspecific dysmorphic features (See Clinical Description.)

Ophthalmologic involvement including strabismus and cortical visual impairment

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Clinical CharacteristicsClinical DescriptionMost individuals with HNRNPH2-related neurodevelopmental disorder (HNRNPH2-NDD) have symptoms early in life, before age 12 months. The major features of HNRNPH2-NDD are developmental delay / intellectual disability, motor and language delays, behavioral and psychiatric disorders, and growth and musculoskeletal

abnormalities. Minor features include dysmorphic facies, gastrointestinal disturbances, epilepsy, and visual defects.To date, 49 individuals from 45 families with pathogenic variants in HNRNPH2 have been identified [Harmsen et al 2019, Jepsen et al 2019, Somashekar et al 2020, Bain et al 2021, Gillentine et al 2021, White-Brown et al 2022]. Initially, because the only affected individuals were phenotypic females presumed to be 46,XX, it was hypothesized that affected 46,XY individuals were embryonic lethal. However, at least 16 affected 46,XY individuals have now been reported [Harmsen et al 2019, Jepsen et al 2019, Gillentine et al 2021, Somashekar et al 2020, Bain et al 2021, Kreienkamp et al 2022].At least one unaffected mother of an affected female was found to have the same HNRNPH2 pathogenic variant as her daughter. This unaffected mother had significantly skewed X-chromosome inactivation [White-Brown et al 2022]. There is not enough information on affected females versus affected males to make any generalizations about phenotypic differences between the two sexes.Table 2. HNRNPH2-Related Neurodevelopmental Disorder: Frequency of Select FeaturesView in own windowFeature# of Personsw/Feature (%)CommentDevelopmental delay /Intellectual disability46/46 (100%)Typically in severe rangeAbnormal tone41/46 (89%)Hypotonia (more common) & hypertonia both reportedSevere language impairment37/45 (82%)Nonverbal or minimally verbalPsychiatric disorders32/42 (76%)Anxiety, ASD, & ADHD are most common.Facial dysmorphism31/44 (70%)See Facial features, following the table.Feeding problems28/41 (68%)Some affected persons require gastrostomy tube for feeding.Orthopedic problems25/37 (68%)Most commonly scoliosisVisual defects29/43 (67%)Strabismus in about halfSeizures18/46 (39%)No characteristic seizure typeSleep problems16/41 (39%)Both falling & staying asleepMicrocephaly16/44 (36%)Commonly acquiredHearing loss~25%ASD = autism spectrum disorder; ADHD = attention=deficit/hyperactivity disorderDevelopmental delay (DD) and intellectual disability (ID) has been reported in all affected individuals and is one of the major phenotypic features of HNRNPH2-NDD. The degree of disability is most commonly in the moderate-to-severe range.Speech and language is severely affected, with the majority of affected individuals being nonverbal or minimally verbal and others with speech apraxia or difficulties with articulation. In those who acquired speech, most did so between ages one and five years.Most

affected individuals have delays in the acquisition of both gross and fine motor skills in infancy. Many affected individuals are nonambulatory. All affected individuals significantly benefit from intensive therapy services, and many also use orthoses in addition to other devices. Referral to a rehabilitation specialist / physiatrist and orthopedist is recommended for appropriate supports. Most individuals require significant support in daily activities.Many affected individuals have low cognitive skills and low adaptive skill sets using the Vineland Adaptive Behavior Scales. Most cognitive scales show floor effects below the first centile for many testing domains of standardized cognitive assessment. Most individuals require special education and support in daily activities into adulthood.Behavioral and psychiatric problems have been validated with formal testing in almost half (47%) of affected individuals.The most common diagnoses include anxiety (68%), self-injurious behaviors (38%), and autism spectrum disorder (34%).Attention-deficit/hyperactivity disorder was diagnosed in about 15% of affected individuals, but a higher number of caregivers reported concerns regarding attention, hyperactivity, and distractibility.Some affected individuals demonstrated stereotypies and intermittent developmental regression that can be suggestive of Rett syndrome (see MECP2 Disorders).

Other neurodevelopmental features

Abnormal muscle tone. Most affected individuals have abnormalities of tone (most commonly hypotonia but also hypertonia), often first observed before age 12 months. Spasticity / muscle rigidity has been noted in about 33% of affected individuals. Some affected individuals have been given a clinical diagnosis of cerebral palsy based on their tone and muscle issues.Weakness. Most affected individuals have generalized muscle weakness and decreased muscle bulk.Electromyography done on one affected individual showed selective lower extremity denervation.Of three affected individuals who underwent muscle biopsy, two were found to have abnormalities and the third was normal. One affected individual was found to have mild type II fiber atrophy; the other affected individual had reduced activity in the respiratory chain enzymes in complexes II and III.Movement disorders. Reported abnormal movements have included the following:Motor planning problemsAtaxiaStereotypiesClumsinessAbnormal gaitIntermittent

developmental regression. Caregivers have reported regression during episodes of illness or after a clinical seizure, followed by recovery of the lost skill once the episode resolves.Seizures have been reported in about 39% of affected individuals, and another 10% have abnormal EEG findings without any known clinical correlation. One affected individual had refractory seizures. In general, affected individuals have responded well to levetiracetam and valproic acid (see Management).The average age of presentation of first seizure is 8.7 years (range: age 3-34 years).The semiology of clinical seizures is variable.Staring episodes (69%) are the most common seizure type.Febrile seizures are present in 23% of affected individuals.Other seizure semiologies include tonic-clonic (43%), tonic (38%), spasms (23%), clonic (15%), and myoclonic (15%).Abnormal EEG findings include diffuse slowing of the background, left-sided posterior and midline epileptic discharges, and paroxysmal activity in the right temporal lobe.Neuroimaging. Brain MRI is normal in most affected individuals who have undergone imaging; however, some individuals have nonspecific findings, including delayed myelination, decreased cerebellar volume (cerebellar hypoplasia), and abnormal corpus callosum (thinning, dysgenesis, and vertical configuration). Two affected individuals underwent MR spectroscopy, with one showing a lactate peak in the basal ganglia region; the other MR spectroscopy was interpreted as normal.Respiratory. Three affected individuals have been noted to have breath-holding spells, but in general HNRNPH2-NDD has not been associated with significant respiratory issues.Sleep disturbances have been observed and are associated with problems falling and staying asleep. Melatonin has been effective in treating these concerns in many affected individuals (see Management) [Author, personal observation]. The sleep disturbances seen in individuals with HNRNPH2-NDD are more likely to be related to issues with sleep onset and maintenance as opposed to sleep apnea.Growth. Four affected individuals were noted to have intrauterine growth restriction on prenatal ultrasound, but most have anthropometric measurements within the normal range for sex at birth. It should be noted that occipital frontal circumference (OFC) was not available for all affected individuals.Weight. About half of reported affected individuals (55%) had difficulty gaining weight, which in most cases was attributed to feeding difficulties during infancy (see Gastrointestinal issues in the text following).Length/height. Six out of 33 affected

individuals were reported to be short for their age and sex, with the shortest individual being 5.5 SD below the mean.Head circumference. About 30% of affected individuals have acquired microcephaly (defined as OFC ≥2 SD below the mean for age and sex). The most severely affected individual had an OFC 4.08 SD below the mean.Gastrointestinal issues are present in most affected individuals. Feeding problems and chronic constipation are the two most common problems.Feeding difficulties have been observed in more than two thirds of affected individuals.Most affected individuals have reported feeding issues before age 12 months, with some having concerns immediately after birth.About 34% of affected individuals have dysphagia accompanied by aspiration.Many affected individuals have persistent feeding issues, along with poor growth, throughout life. Several have required placement of feeding tubes.

Other gastrointestinal issues

Poor appetiteGastroesophageal reflux diseaseSwallowing difficulty (dysphagia)PicaDiarrheaOvereating, which can lead to weight gain in rare affected individualsAbdominal painBloatingVision involvement. A considerable proportion (67%) of affected individuals have visual defects, with strabismus being the most common finding in about 54%. Other findings include cortical visual impairment (33%), myopia (17%), and decreased visual acuity (13%). One individual was reported to have congenital ptosis.Hearing deficits have been reported by parents in one quarter of affected individuals, but the type of hearing loss (sensorineural, conductive, or mixed) is not known for many of these reported individuals. Recurrent ear infections and tinnitus have also been reported.

Other associated features

Orthopedic abnormalities have been reported in individuals of all ages and most commonly include:Pes planusArachnodactylyScoliosis, including kyphosis and lordosis, which is most frequently neuromuscular in originHip dysplasiaRarer findings include:Navicular bone drop with calcaneal adductionBone, muscle, and joint painArthritis and stiffness of jointsCardiovascular abnormalities. Nonspecific cardiac abnormalities have been observed in four affected individuals, including two with mitral valve prolapse, one with congenital aortic dilatation, and one with an atrial

septal defect.Endocrine. One affected individual had precocious puberty and three had delayed puberty.Facial features. No recognizable dysmorphic features have been observed. If present, dysmorphic features are nonspecific. Such features may include:Almond-shaped eyesShort palpebral fissuresShort philtrumLong columellaHypoplastic alae nasiFull lower lipMicrognathiaStroke. One affected individual had a stroke after a first-time seizure at age 34 years. It is unclear if early stroke is a rare finding in affected individuals or if this was a rare co-occurrence of two unrelated findings.Prognosis. It is unknown whether the life span in HNRNPH2-NDD is abnormal. One reported individual was alive at age 38 years [Bain et al 2021], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported. Based on the available data, the clinical course does not appear to be progressive or degenerative into early adulthood.Genotype-Phenotype CorrelationsNo genotype-phenotype correlations have been identified.PrevalenceThe overall prevalence remains unknown; to date, 49 individuals from 45 families have been reported with this disorder.

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adulthood.Behavioral and psychiatric problems have been validated with formal testing in almost half (47%) of affected individuals.The most common diagnoses include anxiety (68%), self-injurious behaviors (38%), and autism spectrum disorder (34%).Attention-deficit/hyperactivity disorder was diagnosed in about 15% of affected individuals, but a higher number of caregivers reported concerns regarding attention, hyperactivity, and distractibility.Some affected individuals demonstrated stereotypies and intermittent developmental regression that can be suggestive of Rett syndrome (see MECP2 Disorders).

Other neurodevelopmental features

Abnormal muscle tone. Most affected individuals have abnormalities of tone (most commonly hypotonia but also hypertonia), often first observed before age 12 months. Spasticity / muscle rigidity has been noted in about 33% of affected individuals. Some affected individuals have been given a clinical diagnosis of cerebral palsy based on their tone and muscle issues.Weakness. Most affected individuals have generalized muscle weakness and decreased muscle bulk.Electromyography done on one affected individual showed selective lower extremity denervation.Of three affected individuals who underwent muscle biopsy, two were found to have abnormalities and the third was normal. One affected individual was found to have mild type II fiber atrophy; the other affected individual had reduced activity in the respiratory chain enzymes in complexes II and III.Movement disorders. Reported abnormal movements have included the following:Motor planning problemsAtaxiaStereotypiesClumsinessAbnormal gaitIntermittent developmental regression. Caregivers have reported regression during episodes of illness or after a clinical seizure, followed by recovery of the lost skill once the episode resolves.Seizures have been reported in about 39% of affected individuals, and another 10% have abnormal EEG findings without any known clinical correlation. One affected individual had refractory seizures. In general, affected individuals have responded well to levetiracetam and valproic acid (see Management).The average age of presentation of first seizure is 8.7 years (range: age 3-34 years).The semiology of clinical seizures is variable.Staring episodes (69%) are the most common seizure type.Febrile seizures are present in 23% of affected individuals.Other seizure semiologies include tonic-clonic (43%), tonic

(38%), spasms (23%), clonic (15%), and myoclonic (15%).Abnormal EEG findings include diffuse slowing of the background, left-sided posterior and midline epileptic discharges, and paroxysmal activity in the right temporal lobe.Neuroimaging. Brain MRI is normal in most affected individuals who have undergone imaging; however, some individuals have nonspecific findings, including delayed myelination, decreased cerebellar volume (cerebellar hypoplasia), and abnormal corpus callosum (thinning, dysgenesis, and vertical configuration). Two affected individuals underwent MR spectroscopy, with one showing a lactate peak in the basal ganglia region; the other MR spectroscopy was interpreted as normal.Respiratory. Three affected individuals have been noted to have breath-holding spells, but in general HNRNPH2-NDD has not been associated with significant respiratory issues.Sleep disturbances have been observed and are associated with problems falling and staying asleep. Melatonin has been effective in treating these concerns in many affected individuals (see Management) [Author, personal observation]. The sleep disturbances seen in individuals with HNRNPH2-NDD are more likely to be related to issues with sleep onset and maintenance as opposed to sleep apnea.Growth. Four affected individuals were noted to have intrauterine growth restriction on prenatal ultrasound, but most have anthropometric measurements within the normal range for sex at birth. It should be noted that occipital frontal circumference (OFC) was not available for all affected individuals.Weight. About half of reported affected individuals (55%) had difficulty gaining weight, which in most cases was attributed to feeding difficulties during infancy (see Gastrointestinal issues in the text following).Length/height. Six out of 33 affected individuals were reported to be short for their age and sex, with the shortest individual being 5.5 SD below the mean.Head circumference. About 30% of affected individuals have acquired microcephaly (defined as OFC ≥2 SD below the mean for age and sex). The most severely affected individual had an OFC 4.08 SD below the mean.Gastrointestinal issues are present in most affected individuals. Feeding problems and chronic constipation are the two most common problems.Feeding difficulties have been observed in more than two thirds of affected individuals.Most affected individuals have reported feeding issues before age 12 months, with some having concerns immediately after birth.About 34% of affected individuals have dysphagia accompanied by

aspiration.Many affected individuals have persistent feeding issues, along with poor growth, throughout life. Several have required placement of feeding tubes.

Other gastrointestinal issues

Poor appetiteGastroesophageal reflux diseaseSwallowing difficulty (dysphagia)PicaDiarrheaOvereating, which can lead to weight gain in rare affected individualsAbdominal painBloatingVision involvement. A considerable proportion (67%) of affected individuals have visual defects, with strabismus being the most common finding in about 54%. Other findings include cortical visual impairment (33%), myopia (17%), and decreased visual acuity (13%). One individual was reported to have congenital ptosis.Hearing deficits have been reported by parents in one quarter of affected individuals, but the type of hearing loss (sensorineural, conductive, or mixed) is not known for many of these reported individuals. Recurrent ear infections and tinnitus have also been reported.

Other associated features

Orthopedic abnormalities have been reported in individuals of all ages and most commonly include:Pes planusArachnodactylyScoliosis, including kyphosis and lordosis, which is most frequently neuromuscular in originHip dysplasiaRarer findings include:Navicular bone drop with calcaneal adductionBone, muscle, and joint painArthritis and stiffness of jointsCardiovascular abnormalities. Nonspecific cardiac abnormalities have been observed in four affected individuals, including two with mitral valve prolapse, one with congenital aortic dilatation, and one with an atrial septal defect.Endocrine. One affected individual had precocious puberty and three had delayed puberty.Facial features. No recognizable dysmorphic features have been observed. If present, dysmorphic features are nonspecific. Such features may include:Almond-shaped eyesShort palpebral fissuresShort philtrumLong columellaHypoplastic alae nasiFull lower lipMicrognathiaStroke. One affected individual had a stroke after a first-time seizure at age 34 years. It is unclear if early stroke is a rare finding in affected individuals or if this was a rare co-occurrence of two unrelated findings.Prognosis. It is unknown whether the life span in HNRNPH2-NDD is abnormal. One reported individual was alive at age 38 years [Bain et al 2021], demonstrating that

survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported. Based on the available data, the clinical course does not appear to be progressive or degenerative into early adulthood.

Table 2. HNRNPH2-Related Neurodevelopmental Disorder: Frequency of Select FeaturesView in own windowFeature# of Personsw/Feature (%)CommentDevelopmental delay /Intellectual disability46/46 (100%)Typically in severe rangeAbnormal tone41/46 (89%)Hypotonia (more common) & hypertonia both reportedSevere language impairment37/45 (82%)Nonverbal or minimally verbalPsychiatric disorders32/42 (76%)Anxiety, ASD, & ADHD are most common.Facial dysmorphism31/44 (70%)See Facial features, following the table.Feeding problems28/41 (68%)Some affected persons require gastrostomy tube for feeding.Orthopedic problems25/37 (68%)Most commonly scoliosisVisual defects29/43 (67%)Strabismus in about halfSeizures18/46 (39%)No characteristic seizure typeSleep problems16/41 (39%)Both falling & staying asleepMicrocephaly16/44 (36%)Commonly acquiredHearing loss~25%ASD = autism spectrum disorder; ADHD = attention=deficit/hyperactivity disorder

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Speech and language is severely affected, with the majority of affected individuals being nonverbal or minimally verbal and others with speech apraxia or difficulties with articulation. In those who acquired speech, most did so between ages one and five years.

Most affected individuals have delays in the acquisition of both gross and fine motor skills in infancy. Many affected individuals are nonambulatory. All affected individuals significantly benefit from intensive therapy services, and many also use orthoses in addition to other devices. Referral to a rehabilitation specialist / physiatrist and orthopedist is recommended for appropriate supports. Most individuals require significant support in daily activities.

Many affected individuals have low cognitive skills and low adaptive skill sets using the Vineland Adaptive Behavior Scales. Most cognitive scales show floor effects below the first centile for many testing domains of standardized cognitive assessment. Most individuals require special education and support in daily activities into adulthood.

The most common diagnoses include anxiety (68%), self-injurious behaviors (38%), and autism spectrum disorder (34%).

Attention-deficit/hyperactivity disorder was diagnosed in about 15% of affected individuals, but a

higher number of caregivers reported concerns regarding attention, hyperactivity, and distractibility.

Some affected individuals demonstrated stereotypies and intermittent developmental regression that can be suggestive of Rett syndrome (see MECP2 Disorders).

Abnormal muscle tone. Most affected individuals have abnormalities of tone (most commonly hypotonia but also hypertonia), often first observed before age 12 months. Spasticity / muscle rigidity has been noted in about 33% of affected individuals. Some affected individuals have been given a clinical diagnosis of cerebral palsy based on their tone and muscle issues.

Weakness. Most affected individuals have generalized muscle weakness and decreased muscle bulk.

Electromyography done on one affected individual showed selective lower extremity denervation.

Of three affected individuals who underwent muscle biopsy, two were found to have abnormalities and the third was normal. One affected individual was found to have mild type II fiber atrophy; the other affected individual had reduced activity in the respiratory chain enzymes in complexes II and III.

Movement disorders. Reported abnormal movements have included the following:

Motor planning problems

Ataxia

Stereotypies

Clumsiness

Abnormal gait

Intermittent developmental regression. Caregivers have reported regression during episodes of illness or after a clinical seizure, followed by recovery of the lost skill once the episode resolves.

The average age of presentation of first seizure is 8.7 years (range: age 3-34 years).

The semiology of clinical seizures is variable.

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Febrile seizures are present in 23% of affected individuals.

Other seizure semiologies include tonic-clonic (43%), tonic (38%), spasms (23%), clonic (15%), and myoclonic (15%).

Abnormal EEG findings include diffuse slowing of the background, left-sided posterior and midline epileptic discharges, and paroxysmal activity in the right temporal lobe.

Weight. About half of reported affected individuals (55%) had difficulty gaining weight, which in most cases was attributed to feeding difficulties during infancy (see Gastrointestinal issues in the text following).

Length/height. Six out of 33 affected individuals were reported to be short for their age and sex, with

the shortest individual being 5.5 SD below the mean.

Head circumference. About 30% of affected individuals have acquired microcephaly (defined as OFC ≥2 SD below the mean for age and sex). The most severely affected individual had an OFC 4.08 SD below the mean.

Feeding difficulties have been observed in more than two thirds of affected individuals.

Most affected individuals have reported feeding issues before age 12 months, with some having concerns immediately after birth.

About 34% of affected individuals have dysphagia accompanied by aspiration.

Many affected individuals have persistent feeding issues, along with poor growth, throughout life. Several have required placement of feeding tubes.

Other gastrointestinal issues

Poor appetite

Gastroesophageal reflux disease

Swallowing difficulty (dysphagia)

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Diarrhea

Overeating, which can lead to weight gain in rare affected individuals

Abdominal pain

Bloating

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Pes planus

Arachnodactyly

Scoliosis, including kyphosis and lordosis, which is most frequently neuromuscular in origin

Hip dysplasia

Rarer findings include:

Navicular bone drop with calcaneal adduction

Bone, muscle, and joint pain

Arthritis and stiffness of joints

Cardiovascular abnormalities. Nonspecific cardiac abnormalities have been observed in four affected individuals, including two with mitral valve prolapse, one with congenital aortic dilatation,

and one with an atrial septal defect.

Endocrine. One affected individual had precocious puberty and three had delayed puberty.

Facial features. No recognizable dysmorphic features have been observed. If present, dysmorphic features are nonspecific. Such features may include:

Almond-shaped eyes

Short palpebral fissures

Short philtrum

Long columella

Hypoplastic alae nasi

Full lower lip

Micrognathia

Stroke. One affected individual had a stroke after a first-time seizure at age 34 years. It is unclear if early stroke is a rare finding in affected individuals or if this was a rare co-occurrence of two unrelated findings.

Genotype-Phenotype CorrelationsNo genotype-phenotype correlations have been identified.

PrevalenceThe overall prevalence remains unknown; to date, 49 individuals from 45 families have been reported with this disorder.

Genetically Related (Allelic) DisordersNo phenotypes other than those discussed in this GeneReview are known to be associated with germline pathogenic variants in HNRNPH2.

Differential DiagnosisTable 3. Selected Disorders of Interest in the Differential Diagnosis of HNRNPH2-Related Neurodevelopmental DisorderView in own windowGene / Genetic MechanismDisorderMOIClinical CharacteristicsComment / Distinguishing FeaturesDeficient expression or function of maternally inherited UBE3A allele
Angelman syndrome
See footnote 1.DD/ID, speech delay, ataxic gait, & limb tremulousness; happy demeanor w/frequent smiling, laughing, & excitabilityPersons w/Angelman syndrome have more persistent regression than those w/HNRNPH2-NDD.
HNRNPH1
HNRNPH1-related syndromic ID 2ADCommon findings incl short stature, microcephaly, ID, & congenital anomalies. Dysmorphic features incl blepharophimosis, ptosis, hypotelorism, medial arched eyebrows, & micrognathia.Persons w/HNRNPH1-related syndromic ID commonly have congenital anomalies & dysmorphic features; most also have abnormalities of the cerebellar vermis on brain MRI.
MECP2
MECP2 classic Rett syndrome (See MECP2 Disorders.)XLDevelopmental regression after period of normal development; more common in females, but males have been reported; other features: slowing head growth, loss of speech, gait abnormalities, replacement of purposeful hand movements w/repetitive stereotypiesThe period of normal development (followed by developmental regression) observed in classic Rett syndrome is not seen in HNRNPH2-NDD.
PURA

PURA-related neurodevelopmental disorders

ADPresents w/ID & developmental & epileptic encephalopathy; characteristic neonatal features: congenital hypotonia, respiratory difficulties (most commonly due to central sleep apnea), feeding difficulties, hypersomnolence, hypothermia60% of persons w/PURA-NDD have drug-resistant epilepsy (most commonly Lennox-Gastaut syndrome); ~50% have abnormal MRI, most commonly delayed myelination & volume loss.

SLC9A6

Christianson syndrome

XLIn males, DD & ID, severe speech delay, ASD or autistic behavior, hyperkinesis, epilepsy, developmental regression, truncal ataxia, acquired microcephaly, eye mvmt abnormalities, & feeding difficulties. Heterozygous females are asymptomatic or have mild ID or behavioral issues.Unlike HNRNPH2-NDD, Christianson syndrome is characteristically seen in males. Hyperkinesis is a prominent feature in affected males.AD = autosomal dominant; ASD = autism spectrum disorder; DD = developmental delay; HNRNPH2-NDD = HNRNPH2-related neurodevelopmental disorder; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked1. Individuals with Angelman syndrome (AS) typically represent simplex cases and have the disorder as the result of a de novo genetic alteration associated with a very low recurrence risk. Less commonly, an individual with AS has the disorder as the result of a genetic alteration associated with an imprinting pattern of autosomal dominant inheritance or variable recurrence risk.2.

Reichert et al [2020]

See also OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Table 3. Selected Disorders of Interest in the Differential Diagnosis of HNRNPH2-Related Neurodevelopmental DisorderView in own windowGene / Genetic

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AD = autosomal dominant; ASD = autism spectrum disorder; DD = developmental delay;

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ManagementNo clinical practice guidelines for HNRNPH2-related neurodevelopmental disorder (HNRNPH2-NDD) have been published.Evaluations Following Initial DiagnosisTo establish the extent of disease and needs in an individual diagnosed with HNRNPH2-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with HNRNPH2-Related Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationComment

Constitutional

Measure growth parameters incl head circumference.To assess for poor growth, short stature, & microcephaly

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Psychiatric/

Behavioral

Neuropsychiatric evalFor persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD

Neurologic

Neurologic eval, incl assessment of toneTo consider if seizures or regression in skills are noted: Brain MRIEEG

Movement

disorders

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of:

Gross motor & fine motor skillsMobility, ADL, & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Respiratory

PolysomnographyFor those who have sleep disturbances &/or signs/symptoms of sleep apnea

Gastrointestinal/

Feeding

Gastroenterology / nutrition / feeding team evalTo assess nutritional statusModified barium swallow or VFSSTo evaluate for aspiration risk & dysphagiaConsider eval for gastric tube placement in patients w/dysphagia &/or aspiration risk.

Eyes

Ophthalmologic evalTo assess for ↓ vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., cortical visual impairment) that may require subspecialty referral

Hearing

Audiologic evalAssess for hearing loss.

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of:

Gross motor & fine motor skillsScoliosisMobility, ADL, & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Cardiovascular

EchocardiogramTo evaluate for valvar or other structural cardiac anomalies

Endocrine

Clinical eval of pubertal status in children & adolescentsTo evaluate for precocious or delayed pubertyConsider referral to endocrinologist if such findings are present.

Genetic

counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of HNRNPH2-NDD to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; VFSS = videofluoroscopic swallowing study1. Medical geneticist, certified genetic counselor, certified advanced genetic nurseTreatment of ManifestationsTable 5. Treatment of Manifestations in Individuals with HNRNPH2-Related Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

Poor weight

gain / Failure to

thrive

Feeding therapyGastrostomy tube placement may be required for persistent feeding issues.

Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or

symptoms of dysphagia

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Psychiatric/

Behavioral

Standard treatment per psychiatrist &/or neurodevelopmental specialist23% of affected persons have received treatment w/SSRIs, antipsychotics, selective norepinephrine reuptake inhibitors, alpha-2-agonists, opioid antagonists, &/or benzodiazepines.

Epilepsy

Standardized treatment w/ASM by experienced neurologistAffected persons have responded well to levetiracetam & valproic acid.Education of parents/caregivers 1

Movement

disorders

Physical medicine & rehab / PT & OT

Abnormal tone

Standard treatment per physical medicine & rehab / PT & OT / orthopedistPositioning & mobility devices may be considered.Consider medications such as baclofen, Botox® for hypertonia.

Constipation

Standard treatmentMay incl stool softeners, prokinetics, osmotic agents, or laxatives as needed

Sleep apnea

Standard treatment per pulmonologist, ENT, &/or sleep specialist

Cortical visual

impairment

Supportive treatment & strategiesEarly intervention program to stimulate visual development & specific CVI strategies

Hearing loss

Hearing aids may be helpful; per otolaryngologist.Community hearing services through early intervention or school district

Musculoskeletal

anomalies

Standard treatment per orthopedistSurgical intervention to correct severe scoliosis, hip dysplasia, & extremity abnormalitiesSupportive braces

Cardiac defects

Standard mgmt per cardiologist

Pubertal

abnormalities

Standard mgmt per endocrinologist

Family/

Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Ongoing assessment of need for palliative care involvement &/or home nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CVI = cortical visual impairment; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy; SSRIs = selective serotonin reuptake inhibitors1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.Developmental Delay / Intellectual Disability Management IssuesThe following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:IEP services:An IEP provides specially designed instruction and related services to children who qualify.IEP services will be reviewed annually to determine whether any changes are needed.Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's

needs may be considered. Specific recommendations regarding types of therapy can be made by a developmental pediatrician.As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.Motor Dysfunction

Gross motor dysfunction

Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).Consider the use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language

pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.Social/Behavioral ConcernsChildren may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.SurveillanceTable 6. Recommended Surveillance for Individuals with HNRNPH2-Related Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationFrequency

Growth

Measurement of growth parametersAt each visit

Gastrointestinal/

Feeding

Eval of nutritional status & safety of oral intakeMonitor for feeding issues, abnormal bowel movements, GERD, pica, abdominal pain, & aspiration risk.

Development

Monitor developmental progress & educational needs.

Psychiatric/

Behavioral

Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior

Neurologic

Monitor those w/seizures as clinically indicated.Low threshold for overnight EEG monitoringAssess for new manifestations such as seizures, changes in tone, mvmt disorders, & developmental regression.

Respiratory

Monitor for evidence of sleep disturbance & signs/symptoms of sleep apnea.

Musculoskeletal

Orthopedic assessment, physical medicine, OT/PT assessment of mobility, self-help skillsAssess for hip dysplasia.In infancy or at each visit in person who is nonambulatoryAssess for scoliosis.At each visit in childhood & adolescence (until skeletal maturity) & in older persons who are nonambulatory

Eyes

Ophthalmologic evalAt least annually or as clinically indicated

Hearing

Audiologic evalAt least annually in childhood or as clinically indicated

Endocrine

Assessment for signs/symptoms of puberty 1At each visit in childhood & adolescence

Family/

Community

Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).At each visitGERD = gastrointestinal reflux disease; OT = occupational therapy; PT = physical therapy1. To assess for precocious or delayed pubertyEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling

purposes.Therapies Under InvestigationNo targeted therapies are approved or under investigation for use in HNRNPH2-NDD at this time. A natural history study of individuals with hnRNP-related disorders is currently under way (NCT03492060).Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Evaluations Following Initial DiagnosisTo establish the extent of disease and needs in an individual diagnosed with HNRNPH2-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with HNRNPH2-Related Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationComment

Constitutional

Measure growth parameters incl head circumference.To assess for poor growth, short stature, & microcephaly

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Psychiatric/

Behavioral

Neuropsychiatric evalFor persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD

Neurologic

Neurologic eval, incl assessment of toneTo consider if seizures or regression in skills are noted:

Brain MRIEEG

Movement

disorders

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of:

Gross motor & fine motor skillsMobility, ADL, & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Respiratory

PolysomnographyFor those who have sleep disturbances &/or signs/symptoms of sleep apnea

Gastrointestinal/

Feeding

Gastroenterology / nutrition / feeding team evalTo assess nutritional statusModified barium swallow or VFSSTo evaluate for aspiration risk & dysphagiaConsider eval for gastric tube placement in patients w/dysphagia &/or aspiration risk.

Eyes

Ophthalmologic evalTo assess for ↓ vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., cortical visual impairment) that may require subspecialty referral

Hearing

Audiologic evalAssess for hearing loss.

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of:

Gross motor & fine motor skillsScoliosisMobility, ADL, & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Cardiovascular

EchocardiogramTo evaluate for valvar or other structural cardiac anomalies

Endocrine

Clinical eval of pubertal status in children & adolescentsTo evaluate for precocious or delayed pubertyConsider referral to endocrinologist if such findings are present.

Genetic

counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of HNRNPH2-NDD to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; VFSS = videofluoroscopic swallowing study1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

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Audiologic evalAssess for hearing loss.

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Genetic

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Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral.

To incl motor, adaptive, cognitive, & speech/language eval

Eval for early intervention / special education

Brain MRI

EEG

Gross motor & fine motor skills

Mobility, ADL, & need for adaptive devices

Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

To evaluate for aspiration risk & dysphagia

Consider eval for gastric tube placement in patients w/dysphagia &/or aspiration risk.

Gross motor & fine motor skills

Scoliosis

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Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

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Treatment of ManifestationsTable 5. Treatment of Manifestations in Individuals with HNRNPH2-Related Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other
Poor weight

gain / Failure to

thrive
Feeding therapyGastrostomy tube placement may be required for persistent feeding issues.

Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Psychiatric/

Behavioral

Standard treatment per psychiatrist &/or neurodevelopmental specialist23% of affected persons have received treatment w/SSRIs, antipsychotics, selective norepinephrine reuptake inhibitors, alpha-2-agonists, opioid antagonists, &/or benzodiazepines.

Epilepsy

Standardized treatment w/ASM by experienced neurologistAffected persons have responded well to levetiracetam & valproic acid.Education of parents/caregivers 1

Movement

disorders

Physical medicine & rehab / PT & OT

Abnormal tone

Standard treatment per physical medicine & rehab / PT & OT / orthopedistPositioning & mobility devices may be considered.Consider medications such as baclofen, Botox® for hypertonia.

Constipation

Standard treatmentMay incl stool softeners, prokinetics, osmotic agents, or laxatives as needed

Sleep apnea

Standard treatment per pulmonologist, ENT, &/or sleep specialist

Cortical visual

impairment

Supportive treatment & strategiesEarly intervention program to stimulate visual development & specific CVI strategies

Hearing loss

Hearing aids may be helpful; per otolaryngologist.Community hearing services through early intervention or school district

Musculoskeletal

anomalies

Standard treatment per orthopedistSurgical intervention to correct severe scoliosis, hip dysplasia, & extremity abnormalitiesSupportive braces

Cardiac defects

Standard mgmt per cardiologist

Pubertal

abnormalities

Standard mgmt per endocrinologist

Family/

Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Ongoing assessment of need for palliative care involvement &/or home nursingConsider

involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CVI = cortical visual impairment; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy; SSRIs = selective serotonin reuptake inhibitors1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.Developmental Delay / Intellectual Disability Management IssuesThe following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:IEP services:An IEP provides specially designed instruction and related services to children who qualify.IEP services will be reviewed annually to determine whether any changes are needed.Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access

to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding types of therapy can be made by a developmental pediatrician.As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.Motor Dysfunction

Gross motor dysfunction

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Poor weight

gain / Failure to

thrive

Feeding therapyGastrostomy tube placement may be required for persistent feeding issues.

Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

DD/ID

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Psychiatric/

Behavioral

Standard treatment per psychiatrist &/or neurodevelopmental specialist23% of affected persons have received treatment w/SSRIs, antipsychotics, selective norepinephrine reuptake inhibitors, alpha-2-agonists, opioid antagonists, &/or benzodiazepines.

Epilepsy

Standardized treatment w/ASM by experienced neurologistAffected persons have responded well to levetiracetam & valproic acid.Education of parents/caregivers 1

Movement

disorders

Physical medicine & rehab / PT & OT

Abnormal tone

Standard treatment per physical medicine & rehab / PT & OT / orthopedistPositioning & mobility devices may be considered.Consider medications such as baclofen, Botox® for hypertonia.

Constipation

Standard treatmentMay incl stool softeners, prokinetics, osmotic agents, or laxatives as needed

Sleep apnea

Standard treatment per pulmonologist, ENT, &/or sleep specialist

Cortical visual

impairment

Supportive treatment & strategiesEarly intervention program to stimulate visual development &

specific CVI strategies

Hearing loss

Hearing aids may be helpful; per otolaryngologist.Community hearing services through early intervention or school district

Musculoskeletal

anomalies

Standard treatment per orthopedistSurgical intervention to correct severe scoliosis, hip dysplasia, & extremity abnormalitiesSupportive braces

Cardiac defects

Standard mgmt per cardiologist

Pubertal

abnormalities

Standard mgmt per endocrinologist

Family/

Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Ongoing assessment of need for palliative care involvement &/or home nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CVI = cortical visual impairment; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy; SSRIs = selective serotonin reuptake inhibitors1. Education of parents/caregivers regarding common seizure

presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Treatment of Manifestations in Individuals with HNRNPH2-Related Neurodevelopmental Disorder

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Gross motor dysfunction

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Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

Consider the use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Social/Behavioral ConcernsChildren may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies

or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

SurveillanceTable 6. Recommended Surveillance for Individuals with HNRNPH2-Related Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationFrequency

Growth

Measurement of growth parametersAt each visit

Gastrointestinal/

Feeding

Eval of nutritional status & safety of oral intakeMonitor for feeding issues, abnormal bowel movements, GERD, pica, abdominal pain, & aspiration risk.

Development

Monitor developmental progress & educational needs.

Psychiatric/

Behavioral

Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior

Neurologic

Monitor those w/seizures as clinically indicated.Low threshold for overnight EEG monitoringAssess for new manifestations such as seizures, changes in tone, mvmt disorders, & developmental regression.

Respiratory

Monitor for evidence of sleep disturbance & signs/symptoms of sleep apnea.

Musculoskeletal

Orthopedic assessment, physical medicine, OT/PT assessment of mobility, self-help skillsAssess for hip dysplasia.In infancy or at each visit in person who is nonambulatoryAssess for scoliosis.At each visit in childhood & adolescence (until skeletal maturity) & in older persons who are nonambulatory

Eyes

Ophthalmologic evalAt least annually or as clinically indicated

Hearing

Audiologic evalAt least annually in childhood or as clinically indicated

Endocrine

Assessment for signs/symptoms of puberty 1At each visit in childhood & adolescence

Family/

Community

Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).At each visitGERD = gastrointestinal reflux disease; OT = occupational therapy; PT = physical therapy1. To assess for precocious or delayed puberty

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System/ConcernEvaluationFrequency

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Eval of nutritional status & safety of oral intake

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Monitor those w/seizures as clinically indicated.

Low threshold for overnight EEG monitoring

Assess for new manifestations such as seizures, changes in tone, mvmt disorders, & developmental regression.

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To assess for precocious or delayed puberty

Evaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under InvestigationNo targeted therapies are approved or under investigation for use in HNRNPH2-NDD at this time. A natural history study of individuals with hnRNP-related disorders is currently under way (NCT03492060).Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic

risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.Mode of InheritanceHNRNPH2-related neurodevelopmental disorder (HNRNPH2-NDD) is an X-linked disorder typically caused by a de novo pathogenic variant.Risk to Family Members

Parents of a female proband

Almost all females reported to date with HNRNPH2-NDD represent simplex cases (i.e., a single occurrence in the family).Rarely, a female diagnosed with HNRNPH2-NDD has the disorder as the result of a pathogenic variant inherited from a mother (vertical transmission from a hemizygous father to a female proband has not been reported to date).Vertical transmission of an HNRNPH2 pathogenic variant from a heterozygous unaffected mother (with skewed X-chromosome inactivation) to her affected daughter has been reported [White-Brown et al 2022].Affected male and female sibs born to consanguineous parents are presumed to have HNRNPH2-NDD as the result of a pathogenic variant inherited from a mother with germline mosaicism [Somashekar et al 2020].Molecular genetic testing of the parents is recommended to confirm parental genetic status and to allow reliable recurrence risk assessment.The mother of a proband who is found to be heterozygous for an HNRNPH2 pathogenic variant may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected [White-Brown et al 2022].If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:The proband has a de novo pathogenic variant.The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only [Somashekar et al 2020].Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:If the mother of the proband has an HNRNPH2 pathogenic variant, the chance of the mother transmitting it in each pregnancy is

50%.Females who inherit the pathogenic variant are at high risk of being affected; however, a female with favorably skewed X-chromosome inactivation may be unaffected or have a mild phenotype [White-Brown et al 2022]. (See Clinical Description.)Males who inherit the pathogenic variant will be affected. Hemizygous males have variable phenotypes ranging from severe manifestations (described in 11 of the 16 affected males reported to date) to only mild developmental delay with autism spectrum disorder and psychiatric diagnoses (described in five males) [Kreienkamp et al 2022].If the father of the proband has a mosaic HNRNPH2 pathogenic variant, all his daughters are at risk of inheriting the pathogenic variant; his sons are not at risk of inheriting the pathogenic variant.If a female proband represents a simplex case and if the HNRNPH2 pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is approximately 1% because of the possibility of parental mosaicism [Somashekar et al 2020, Kreienkamp et al 2022].

Parents of a male proband

The father of an affected male will not have the disorder, nor will he be hemizygous for the HNRNPH2 pathogenic variant; therefore, he does not require further evaluation/testing.If a male is the only affected family member, the mother may be a heterozygote, the affected male may have a de novo

HNRNPH2 pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism. Fourteen * of the 16 males with HNRNPH2-NDD reported to date have the disorder as the result of a de novo pathogenic variant. * Including monozygotic twin males [Kreienkamp et al 2022]Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:If the proband represents a simplex case and the HNRNPH2 pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism [Somashekar et al 2020, Kreienkamp et al 2022].If the mother of the proband has an HNRNPH2

pathogenic variant, the chance of transmitting it in each pregnancy is 50%.Females who inherit the pathogenic variant are at high risk of being affected; however, a female with favorably skewed X-chromosome inactivation may be unaffected or have a mild phenotype [White-Brown et al 2022]. (See Clinical Description.)Males who inherit the pathogenic variant will be affected. Hemizygous males have variable phenotypes ranging from severe manifestations (described in 11 of the 16 males reported to date) to only mild developmental delay with autism spectrum disorder and psychiatric diagnoses (described in 5 males) [Kreienkamp et al 2022].

Offspring of a proband

Females with an HNRNPH2 pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child. Affected females are not known to reproduce.Affected males are not known to reproduce.Other family members. The risk to other family members depends on the genetic status of the proband's mother: if the mother has a pathogenic HNRNPH2 pathogenic variant, her family members may be at risk.Note: Molecular genetic testing may be able to identify the family member in whom a de novo pathogenic variant arose, information that could help determine genetic risk status of the extended family.Related Genetic Counseling Issues

Family planning

The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are heterozygotes or who are at increased risk of being heterozygotes.Prenatal Testing and Preimplantation Genetic TestingOnce the HNRNPH2 pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Mode of InheritanceHNRNPH2-related neurodevelopmental disorder (HNRNPH2-NDD) is an

X-linked disorder typically caused by a de novo pathogenic variant.

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Parents of a female proband

Almost all females reported to date with HNRNPH2-NDD represent simplex cases (i.e., a single occurrence in the family).Rarely, a female diagnosed with HNRNPH2-NDD has the disorder as the result of a pathogenic variant inherited from a mother (vertical transmission from a hemizygous father to a female proband has not been reported to date).Vertical transmission of an HNRNPH2 pathogenic variant from a heterozygous unaffected mother (with skewed X-chromosome inactivation) to her affected daughter has been reported [White-Brown et al 2022].Affected male and female sibs born to consanguineous parents are presumed to have HNRNPH2-NDD as the result of a pathogenic variant inherited from a mother with germline mosaicism [Somashekar et al 2020].Molecular genetic testing of the parents is recommended to confirm parental genetic status and to allow reliable recurrence risk assessment.The mother of a proband who is found to be heterozygous for an HNRNPH2 pathogenic variant may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected [White-Brown et al 2022].If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:The proband has a de novo pathogenic variant.The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only [Somashekar et al 2020].Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:If the mother of the proband has an HNRNPH2 pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%.Females who inherit the pathogenic variant are at high risk of being affected; however, a female with favorably skewed X-chromosome inactivation may be unaffected or have a mild phenotype [White-Brown et al 2022]. (See Clinical Description.)Males who inherit the pathogenic

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Parents of a male proband

The father of an affected male will not have the disorder, nor will he be hemizygous for the HNRNPH2 pathogenic variant; therefore, he does not require further evaluation/testing.If a male is the only affected family member, the mother may be a heterozygote, the affected male may have a de novo

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Vertical transmission of an HNRNPH2 pathogenic variant from a heterozygous unaffected mother (with skewed X-chromosome inactivation) to her affected daughter has been reported [White-Brown et al 2022].

Affected male and female sibs born to consanguineous parents are presumed to have HNRNPH2-NDD as the result of a pathogenic variant inherited from a mother with germline mosaicism [Somashekar et al 2020].

Molecular genetic testing of the parents is recommended to confirm parental genetic status and to allow reliable recurrence risk assessment.

The mother of a proband who is found to be heterozygous for an HNRNPH2 pathogenic variant may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected [White-Brown et al 2022].

If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:

The proband has a de novo pathogenic variant.

The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only [Somashekar et al 2020].

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Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

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Males who inherit the pathogenic variant will be affected. Hemizygous males have variable phenotypes ranging from severe manifestations (described in 11 of the 16 males reported to date) to only mild developmental delay with autism spectrum disorder and psychiatric diagnoses (described in 5 males) [Kreienkamp et al 2022].

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Prenatal Testing and Preimplantation Genetic TestingOnce the HNRNPH2 pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

Global Genes

Phone: 949-248-RARE (7273)Email: careaboutrare@globalgenes.org

HNRNPH2 Related Disorder

National Organization for Rare Disorders (NORD)

Bain type of X-linked syndromic intellectual disability

To Cure a Rose Foundation

www.tocurearose.org

Yellow Brick Road Project

The Yellow Brick Road Project is a charitable foundation whose mission is to fund research to identify, understand, treat, and ultimately cure those impacted by HNRNPH2 mutations.

Email: projectybr@gmail.com

www.yellowbrickroadproject.org

American Association on Intellectual and Developmental Disabilities (AAIDD)

Phone: 202-387-1968Fax: 202-387-2193

www.aaidd.org

CDC - Developmental Disabilities

Phone: 800-CDC-INFOEmail: cdcinfo@cdc.gov

Intellectual Disability

MedlinePlus

Intellectual Disability

Simons Searchlight Registry

Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.

Phone: 855-329-5638Fax: 570-214-7327Email: coordinator@simonssearchlight.org

www.simonssearchlight.org

Global Genes

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Yellow Brick Road Project

The Yellow Brick Road Project is a charitable foundation whose mission is to fund research to identify, understand, treat, and ultimately cure those impacted by HNRNPH2 mutations.

Email: projectybr@gmail.com

www.yellowbrickroadproject.org

American Association on Intellectual and Developmental Disabilities (AAIDD)

Phone: 202-387-1968

Fax: 202-387-2193

www.aaidd.org

CDC - Developmental Disabilities

Phone: 800-CDC-INFO

Email: cdcinfo@cdc.gov

Intellectual Disability

MedlinePlus

Intellectual Disability

Simons Searchlight Registry

Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.

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Email: coordinator@simonssearchlight.org

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Molecular GeneticsInformation in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.Table A.HNRNPH2-Related Neurodevelopmental Disorder: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

HNRNPH2

Xq22.1

Heterogeneous nuclear ribonucleoprotein H2

HNRNPH2 @ LOVD

HNRNPH2

HNRNPH2

Data are compiled from the following standard references: gene from

HGNC;

chromosome locus from

OMIM;

protein from UniProt.

For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.Table B.OMIM Entries for HNRNPH2-Related Neurodevelopmental Disorder (View All in OMIM) View in own window

300610HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN H2; HNRNPH2

300986INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, BAIN TYPE; MRXSBMolecular PathogenesisHeterogeneous nuclear ribonucleoproteins (HNRNPs) are a group of proteins that bind to RNA and have multiple roles in RNA metabolism, including transcription, splicing, translation, transfer to the cytoplasm, and mRNA stability and decay. There are more than 20 HNRNPs, designated HNRNP A-U. Pathogenic variants affecting the genes that encode the HNRNPs result in various neurodevelopmental and neurodegenerative disorders [Bain et al 2016, Geuens et al 2016, Bain et al 2021, Gillentine et al 2021, Kreienkamp et al 2022].HNRNPH2 is located on the X chromosome at Xq22.1. The 449-amino-acid protein product has five domains including three quasi-RNA-recognition motifs (RRMs) and two glycine-rich domains (GRD). The GRDs are essential for the nuclear localization of the protein. A highly conserved nuclear localization sequence (NLS) between amino acids 194 and 220 has been recognized to interact with transportin 1 (Trn1), a nuclear transport receptor.HNRNPH2 is expressed ubiquitously and its protein product is largely found in the cytoplasm. HNRNPH2 is predominantly involved in alternative splicing of the pre-mRNA and acting as a shuttle between the nucleus and the cytoplasm. Most pathogenic variants are located within or near the NLS.Mechanism of disease causation. The specific mechanism leading to disease is unknown; a toxic gain-of-function mechanism has been proposed (see bioRxiv).Consistent with this, more than 90% of individuals with HNRNPH2-related neurodevelopmental disorder have the condition as a result of a pathogenic missense variant located either adjacent to or within the NLS. The two most common pathogenic variants are c.616C>T (p.Arg206Trp) and c.617G>A (p.Arg206Gln) (NM_019597.5 / NP_062543.1) [Bain et al 2016, Geuens et al 2016, Bain et al 2021, Kreienkamp et al 2022].

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Heterogeneous nuclear ribonucleoprotein H2

HNRNPH2 @ LOVD

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Table B.OMIM Entries for HNRNPH2-Related Neurodevelopmental Disorder (View All in OMIM)

View in own window

300610HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN H2; HNRNPH2

300986INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, BAIN TYPE; MRXSB

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300986INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, BAIN TYPE; MRXSB

Molecular PathogenesisHeterogeneous nuclear ribonucleoproteins (HNRNPs) are a group of proteins that bind to RNA and have multiple roles in RNA metabolism, including transcription, splicing, translation, transfer to the cytoplasm, and mRNA stability and decay. There are more than 20 HNRNPs, designated HNRNP A-U. Pathogenic variants affecting the genes that encode the HNRNPs result in various neurodevelopmental and neurodegenerative disorders [Bain et al 2016, Geuens et al 2016, Bain et al 2021, Gillentine et al 2021, Kreienkamp et al 2022].HNRNPH2 is

located on the X chromosome at Xq22.1. The 449-amino-acid protein product has five domains including three quasi-RNA-recognition motifs (RRMs) and two glycine-rich domains (GRD). The GRDs are essential for the nuclear localization of the protein. A highly conserved nuclear localization sequence (NLS) between amino acids 194 and 220 has been recognized to interact with transportin 1 (Trn1), a nuclear transport receptor.HNRNPH2 is expressed ubiquitously and its protein product is largely found in the cytoplasm. HNRNPH2 is predominantly involved in alternative splicing of the pre-mRNA and acting as a shuttle between the nucleus and the cytoplasm. Most pathogenic variants are located within or near the NLS.Mechanism of disease causation. The specific mechanism leading to disease is unknown; a toxic gain-of-function mechanism has been proposed (see bioRxiv).Consistent with this, more than 90% of individuals with HNRNPH2-related neurodevelopmental disorder have the condition as a result of a pathogenic missense variant located either adjacent to or within the NLS. The two most common pathogenic variants are c.616C>T (p.Arg206Trp) and c.617G>A (p.Arg206Gln) (NM_019597.5 / NP_062543.1) [Bain et al 2016, Geuens et al 2016, Bain et al 2021, Kreienkamp et al 2022].

Chapter NotesAuthor NotesSee HNRNPH2-Related Disorders.AcknowledgmentsWe would like to thank the families who are affected by HNRNPH2-related neurodevelopmental disorder for sharing their personal stories. We appreciate their participation in the ongoing natural history study (NCT03492060) to better understand the disorder. We are appreciative of the support of the two patient advocacy groups Yellow Brick Road Project and To Cure a Rose Foundation.Dr Bain would like to personally thank the first research assistant to work on this project, Ms Olivia Thornburg. The natural history study would not be as successful without her dedication and hard work.Revision History15 September 2022 (ma) Review posted live1 June 2022 (sm) Original submission

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