HNRNPH2-Related Neurodevelopmental Disorder

Synonyms: Bain Type Syndromic Intellectual Disability; X-Linked Syndromic Intellectual Developmental Disorder, Bain Type

Madhok S, Bain J.

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Summary

Clinical 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.

Diagnosis

For the purposes of this *GeneReview*, the terms "male" and " lefined 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 Findings

HNRNPH2-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 impairment
  AND
- Any of the following features in infancy or childhood:
  - Developmental regression
  - Generalized hypotonia of infancy
  - Infant feeding difficulties
  - Acquired microcephaly
  - Poor growth
  - Movement disorders, such as hand stereotypies
  - 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

Family 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 Diagnosis

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 (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 Disorder

Clinical Characteristics

Clinical Description

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.

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 Features

Developmental 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 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.

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 appetite
    - Gastroesophageal reflux disease
    - Swallowing difficulty (dysphagia)
    - Pica
    - Diarrhea

- Overeating, which can lead to weight gain in rare affected individuals
- Abdominal pain
- Bloating

Vision 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 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.

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 Correlations

No genotype-phenotype correlations have been identified.

Prevalence

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

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *HNRNPH2*.

Differential Diagnosis

Table 3.

Selected Disorders of Interest in the Differential Diagnosis of *HNRNPH2*-Related Neurodevelopmental Disorder

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

Management

No clinical practice guidelines for *HNRNPH2*-related neurodevelopmental disorder (*HNRNPH2*-NDD) have been published.

Evaluations Following Initial Diagnosis

To 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 Disorder

Treatment of Manifestations

Table 5.

Treatment of Manifestations in Individuals with *HNRNPH2*-Related Neurodevelopmental Disorder

Developmental Delay / Intellectual Disability Management Issues

The 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 Concerns

Children 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.

Surveillance

Table 6.

Recommended Surveillance for Individuals with *HNRNPH2*-Related Neurodevelopmental Disorder

Evaluation of Relatives at Risk

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

Therapies Under Investigation

No 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 Inheritance

HNRNPH2-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 Testing

Once 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
- **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: 202-387-1968
  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.
  Phone: 855-329-5638

Fax: 570-214-7327
Email: coordinator@simonssearchlight.org
www.simonssearchlight.org

Molecular Genetics

Information 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 Databases

Table B.

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

Molecular Pathogenesis

Heterogeneous 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 Notes

Author Notes

See *HNRNPH2*-Related Disorders.

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Publication Details

Author Information and Affiliations

Sehajvir Madhok, MD

Child Neurology

New York-Presbyterian

Columbia University Irving Medical Center

New York, New York

Email: sm5168@cumc.columbia.edu

Jennifer Bain, MD, PhD
Columbia University Irving Medical Center
New York, New York
Email: jb3634@cumc.columbia.edu

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