HNRNPU-related disorder

https://www.ncbi.nlm.nih.gov/books/NBK578573/

SummaryClinical 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.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.

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DiagnosisNo consensus clinical diagnostic criteria for HNRNPU-related neurodevelopmental disorder (HNRNPU-NDD) have been published.Suggestive FindingsHNRNPU-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 infancyInfant feeding difficultiesSpeech and language delay and/ or absent speechAutism spectrum disorder or autistic traitsNonspecific dysmorphic facial features (See Clinical Description.)Epilepsy, including generalized tonic-clonic seizures and absence seizuresShort statureStrabismusBrain MRI findings. The most common brain MRI findings are nonspecific but include:VentriculomegalyThinning of the corpus callosumFamily 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 DiagnosisThe 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 possibleFor 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 DisorderView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2, 3 Detectable by Method

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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].

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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

Ventriculomegaly

Thinning of the corpus callosum

Establishing the DiagnosisThe 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

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Clinical CharacteristicsClinical DescriptionTo 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 DisorderView in own windowFeature% of Personsw/FeatureCommentDevelopmental delay100%Dysmorphic craniofacial features97%See Dysmorphic features following this table.Seizure disorder95%~90% have 1st seizure before age 24 mos (tonic-clonic in ~60%, absence in ~44%) 1Intellectual disability84%Typically moderate to severeSpeech delay80%Usually limited or no speechHypotonia79%Slightly fewer than 50% have congenital hypotonia.Feeding difficulties57%Some require supplemental nasogastric feeding or percutaneous gastrostomy.Behavioral issues50%Autistic features are observed in ~33% of affected persons.Eye anomalies36%The most common finding is strabismus.Cardiac abnormalities30%Septal defects are the most common.Renal anomalies<10%Hyperventilation & apneaRare1. 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 behaviorHand flappingAgitationHyperventilation episodes (See also Respiratory abnormalities.)Attention-deficit disorderDysmorphic 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 foreheadHighly arched, thin eyebrowsPalpebral fissure abnormalities (both upslanted and downslanted)EpicanthusThin vermilion of the upper lipLow-hanging columellaWidely spaced teethGrowth. 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 defectVentricular septal defectPatent ductus arteriosusTricuspid atresia, tetralogy of Fallot, aortic dilatation, and transposition of the great arteries together in one affected individualEyes. 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 3Fifth digit clinodactylyHallux valgusPrognosis. 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 CorrelationsNo genotype-phenotype correlations have been identified.PrevalenceThe prevalence of this condition is unknown. To date, approximately 83 individuals with HNRNPU-NDD have been reported.

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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 behaviorHand flappingAgitationHyperventilation episodes (See also Respiratory abnormalities.)Attention-deficit disorderDysmorphic 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 foreheadHighly arched, thin eyebrowsPalpebral fissure abnormalities (both upslanted and downslanted)EpicanthusThin vermilion of the upper lipLow-hanging columellaWidely spaced teethGrowth. 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 defectVentricular septal defectPatent ductus arteriosusTricuspid atresia, tetralogy of Fallot, aortic dilatation, and transposition of the great arteries together in one affected individualEyes. 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 3Fifth digit clinodactylyHallux valgusPrognosis. 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.

Table 2. Select Features of HNRNPU-Related Neurodevelopmental DisorderView in own windowFeature% of Personsw/FeatureCommentDevelopmental delay100%Dysmorphic craniofacial features97%See Dysmorphic features following this table.Seizure disorder95%~90% have 1st seizure before age 24 mos (tonic-clonic in ~60%, absence in ~44%) 1Intellectual disability84%Typically moderate to severeSpeech delay80%Usually limited or no speechHypotonia79%Slightly fewer than 50% have congenital hypotonia.Feeding difficulties57%Some require supplemental nasogastric feeding or percutaneous

gastrostomy.Behavioral issues50%Autistic features are observed in ~33% of affected persons.Eye anomalies36%The most common finding is strabismus.Cardiac abnormalities30%Septal defects are the most common.Renal anomalies<10%Hyperventilation & apneaRare1. Of note, some persons have both types of seizures, such that the combined percentages are more than 100%.

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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.

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

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

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

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.

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

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

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

Genetically Related (Allelic) DisordersNo 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 DiagnosisBecause 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.

ManagementNo clinical practice guidelines for HNRNPU-related neurodevelopmental disorder (HNRNPU-NDD) have been published.Evaluations Following Initial DiagnosisTo 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 DisorderView in own windowSystem/ConcernEvaluationComment

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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, ADD, aggressive or destructive behaviors, &/or traits suggestive of ASD

Gastrointestinal/

Feeding

Gastroenterology / nutrition / feeding team evalTo incl eval of feeding ability & nutritional statusConsider eval for swallowing dysfunction & gastric tube placement in those w/dysphagia or continued poor growth on oral feedings alone. 1

Cardiovascular

EchocardiogramTo assess valvular problems & anatomic heart defects

Respiratory/

Sleep

Evaluate for signs & symptoms of sleep apneaConsider polysomnogram if concerns about sleep disturbance or apnea.

Eyes

Ophthalmologic evalTo assess for strabismus

Hearing

Audiologic evalTo assess for hearing loss

Genitourinary

Physical exam for undescended testes in malesConsider 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 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)

Genetic

counseling

By genetics professionals 2To 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 infection1. See also Oral motor dysfunction in Treatment of Manifestations.2. Medical geneticist, certified genetic counselor, certified advanced genetic nurseTreatment of ManifestationsTable 4. Treatment of Manifestations in Individuals with HNRNPU-Related Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

Hypotonia/

Hypertonia

Orthopedics / physical medicine & rehab / PT & OT incl exercises to address muscle tone issuesConsider 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 neurologistMany ASMs may be effective; sodium

valproate is the most commonly used & effective medication. 1Ketogenic 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 pulmonologistCombined 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

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; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy1. 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 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 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 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.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.SurveillanceTable 5. Recommended Surveillance for Individuals with HNRNPU-Related Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationFrequency

Growth/Feeding

Measurement of growth parametersEval 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 evalAnnually or as clinically indicated

Hearing

Audiologic evalOT = occupational therapy; PT = physical therapyAgents/Circumstances to AvoidAvoid activities and agents that may induce seizures, as the majority of affected individuals have a seizure disorder.Evaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSustained

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.

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Physical exam for undescended testes in malesConsider referral to urologist, if present.Consider renal ultrasound to assess for renal anomalies.In those w/unexplained hypertension &/or history of UTIs

Musculoskeletal

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Genetic

counseling

By genetics professionals 2To 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 infection1. See also Oral motor dysfunction in Treatment of Manifestations.2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

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

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 infection1. See also Oral motor dysfunction in Treatment of Manifestations.2. Medical geneticist,

certified genetic counselor, certified advanced genetic nurse

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See also Oral motor dysfunction in Treatment of Manifestations.

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Treatment of ManifestationsTable 4. Treatment of Manifestations in Individuals with HNRNPU-Related Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

Hypotonia/

Hypertonia

Orthopedics / physical medicine & rehab / PT & OT incl exercises to address muscle tone issuesConsider 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 neurologistMany ASMs may be effective; sodium

valproate is the most commonly used & effective medication. 1Ketogenic 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 pulmonologistCombined 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

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; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy1. 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 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 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 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.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.

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Hearing loss

Hearing aids may be helpful; per otolaryngologist.Consider community hearing services through early intervention or school district in severe cases.

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Family/

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

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SurveillanceTable 5. Recommended Surveillance for Individuals with HNRNPU-Related Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationFrequency

Growth/Feeding

Measurement of growth parametersEval 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 evalAnnually or as clinically indicated

Hearing

Audiologic evalOT = occupational therapy; PT = physical therapy

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Agents/Circumstances to AvoidAvoid activities and agents that may induce seizures, as the majority of affected individuals have a seizure disorder.

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

Therapies Under InvestigationSustained 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 InheritanceHNRNPU-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 TestingRisk 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.

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

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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

www.aesnet.org

Canadian Epilepsy Alliance

CanadaPhone: 1-866-EPILEPSY (1-866-374-5377)

www.canadianepilepsyalliance.org

Epilepsy Foundation

Phone: 301-459-3700Fax: 301-577-2684

www.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 KingdomPhone: +44 (0) 1883 723356Email: info@rarechromo.org

www.rarechromo.org

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

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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.HNRNPU-Related Neurodevelopmental Disorder: Genes and DatabasesView in own windowGeneChromosome LocusProteinHGMDClinVar

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)

View in own window

602869HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN U; HNRNPU

617391DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 54; DEE54Molecular PathogenesisHNRNPU, 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

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Chapter NotesAuthor NotesIn 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

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