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HNRNPU-Related Neurodevelopmental Disorder

Synonyms: Developmental and Epileptic Encephalopathy 54, Early Infantile Epileptic Encephalopathy Type 54

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Summary

Clinical characteristics

HNRNPU-related neurodevelopmental disorder (*HNRNPU*-NDD) is characterized by developmental delay and intellectual disability – typically moderate to severe – with speech and language delay and/or absent speech. Affected individuals may also display autistic features. There may be feeding difficulties during the neonatal period as well as hypotonia, which often remains lifelong. Dysmorphic features have been described but they are nonspecific. Affected individuals are likely to experience seizures (most commonly tonic-clonic or absence) that may be refractory to treatment. Nonspecific brain MRI findings include ventriculomegaly and thinning of the corpus callosum. Less common findings include cardiac abnormalities, strabismus, undescended testes in males, renal anomalies, and skeletal features, including joint laxity, polydactyly, and scoliosis. Rarely, abnormal breathing patterns, including hyperventilation and apnea, may be present and can lead to sleep disturbance.

Diagnosis/testing

The diagnosis of *HNRNPU*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *HNRNPU* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment of seizures with anti-seizure medications (sodium valproate is often used and is frequently effective); consider instituting the ketogenic diet and/or newer generation anti-seizure medications in those with refractory seizures. Feeding therapy; consider a temporary or permanent feeding tube for those with persistent feeding issues. Consider supplemental oxygen, CPAP, or BiPAP in those with sleep apnea. Standard treatment for tone abnormalities, intellectual disability, behavioral problems, hyperventilation / abnormal breathing patterns, congenital heart defects, strabismus, hearing loss, renal anomalies, undescended testes, and limb defects.

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Surveillance: At each visit: measurement of growth parameters; evaluation of nutritional status and safety of oral intake; monitor for evidence of constipation, new seizures, hyperventilation, apnea, and changes in tone; assessment of developmental progress and behavior. Annually or as clinically indicated: ophthalmologic and audiologic evaluations.

Agents/circumstances to avoid: Activities and agents that may induce seizures.

Genetic counseling

HNRNPU-NDD is expressed in an autosomal dominant manner and typically caused by a *de novo HNRNPU* pathogenic variant. The risk to other family members is hypothesized to be low. Presumed parental germline mosaicism has been reported in one family with two affected sibs. Once the *HNRNPU* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *HNRNPU*-related neurodevelopmental disorder (*HNRNPU*-NDD) have been published.

Suggestive Findings

HNRNPU-NDD **should be considered** in individuals with the following clinical and brain MRI findings.

Clinical findings (presenting in infancy or childhood). Moderate-to-severe developmental delay (DD) or intellectual disability (ID) AND any of the following:

- Generalized hypotonia of infancy
- Infant feeding difficulties
- Speech and language delay and/ or absent speech
- Autism spectrum disorder or autistic traits
- Nonspecific dysmorphic facial features (See Clinical Description.)
- Epilepsy, including generalized tonic-clonic seizures and absence seizures
- Short stature
- Strabismus

Brain MRI findings. The most common brain MRI findings are nonspecific but include:

- Ventriculomegaly
- Thinning of the corpus callosum

Family history. Because *HNRNPU*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). However, a report of two affected sibs suggests the possibility of germline mosaicism in a parent [Durkin et al 2020] (see Genetic Counseling).

Establishing the Diagnosis

The diagnosis of *HNRNPU*-related neurodevelopmental disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *HNRNPU* 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 *HNRNPU* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability often begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *HNRNPU*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *HNRNPU*) that cannot be detected by sequence analysis.
- **An intellectual disability or epileptic encephalopathy multigene panel** that includes *HNRNPU* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA 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*. Of note, given the rarity of *HNRNPU*, some panels for intellectual disability may not include this gene. (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(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID and/or epileptic encephalopathy whereas some multigene panels may not. **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 *HNRNPU*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
HNRNPU	Sequence analysis [4]	98% [5]
	Gene-targeted deletion/duplication analysis [6]	2% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Three additional individuals with contiguous gene deletions or duplications (not included in these calculations) have been reported (see Genetically Related Disorders) [Caliebe et al 2010, Thierry et al 2012, Bramswig et al 2017].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Caliebe et al [2010] and Thierry et al [2012]) may not be detected by these methods.
7. One affected individual had deletion of the last three exons of *HNRNPU* [Durkin et al 2020]. One affected individual has been identified with an *HNRNPU* deletion that includes exons 1-11 [Taylor et al 2022].

Clinical Characteristics

Clinical Description

To date, 83 individuals have been identified with a pathogenic variant in *HNRNPU* [Caliebe et al 2010, Need et al 2012, Thierry et al 2012, Allen et al 2013, de Kovel et al 2016, Bramswig et al 2017, Depienne et al 2017, Leduc et al 2017, Yates et al 2017, Durkin et al 2020, Song et al 2021, Taylor et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *HNRNPU*-Related Neurodevelopmental Disorder

Feature	% of Persons w/Feature	Comment
Developmental delay	100%	
Dysmorphic craniofacial features	97%	See **Dysmorphic features** following this table.
Seizure disorder	95%	~90% have 1st seizure before age 24 mos (tonic-clonic in ~60%, absence in ~44%) [1]
Intellectual disability	84%	Typically moderate to severe
Speech delay	80%	Usually limited or no speech
Hypotonia	79%	Slightly fewer than 50% have congenital hypotonia.
Feeding difficulties	57%	Some require supplemental nasogastric feeding or percutaneous gastrostomy.
Behavioral issues	50%	Autistic features are observed in ~33% of affected persons.
Eye anomalies	36%	The most common finding is strabismus.
Cardiac abnormalities	30%	Septal defects are the most common.
Renal anomalies	<10%	
Hyperventilation & apnea	Rare	

1. Of note, some persons have both types of seizures, such that the combined percentages are more than 100%.

Developmental delay (DD) and intellectual disability (ID), typically affecting all developmental domains and falling into the moderate-to-severe range, have been found in all reported individuals to date.

- Speech delay is common and most reported individuals are nonverbal, although ascertainment bias against more mildly affected individuals may have skewed this finding to the more severe end of the *HNRNPU*-related neurodevelopmental disorder (*HNRNPU*-NDD) spectrum.
- Limited speech and ability to speak in short sentences has been described in some individuals.
- To date, most individuals have required special educational provisions, although children with *HNRNPU*-NDD may be able to attend a mainstream school with dedicated support.
- The vast majority of reported adults have required assisted living, which has allowed them some degree of independence.

Other neurodevelopmental features

- **Hypotonia** is a common feature seen in about 80% of individuals with *HNRNPU*-NDD, especially during the neonatal period and in early infancy, and may persist into later childhood and adulthood. With time, some individuals may develop hypertonia leading to spasticity.
- **Infant feeding difficulties** are observed in about 58% of affected individuals. The severity of feeding difficulties varies considerably and could be attributed to a combination of gastroesophageal reflux, hypotonia, and oromotor dysfunction, with some children requiring long-term gastrostomy tube insertion, while in others feeding may be improved with the use of temporary nasogastric tube feeding.
- **Seizures** are seen in around 95% of reported individuals, with more than 90% presenting with their first seizure before age 24 months.
    - About 60% of individuals have generalized tonic-clonic seizures; 44% have absence seizures.
    - Rarer types of seizures have included the following: two individuals with West syndrome [Bramswig et al 2017, Leduc et al 2017]; one individual with Lennox-Gastaut syndrome [Leduc et al 2017]; and one individual with Doose syndrome [Hinokuma et al 2020].
    - Most affected individuals have seizures as a presenting feature along with developmental delay.
    - Seizures often respond to standard anti-seizure medication, although some may require more than one anti-seizure medication or a trial of such medications to attain reasonable seizure control.
    - Ketogenic diet and newer medications to control seizures have been trialed (see Management).
- **Sleep disturbance** is a common finding, with some affected individuals reported to have sleep apnea, warranting a sleep study and further evaluation to establish a cause.

Respiratory abnormalities. Some affected individuals have abnormal breathing patterns. At least two have been reported with hyperventilation and apnea [Shimada et al 2018, Spagnoli et al 2021]. Other findings have included breath-holding episodes and irregular breathing patterns (particularly at night) that coincide with sleep disturbances.

Behavioral issues. More than half of affected individuals have significant behavioral, social, and communication difficulties with substantial impact on the individuals and their families.

- About one third meet the formal clinical diagnostic criteria of an autism spectrum disorder, whereas others have autistic-like features.
- In contrast, some are described as having a very friendly, placid personality.
- Less common behavioral phenotypes included obsessive-compulsive disorder and self-stimulatory behaviors.
- Other associated behaviors (more rarely seen):
    - Aggressive or destructive behavior
    - Hand flapping
    - Agitation

- Hyperventilation episodes (See also **Respiratory abnormalities**.)
- Attention-deficit disorder

Dysmorphic features. No dysmorphic features that are specific to *HNRNPU*-NDD have been observed. If present, dysmorphic features are nonspecific. Features described in the literature include the following:

- Abnormal head shape (frontal bossing, microcephaly, dolichocephaly)
- Prominent forehead
- Highly arched, thin eyebrows
- Palpebral fissure abnormalities (both upslanted and downslanted)
- Epicanthus
- Thin vermilion of the upper lip
- Low-hanging columella
- Widely spaced teeth

Growth. Proportionate short stature has been observed in about 50% of individuals for whom data have been reported; further studies are required to determine the cause. One individual had microcephaly.

Cardiac issues. Nineteen individuals with cardiac abnormalities have been described. The following have been reported, in order from most to least frequent:

- Atrial septal defect
- Ventricular septal defect
- Patent ductus arteriosus
- Tricuspid atresia, tetralogy of Fallot, aortic dilatation, and transposition of the great arteries together in one affected individual

Eyes. About 30% of affected individuals have strabismus. Hypermetropia has been described in at least two individuals.

Abnormalities of genitalia. Undescended testis is reported in approximately 20% of affected males.

Neuroimaging. There do not appear to be uniform findings on brain imaging in affected individuals that would specifically suggest this diagnosis; similarly, a normal brain MRI would not preclude this as a diagnosis.

- Of 62 individuals reported in the literature who had a brain MRI imaging, 38 (61%) had abnormalities noted.
- The most common abnormality was ventriculomegaly, followed by thinning of the corpus callosum.

Other associated features, seen in fewer than 10% of individuals:

- **Hearing loss.** Two individuals with *HNRNPU*-NDD and sensorineural hearing impairment have been reported.
- **Renal abnormalities.** Anatomic renal abnormalities are more likely to be seen in individuals with 1q44 deletion (see Genetically Related Disorders). About 8% of individuals with *HNRNPU*-NDD have renal issues including agenesis of the kidney, unilateral multicystic kidney, and renal pelvic ectasia.
- **Musculoskeletal features** are rare [Thierry et al 2012, Depienne et al 2017, Leduc et al 2017, Durkin et al 2020]:
  - Joint hyperlaxity (in 8 individuals)
  - Butterfly vertebrae (1 individual) and scoliosis (3 individuals)
  - Polydactyly, including bilateral postaxial polydactyly of the hand (1 individual) and preaxial polydactyly of the right foot (3 individuals)
  - Cutaneous syndactyly of fingers 2 and 3
  - Fifth digit clinodactyly

- Hallux valgus

Prognosis. It is unknown whether life span in *HNRNPU*-NDD is abnormal. Based on current data, life span is not significantly limited by this condition, as several adults have been reported. Data on possible progression of behavior abnormalities or neurologic findings are still emerging. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

The prevalence of this condition is unknown. To date, approximately 83 individuals with *HNRNPU*-NDD have been reported.

Genetically Related (Allelic) Disorders

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

Chromosome 1q44 deletion. Individuals with larger deletions of 1q44 that include *HNRNPU* and adjacent genes have been described with a phenotype of severe developmental delay (particularly affecting speech development), microcephaly, hypogenesis/agenesis of the corpus callosum, and seizures. Renal abnormalities, strabismus, and hypotonia are more commonly described in individuals with a larger deletion that includes *HNRNPU* and adjacent genes. Upslanted palpebral fissures, widely spaced eyes, telecanthus, thin vermilion border of the lip, and exaggerated Cupid's bow are facial features described in individuals with deletion of this chromosomal region. Analysis of the smallest region of overlap identified *HNRNPU* as a candidate gene for the epilepsy and intellectual disability (ID) phenotype associated with this deletion [Caliebe et al 2010, Thierry et al 2012]. Depienne et al [2017] showed that deletions of the 1q43q44 region that include *HNRNPU* determined the epilepsy phenotype in those with the 1q44 deletion syndrome, and had a significant influence on the degree of ID.

Differential Diagnosis

Because the phenotypic features associated with *HNRNPU*-related neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with epileptic encephalopathy and intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Developmental and Epileptic Encephalopathy Phenotypic Series.

Management

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

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *HNRNPU*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *HNRNPU*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To incl weight, length/height, & head circumference
Neurologic	Neurologic eval	• To incl brain MRI if unresolved/refractory seizures are present • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADD, aggressive or destructive behaviors, &/or traits suggestive of ASD
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of feeding ability & nutritional status • Consider eval for swallowing dysfunction & gastric tube placement in those w/dysphagia or continued poor growth on oral feedings alone. [1]
Cardiovascular	Echocardiogram	To assess valvular problems & anatomic heart defects
Respiratory/ Sleep	Evaluate for signs & symptoms of sleep apnea	Consider polysomnogram if concerns about sleep disturbance or apnea.
Eyes	Ophthalmologic eval	To assess for strabismus
Hearing	Audiologic eval	To assess for hearing loss
Genitourinary	Physical exam for undescended testes in males	Consider referral to urologist, if present.
	Consider renal ultrasound to assess for renal anomalies.	In those w/unexplained hypertension &/or history of UTIs
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • 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)
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *HNRNPU*-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.

ADD = attention-deficit disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; UTI = urinary tract infection

1. See also **Oral motor dysfunction** in Treatment of Manifestations.

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *HNRNPU*-Related Neurodevelopmental Disorder

Manifestation/ Concern	Treatment	Considerations/Other
Hypotonia/ Hypertonia	Orthopedics / physical medicine & rehab / PT & OT incl exercises to address muscle tone issues	Consider need for positioning & mobility devices, disability parking placard.
	Consider involving appropriate specialists to aid in mgmt of baclofen, tizanidine, Botox®, or orthopedic procedures.	For those w/severe hypertonia
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; sodium valproate is the most commonly used & effective medication. [1] • Ketogenic diet & newer ASMs may be required for refractory seizures. • Education of parents/caregivers [2]
DD/ID / Behavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / Failure to thrive	Feeding therapy; nasogastric or gastrostomy 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
Congenital heart defects	Standard treatment per cardiologist	
Sleep apnea	In conjunction w/sleep specialist, appropriate treatment options may incl supplemental oxygen, CPAP, or BiPAP.	It is important to consider additional factors that may contribute to sleep apnea, incl opioids & ASM.
Hyperventilation / Abnormal breathing patterns	Standard treatment per pulmonologist	Combined treatment w/acetazolamide, alprazolam, & aripiprazole successfully used in 1 person. [3]
Strabismus	Standard treatment(s) per ophthalmologist	
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Consider community hearing services through early intervention or school district in severe cases.
Renal anomalies	Standard treatment per nephrologist	
Undescended testes	Standard treatment per urologist	
Limb anomalies	Standard treatment per orthopedist	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
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 nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

1. For individuals on valproate and other ASMs, routine monitoring of liver function tests and observation for behavioral dysregulation should be considered.

2. 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.

3. Spagnoli et al [2021]

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 type 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 use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, or orthopedic procedures.

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.

Very occasionally, individuals with a *HNRNPU*-NDD have aggressive outbursts and may need further evaluation. Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *HNRNPU*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Growth/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures & changes in tone.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Respiratory	Monitor for evidence of hyperventilation & apnea.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	
Eyes	Ophthalmologic eval	Annually or as clinically indicated
Hearing	Audiologic eval	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoid activities and agents that may induce seizures, as the majority of affected individuals have a seizure 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

Sustained single-dose gene therapy treatments for genetic forms of epilepsy, including *HNRNPU*-NDD, are currently being explored. This approach will be based on developing mRNA therapies and/or using a viral vector, such as AAV-9 (adeno-associated vector serotype 9), to deliver therapeutic protein to treat those forms of epilepsy caused by haploinsufficiency of proteins such as HNRNPU.

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

HNRNPU-related neurodevelopmental disorder (*HNRNPU*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *HNRNPU*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo HNRNPU* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- 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. Presumed parental mosaicism has been reported in one family with two affected sibs [Durkin et al 2020].

      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.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *HNRNPU* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Durkin et al 2020].

Offspring of a proband

- Each child of an individual with *HNRNPU*-NDD has a 50% chance of inheriting the *HNRNPU* pathogenic variant.
- Individuals with *HNRNPU*-NDD are not known to have reproduced; however, many are not yet of reproductive age.

Other family members. Given that most probands with *HNRNPU*-NDD have the disorder as the result of a *de novo HNRNPU* pathogenic variant, the risk to other family members is presumed to be low.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo HNRNPU* pathogenic variant. There is, however, a recurrence risk to sibs based on the possibility of parental germline mosaicism [Durkin et al 2020]. Given this risk, prenatal and preimplantation genetic testing may be considered.

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.

- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org
- **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. HNRNPU-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

HNRNPU	1q44	Heterogeneous nuclear ribonucleoprotein U	HNRNPU	HNRNPU

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 HNRNPU-Related Neurodevelopmental Disorder (View All in OMIM)

602869	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN U; HNRNPU
617391	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 54; DEE54

Molecular Pathogenesis

HNRNPU, located on 1q44, encodes for HNRNPU, which is a DNA- and RNA-binding protein. It is involved in nuclear chromatin organization, telomere-length regulation, mRNA alternative splicing and stability, Xist-mediated transcriptional silencing, and mitotic cell cycle regulation. Additionally, it negatively regulates glucocorticoid-mediated transcriptional activation and participates in circadian regulation [Hasegawa et al 2010, Bi et al 2013, Nozawa et al 2017, Havrilla et al 2019]. Thierry et al [2012] showed that HNRNPU is expressed in at least six different tissues: adult brain, heart, kidney, liver, cerebellum, and fetal brain, with the strongest expression in the cerebellum.

De novo loss-of-function variants in *HNRNPU* can lead to a disease phenotype characterized by a variable neurodevelopmental syndrome with moderate-to-severe intellectual disability, seizures, behavioral abnormalities, and agenesis of the corpus callosum. A study by Leduc et al [2017] in which whole-exome sequencing was used suggested that haploinsufficiency was the main mechanism of pathogenicity.

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

In the area of pediatric dysmorphology / genomic medicine, Dr Balasubramanian has led several studies focused on genotype-phenotype correlation in newly identified genes from next-generation sequencing studies such as the Deciphering Developmental Disorders (DDD) study, and has several first/senior author articles published in this area on large cohorts of individuals with new syndromal diagnoses. Her research is now focused on exploring disease mechanisms and establishing international registries for these disorders to better understand the natural history of these conditions. Dr Balasubramanian has published the largest cohort of people so far with *HNRNPU*-related neurodevelopmental disorder and has gathered phenotypic data on more than 50 individuals with *HNRNPU*-related neurodevelopmental disorder. She has also written the Unique patient support group information leaflet on the condition along with Anna Pelling from Unique (rarechromo.org).

Dr Balasubramanian's web pages: www.sheffield.ac.uk and www.mellanbycentre.org

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References

Literature Cited

Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR, et al. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217–21. PubMed PMID: 23934111.

Bi HS, Yang XY, Yuan JH, Yang F, Xu D, Guo YJ, Zhang L, Zhou CC, Wang F, Sun SH. H19 inhibits RNA polymerase II-mediated transcription by disrupting the hnRNP U-actin complex. Biochim Biophys Acta. 2013;1830:4899–906. PubMed PMID: 23811339.

Bramswig NC, Lüdecke HJ, Hamdan FF, Altmüller J, Beleggia F, Elcioglu NH, Freyer C, Gerkes EH, Demirkol YK, Knupp KG, Kuechler A. Heterozygous HNRNPU variants cause early onset epilepsy and severe intellectual disability. Hum Genet. 2017;136:821–34. PubMed PMID: 28393272.

Caliebe A, Kroes HY, van der Smagt JJ, Martin-Subero JI, Tonnies H, van't Slot R, Nievelstein AJ, Muhle H, Stephani U, Alfke K, Stefanova I, Hellenbroich Y, Gillessen-Kaesbach G, Hochstenbach R, Siebert R, Poot M. Four patients with speech delay, seizures, and variable corpus callosum thickness sharing a 0.440 Mb deletion in region 1q44 containing the HNRPU gene. Eur J Med Genet. 2010;53:179–85. PubMed PMID: 20382278.

de Kovel CG, Brilstra EH, van Kempen MJ, Van't Slot R, Nijman IJ, Afawi Z, De Jonghe P, Djémié T, Guerrini R, Hardies K, Helbig I, Hendrickx R, Kanaan M, Kramer U, Lehesjoki AE, Lemke JR, Marini C, Mei D, Møller RS, Pendziwiat M, Stamberger H, Suls A, Weckhuysen S, Koeleman BP, et al. Targeted sequencing of 351 candidate genes for epileptic encephalopathy in a large cohort of patients. Mol Genet Genomic Med. 2016;4:568–80. PubMed PMID: 27652284.

Depienne C, Nava C, Keren B, Heide S, Rastetter A, Passemard S, Chantot-Bastaraud S, Moutard ML, Agrawal PB, VanNoy G, Stoler JM. Genetic and phenotypic dissection of 1q43q44 microdeletion syndrome and neurodevelopmental phenotypes associated with mutations in ZBTB18 and HNRNPU. Hum Genet. 2017;136:463–79. PubMed PMID: 28283832.

Durkin A, Albaba S, Fry AE, Morton JE, Douglas A, Beleza A, Williams D, Volker-Touw CML, Lynch SA, Canham N, Clowes V, Straub V, Lachlan K, Gibbon F, Gamal ME, Varghese V, Parker MJ, Newbury-Ecob R, Turnpenny PE, Gardham A, Ghali N, Balasubramanian M. Clinical findings of 21 previously unreported probands with HNRNPU-related syndrome and comprehensive literature. Am J Med Genet A. 2020;182:1637–54. PubMed PMID: 32319732.

Hasegawa Y, Brockdorff N, Kawano S, Tsutui K, Tsutui K, Nakagawa S. The matrix protein hnRNP U is required for chromosomal localization of Xist RNA. Dev Cell. 2010;19:469–76. PubMed PMID: 20833368.

Havrilla JM, Pedersen BS, Layer RM, Quinlan AR. A map of constrained coding regions in the human genome. Nat Genet. 2019;51:88–95. PubMed PMID: 30531870.

Hinokuma N, Nakashima M, Asai H, Nakamura K, Akaboshi S, Fukuoka M, Togawa M, Oana S, Ohno K, Kasai M, Ogawa C, Yamamoto K, Okumiya K, Chong PF, Kira R, Uchino S, Fukuyama T, Shinagawa T, Miyata Y, Abe Y, Hojo A, Kobayashi K, Maegaki Y, Ishikawa N, Ikeda H, Amamoto M, Mizuguchi T, Iwama K, Itai T, Miyatake S, Saitsu H, Matsumoto N, Kato M. Clinical and genetic characteristics of patients with Doose syndrome. Epilepsia Open. 2020;5:442–50. PubMed PMID: 32913952.

Leduc MS, Chao HT, Qu C, Walkiewicz M, Xiao R, Magoulas P, Pan S, Beuten J, He W, Bernstein JA, Schaaf CP. Clinical and molecular characterization of de novo loss of function variants in HNRNPU. Am J Med Genet A. 2017;173:2680–9. PubMed PMID: 28815871.

Need AC, Shashi V, Hitomi Y, Schoch K, Shianna KV, McDonald MT, Meisler MH, Goldstein DB. Clinical application of exome sequencing in undiagnosed genetic conditions. J Med Genet. 2012;49:353–61. PubMed PMID: 22581936.

Nozawa RS, Boteva L, Soares DC, Naughton C, Dun AR, Buckle A, Ramsahoye B, Bruton PC, Saleeb RS, Arnedo M, Hill B. SAF-A regulates interphase chromosome structure through oligomerization with chromatin-associated RNAs. Cell. 2017;169:1214–27.e18. PubMed PMID: 28622508.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Shimada S, Oguni H, Otani Y, Nishikawa A, Ito S, Eto K, Nakazawa T, Yamamoto-Shimojima K, Takanashi JI, Nagata S, Yamamoto T. An episode of acute encephalopathy with biphasic seizures and late reduced diffusion followed by hemiplegia and intractable epilepsy observed in a patient with a novel frameshift mutation in HNRNPU. Brain Dev. 2018;40:813–8. PubMed PMID: 29858110.

Song Z, Zhang Y, Yang C, Yi Z, Li F, Xue J, Yang X, Li B. De novo frameshift variants of HNRNPU in patients with early infantile epileptic encephalopathy: two case reports and literature review. Int J Dev Neurosci. 2021;81:663–8. PubMed PMID: 33914968.

Spagnoli C, Rizzi S, Salerno GG, Frattini D, Koskenvuo J, Fusco C. Pharmacologic treatment of severe breathing abnormalities in a case of HNRNPU epileptic encephalopathy. Mol Syndromol. 2021;12:101–5. PubMed PMID: 34012379.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Taylor J, Spiller M, Ranguin K, Vitobello A, Philippe C, Bruel AL, Cappuccio G, Brunetti-Pierri N, Willems M, Isidor B, Park K, Balasubramanian M. Expanding the phenotype of HNRNPU-related neurodevelopmental disorder with emphasis on seizure phenotype and review of literature. Am J Med Genet A. 2022;188:1497–514. PubMed PMID: 35138025.

Thierry G, Bénéteau C, Pichon O, Flori E, Isidor B, Popelard F, Delrue MA, Duboscq-Bidot L, Thuresson AC, van Bon BW, Cailley D, Rooryck C, Paubel A, Metay C, Dusser A, Pasquier L, Béri M, Bonnet C, Jaillard S, Dubourg C, Tou B, Quéré MP, Soussi-Zander C, Toutain A, Lacombe D, Arveiler B, de Vries BB, Jonveaux P, David A, Le Caignec C. Molecular characterization of 1q44 microdeletion in 11 patients reveals three candidate genes for intellectual disability and seizures. Am J Med Genet A. 2012;158A:1633–40. PubMed PMID: 22678713.

Yates TM, Vasudevan PC, Chandler KE, Donnelly DE, Stark Z, Sadedin S, Willoughby J, Balasubramanian M, et al. De novo mutations in HNRNPU result in a neurodevelopmental syndrome. Am J Med Genet A. 2017;173:3003–12. PubMed PMID: 28944577.

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