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DDX3X-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

DDX3X-related neurodevelopmental disorder (*DDX3X*-NDD) typically occurs in females and very rarely in males. All affected individuals reported to date have developmental delay / intellectual disability ranging from mild to severe; about 50% of affected girls remain nonverbal after age five years. Hypotonia, a common finding, can be associated with feeding difficulty in infancy. Behavioral issues can include autism spectrum disorder, attention-deficit/hyperactivity disorder and hyperactivity, self-injurious behavior, poor impulse control, and aggression. Other findings can include seizures, movement disorders (dyskinesia, spasticity, abnormal gait), vision and hearing impairment, congenital heart defects, respiratory difficulties, joint laxity, and scoliosis. Neuroblastoma has been observed in three individuals.

Diagnosis/testing

The diagnosis of *DDX3X*-NDD is established in a female proband with suggestive findings and a heterozygous *de novo DDX3X* pathogenic variant identified by molecular genetic testing and in a male proband with suggestive findings and a hemizygous *DDX3X* pathogenic variant.

Management

Treatment of manifestations: Treatment is symptomatic and focuses on optimizing the individual's abilities using a multidisciplinary approach that should also include psychosocial support for family members. Management of feeding difficulty, intellectual disability, behavioral issues, seizures, spasticity and other movement disorders,

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vision and hearing impairment, congenital heart defects, respiratory difficulties, joint laxity, and scoliosis as per standard care.

Surveillance: Periodic evaluation by the multidisciplinary team regarding growth, developmental progress and educational needs, and psychiatric/behavioral issues; regular assessment of vision and hearing, of the spine for scoliosis, for seizure control (when relevant), and for cardiac and respiratory issues. Starting at age eight years, assess girls for evidence of precocious puberty.

Genetic counseling

DDX3X-NDD is an X-linked disorder.

- **Females.** Most female probands represent simplex cases (i.e., a single occurrence in a family) and have the disorder as the result of a *de novo* pathogenic variant.
- **Males.** *DDX3X*-NDD in males is caused by either a pathogenic variant inherited from an unaffected heterozygous mother or a *de novo* pathogenic variant. If the mother of an affected male has a *DDX3X* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and are not expected to manifest a neurodevelopmental phenotype.

If the proband is female and represents a simplex case and if the *DDX3X* pathogenic variant cannot be detected in the leukocyte DNA of either parent – or the proband is male and the *DDX3X* pathogenic variant cannot be detected in the leukocyte DNA of the mother – the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism.

Once the *DDX3X* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for *DDX3X*-related neurodevelopmental disorder (*DDX3X*-NDD) have not been established.

Suggestive Findings

DDX3X-NDD can be considered in an individual with several of the following clinical and brain imaging findings [Snijders Blok et al 2015, Lennox et al 2020].

Clinical findings

- Developmental delay (DD) or mild to severe intellectual disability (ID)
- Hypotonia (primarily truncal)
- Behavior problems: autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), inappropriate behavior, self-injurious behavior, poor impulse control and aggression
- Language impairment, often with significant verbal dyspraxia
- Borderline microcephaly
- Dysmorphic facial features. Although there are no characteristic dysmorphic features, a long and/or hypotonic face, a high and/or broad forehead, and a wide nasal bridge and/or bulbous upturned nasal tip are frequently observed (Figure 1) [Snijders Blok et al 2015, Fieremans et al 2016].

Brain MRI findings in decreasing order of frequency:

- Corpus callosum hypoplasia ranging from complete agenesis (rare) to a milder malformation with only a thin posterior body and splenium (common)

- Ventricular enlargement and/or keyhole-shaped temporal horns of the lateral ventricles
- Polymicrogyria
- Other. Decreased white matter volume, decreased cingulum bundle density, diminished anterior commissure, small pons and small inferior cerebellar vermis

Establishing the Diagnosis

Female proband. The diagnosis of *DDX3X*-NDD **is usually established** in a female proband with suggestive findings and a heterozygous *de novo DDX3X* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

Male proband. The diagnosis of *DDX3X*-NDD **is established** in a male proband with suggestive findings and either a hemizygous *DDX3X* pathogenic (or likely pathogenic) variant inherited from an unaffected heterozygous female or a hemizygous *de novo DDX3X* pathogenic (or likely pathogenic) variant 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 *DDX3X* variant of uncertain significance in a female or a hemizygous *DDX3X* variant of uncertain significance in a male does not establish or rule out a diagnosis of *DDX3X*-NDD.

Molecular Genetic Testing

Because the phenotype of *DDX3X*-NDD is indistinguishable from many other genetic disorders with intellectual disability, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *DDX3X,* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability (ID) or hypotonia (for young children) multigene panel** that includes *DDX3X* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, some panels for ID may not (yet) 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; **genome sequencing** is also possible.

  Exome array (when clinically available) may be considered if exome sequencing is not diagnostic. Copy number variation in *DDX3X* has not been studied in detail, but deletions are found in females and duplications in both sexes (see Decipher Database).

Figure 1. Facial profiles of females heterozygous for a de novo *DDX3X* pathogenic variant

Facial features of 30 of 38 females with a *de novo DDX3X* pathogenic variant. Common facial features include a long and/or hypotonic face, a high and/or broad forehead, a wide nasal bridge and/or bulbous nasal tip, narrow alae nasi and/or anteverted nostrils, and hypertelorism.

From Snijders Blok et al [2015]. Republished with permission.

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 *DDX3X*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DDX3X	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. 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.
4. Snijders Blok et al [2015], Wang et al [2018], Beal et al [2019], Lennox et al [2020]
5. 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.
6. No data on gene-targeted deletions/duplications are available.

Clinical Characteristics

Clinical Description

DDX3X-related neurodevelopmental disorder (*DDX3X*-NDD) typically occurs in females and rarely in males. *DDX3X*-NDD in both females and males is associated with a broad spectrum of clinical features with variable expression and severity. Table 2 presents the most common clinical characteristics observed in the three largest cohorts of females with *DDX3X*-NDD observed to date comprising a total of 149 unique individuals [Snijders Blok et al 2015, Wang et al 2018, Lennox et al 2020]. Note that data from individuals included in more than one report were removed. Data from four smaller reports are included in the discussion following Table 2 [Kellaris et al 2018, Beal et al 2019, Nicola et al 2019, Scala et al 2019].

Characteristics typically present are intellectual disability (ID), tone abnormalities, and associated feeding difficulty, joint laxity, and scoliosis. Other common features include ophthalmologic abnormalities, hearing loss, congenital heart defects, and respiratory difficulties. Neuroblastoma has been observed in three individuals, all of whom presented early in life and responded favorably to treatment.

Table 2. Clinical Findings in Females with *DDX3X*-Related Neurodevelopmental Disorder

Finding	Report 1 [Snijders Blok et al 2015]	Report 2 [Wang et al 2018]	Report 3 [Lennox et al 2020]
DD/ID	38/38 (100%)	28/28 (100%)	84/84 (100%)
Behavior issues	20/38 (53%)	6/28 (21%)	See footnote 1.
Hypotonia	29/38 (76%)	19/28 (68%)	66/83 (80%)
Hypertonia alone or a mixture of hyper- & hypotonia	See footnote 2.	2/12 (17%)	38/83 (46%)
Epilepsy/seizures	6/38 (16%)	NA	17/83 (20%)
Movement disorders	17/38 (45%) [2]	17/28 (61%)	18/83 (22%)
Microcephaly	12/38 (32%)	7/28 (25%)	25/74 (34%)
Vision issues	13/38 (34%)	9/28 (32%)	32/82 (39%)
Respiratory	NA	5/28 (18%)	NA

Table 2. continued from previous page.

Finding	Report 1 [Snijders Blok et al 2015]	Report 2 [Wang et al 2018]	Report 3 [Lennox et al 2020]
Congenital heart abnormalities	NA	5/7 [3] (71%)	11/82 (13%)
Skeletal (scoliosis)	4/38 (11%)	NA	8/82 (10%)
Hearing impairment	3/38 (8%)	NA	4/78 (5%)
Precocious puberty	5/38 (13%)	NA	7/82 (9%)
Cleft lip/palate/uvula	3/38 (8%)	NA	NA

NA = not applicable
Note: Some overlap of participants exists in the three reported cohorts; to address the overlap, cohort 1 has been reported in its entirety and the overlaps subtracted from cohorts 2 and 3. One male overlaps in Reports 1 and 2, but (being male) is not counted in the table. Twenty of the 104 females in Report 3 were previously reported.
DD = developmental delay; ID = intellectual disability; NA = not applicable (not specified or reported in the study)
1. In Lennox et al [2020], 49 children were assessed using the Child Behavior Checklist (CBCL) self-reported by parents. The mean CBCL was 58.3, with a SD of 10 – significantly different from neurotypical controls, $p<0.001$.
2. In Snijders Blok et al [2015], movement disorders include spasticity.
3. Evaluated by echocardiogram

DDX3X-Related Neurodevelopmental Disorder in Females

Developmental delay/disability. All females with *DDX3X*-NDD reported to date (within the limits of ascertainment) likely meet criteria for ID (or developmental delays when too young for the diagnosis of a disability), ranging from mild to severe [Snijders Blok et al 2015, Wang et al 2018, Lennox et al 2020].

Systematic IQ testing has not been published for females with *DDX3X*-NDD, so in most instances the term ID is inferentially chosen from parentally reported delayed milestones. In one report four categories were identified: 10/38 individuals with mild or moderate ID, 10/38 with moderate or moderate to severe ID, 15/38 with severe ID, and 3/38 with developmental delay (DD) who were younger than age five years [Snijders Blok et al 2015].

In another study, in which the parents of 53 affected girls used the Vineland Adaptive Behavior Scales (VABS) to self-report their child's adaptive behavioral skills, the mean composite standard score was 56.6, which is significantly below the mean score of 100 (standard deviation: 15) in the neurotypical population.

In addition, affected individuals with polymicrogyria (PMG) were more delayed developmentally, with an average VABS of 43.8 versus 57.5 in those without PMG ($p<0.05$) [Lennox et al 2020].

Speech-language delays or disorders are common: After age five years, 52% of females with *DDX3X*-NDD were nonverbal [Lennox et al 2020]. While a systematic review of progression of milestones has not been reported, in one report a female age 47 years was reported to have learned to sit at age two years, walk at age eight years, and say simple words [Wang et al 2018]. Data on the use of sign language or alternative communication methods have not been reported.

Behavioral issues include autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and hyperactivity, self-injurious behavior, poor impulse control, aggression, and other inappropriate behaviors [Snijders Blok et al 2015, Wang et al 2018, Lennox et al 2020]. In one study of 42 individuals, scores on the Social Communication Questionnaire completed by parents/caregivers indicated that 67% were above the at-risk threshold for ASD [Lennox et al 2020].

Tone abnormalities included either isolated hypotonia or a mixture of hypertonia and hypotonia in which truncal tone is lower and limb tone is increased.

Movement disorders are present at a young age and can include dyskinesia, ataxia, and dystonia, sometimes expressed as a stiff-legged or wide-based gait. One female was reported to have striking dystonic episodes [Beal et al 2019].

Seizure types include myoclonic-atonic seizures (episodes of brief shock-like jerks of a muscle or group of muscles as well as drop attacks), infantile spasms, focal partial seizures, or generalized absence spells. Seizures are more common in females with polymicrogyria [Lennox et al 2020].

Microcephaly is more frequent in persons with polymicrogyria (6/9) [Lennox et al 2020], nearly all of whom had an occipital frontal circumference two to three standard deviations below the mean.

Ophthalmologic findings include refractive errors, cortical visual impairment, optic atrophy, coloboma (type not specified in 4/92 individuals in Lennox et al), nystagmus, and strabismus (25/92, or 27%) [Wang et al 2018, Lennox et al 2020].

Respiratory findings can include obstructive sleep apnea, tachypnea, and chronic respiratory failure [Wang et al 2018].

Cardiac abnormalities, in addition to those included in Table 2, include atrial septal defect (ASD), patent ductus arteriosus (PDA), and patent foramen ovale (PFO) [Nicola et al 2019], ASD and ventricular septal defect (VSD) [Dikow et al 2017], and (in 1 of 6 females) a VSD [Beal et al 2019].

Skeletal. Scoliosis is likely secondary to hypotonia. In one report 37% (14/38) of individuals had joint laxity [Snijders Blok et al 2015].

Hearing impairment can be conductive, sensorineural, or both. Age of onset is unknown; whether hearing loss is progressive or not is unknown.

Precocious puberty (defined as onset of pubertal changes before age 8 years in girls and age 9 years in boys). While observed in a minority of females [Snijders Blok et al 2015, Lennox et al 2020], the real frequency may be higher, as both cohorts include females younger than the average age at which precocious puberty is observed.

Other

- **Gastrointestinal** manifestations reported include feeding issues, gastroesophageal reflux, and constipation. There are isolated cases of anal atresia or stenosis, esophagitis, intestinal volvulus, and cyclic vomiting [Dikow et al 2017; Lennox et al 2020].
- **Cleft lip, palate, or uvula** is reported in a few individuals [Snijders Blok et al 2015, Fieremans et al 2016].
- **Malignancy.** It is currently unclear whether the risk for specific malignancies is increased in children with germline *DDX3X* pathogenic variants.

  Neuroblastoma has been observed in three females ages 4-7 months [Lennox et al 2020; Sherr, personal communication]. In two of the three, neuroblastoma was detected incidentally (while obtaining spine MRIs). All three were disease free at annual follow ups [Sherr & Johnson-Kerner, personal communication].

  A pilocytic astrocytoma, incidentally found on head imaging, was reported in a female age eight years [Scala et al 2019].

DDX3X-Related Neurodevelopmental Disorder in Males

To date, males from at least ten different families have been reported with a hemizygous *DDX3X* variant [Snijders Blok et al 2015, Kellaris et al 2018, Wang et al 2018]. While data are insufficient to characterize a detailed phenotype, all males had intellectual disability, ranging from mild to severe.

In one report, two of five males had a head circumference more than two standard deviations below the mean [Snijders Blok et al 2015]. In another report, two brothers had macrocephaly – the significance of which is unknown as it was also present in the otherwise asymptomatic father and sister [Kellaris et al 2018].

Additional features similar to those reported in affected females included behavioral findings, spasticity, tremor, hypotonia, vision issues, congenital heart disease, and delayed puberty [Snijders Blok et al 2015, Nicola et al 2019]. Brain MRI anomalies include corpus callosum abnormalities, ventriculomegaly, and white matter abnormalities.

Genotype-Phenotype Correlations

Females. Affected females with a subset of missense variants generally are more severely affected than those with truncating variants [Lennox et al 2020].

Polymicrogyria has been associated with missense or in-frame deletions [Lennox et al 2020].

Males. While all affected males have had missense *DDX3X* variants (see Table 6), their female relatives who are heterozygous for the same *DDX3X* variant do not manifest an atypical neurodevelopmental phenotype.

Prevalence

Although *DDX3X*-NDD is rare, variants in *DDX3X* are among the most commonly reported causes in females with neurodevelopmental disorders [Deciphering Developmental Disorders Study Group 2015]:

- In one study that included more than 6,000 individuals, variants in *DDX3X* accounted for 1%-3% of unexplained intellectual disability in females [Snijders Blok et al 2015].
- Another study reported that among approximately 450 genes, the occurrence of *de novo* variants ranked third in *DDX3X*, after the genes *ARID1B* and *ANKRD11* [Wang et al 2018].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DDX3X*.

Sporadic tumors (including medulloblastoma and lymphoma [Jones et al 2012, Pugh et al 2012, Robinson et al 2012, Jiang et al 2015]) occurring in the absence of any findings of *DDX3X*-NDD frequently harbor somatic variants in *DDX3X* that are **not** present in the germline. In these circumstances predisposition to these tumors is not considered heritable. Of note, in some instances the same *DDX3X* variant has been found as a germline variant in *DDX3X*-NDD and as a somatic variant in cancer.

Differential Diagnosis

Because the phenotypic features associated with *DDX3X*-related neurodevelopmental disorder in females are not sufficient to diagnose this condition, many disorders with intellectual disability without other clearly distinctive findings should be considered in the differential diagnosis (including autism spectrum disorder and cerebral palsy). See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Two females with features of Toriello-Carey syndrome (T-CS) (anal atresia, congenital heart defects, corpus callosum anomalies, hypotonia, and developmental delay) (OMIM 217980) were found to have a *DDX3X* variant [Dikow et al 2017]. T-CS, a disorder with significant phenotypic variability [Toriello et al 2003], was first described as postnatal growth delay and microcephaly, intellectual disability, abnormal corpus callosum, Pierre Robin sequence, laryngeal abnormalities, cardiac defects, typical facial features, and other abnormalities

[Toriello & Carey 1988]. T-CS is genetically heterogeneous, as various cytogenetic changes and *UBE3B* variants have been reported as causative [Toriello & Hatchwell 2008, McGoey et al 2010, Basel-Vanagaite et al 2014].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *DDX3X*-related neurodevelopmental disorder (*DDX3X*-NDD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *DDX3X*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Constitutional	Assess height, weight, & head circumference.	Check for evidence of FTT.
Neurodevelopment	Neurodevelopmental assessment to identify delays	To incl motor, speech-language eval, general cognitive, & adaptive skills by available & appropriate services (e.g., eval by early intervention program (ages 0-3 yrs), public school district (ages 3-21 yrs), or possibly by developmental/behavioral pediatrician
Speech & language	Eval by speech-language pathologist	Assessment of speech, language, & communication abilities
Neurologic	Neurologic eval for hypotonia, movement disorder, spasticity	If seizures are suspected: EEG & consideration of brain MRI
Psychiatric/ Behavioral	Consider assessment by behavioral pediatrician to assess maladaptive behaviors or by psychiatrist for more severe behavioral issues.	Persons age >12 mos: incl screening for behavior issues, e.g., sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD.
Cardiovascular	Eval by cardiologist	• Especially those w/FTT & feeding difficulties • Consider autonomic instability in those w/syncope, tachycardia, &/or orthostatic hypotension
Respiratory	Eval by pulmonologist	Patients w/apnea, tachypnea, other respiratory manifestations, &/or respiratory failure
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	If feeding difficulties, GERD, &/or FTT are present: • Swallowing, feeding, & nutritional status assessment to determine safety of oral vs gastrostomy feeding • Mgmt of constipation, if present
Musculoskeletal	Orthopedics / physiatry / PT & OT eval	• Eval for scoliosis if referred by pediatrician • Determination of DME needs
Eyes/Vision	Ophthalmologic exam	Exam for refractive errors, cortical visual impairment, optic atrophy, coloboma, nystagmus, & strabismus
Hearing loss	Audiologic eval	For SNHL, conductive HL, or both
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of *DDX3X*-NDD in order to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DME = durable medical equipment; FTT = failure to thrive; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SNHL = sensorineural hearing loss

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

Treatment of Manifestations

Treatment should be targeted to individual needs.

Table 4. Treatment of Manifestations in Individuals with *DDX3X*-Related Neurodevelopmental Disorder

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Educational Issues.	
Speech & language	By speech-language pathologist	Use of augmentative & alternative communication strategies as needed
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	• For those w/scoliosis: consider bracing to prevent progression & secondary morbidity (e.g., pain, impaired ambulation, restrictive lung disease). • For those w/hypotonia/hypertonia: consider ankle-foot orthoses. If hypertonia is present evaluate need for spasticity treatment (e.g., baclofen, Botox®). • Consider need for positioning & mobility devices, disability parking placard.
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for *DDX3X*-NDD. • Education of parents/caregivers [1]
Psychiatric/ Behavioral	See Developmental Delay / Intellectual Disability Educational Issues.	
Poor weight gain/ Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	
Bowel dysfunction	For constipation	Stool softeners, prokinetics, osmotic agents or laxatives as needed
Abnormal vision	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
Hearing	Hearing aids may be helpful; per audiologist.	Community hearing services through early intervention or school district
Cardiovascular	Standard care per treating cardiologist	
Respiratory	Standard care per treating pulmonologist	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Precocious puberty	Standard care per treating endocrinologist	
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment for need of home nursing • Consider involvement in adaptive sports.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Educational 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. In the US, early intervention (also called Birth to Three) is a federally funded program available in all states. Early intervention provides therapies in the natural environment (i.e., home, daycare). The initial evaluation will determine needed services and therapies and an individualized family service plan (IFSP) is developed.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is completed to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP should be developed by the local public school district based on results of the psychoeducational evaluation and the presence of a qualifying disability. IEP reevaluations will occur on a regular basis. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, residential living, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.
- Families should establish guardianship or power of attorney as appropriate when their child reaches age 18 years.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life. Some issues to consider:

- Use of 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.
- In the US, Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals regardless of income. 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) and/or Medicaid waivers for their child with a disability.

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 is typically performed one on one with a board-certified behavior analyst. Depending on the state and insurance type, ABA therapy can be difficult to access without a diagnosis of autism spectrum disorder.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavioral management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Social/emotional and behavioral support within school can be obtained through the IEP.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *DDX3X*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Constitutional	Measure height, weight, BMI, & head circumference.	Annually or more frequently if FTT
Eyes	Ophthalmologic eval	Annually or more frequently as needed
Hearing	Audiologic assessment	Reevaluate as needed for suspected hearing loss.
Gastrointestinal/ Feeding	Assess nutritional status & feeding w/attention to poor weight gain, choking/gagging during feeds, & feeding refusal not otherwise explained.	Annually or more frequently if FTT
Musculoskeletal	• Eval for effects of hypotonia • PT follow up for gait abnormality	• If needs are present, PT assessment at least 1x/mo recommended • Once stable, gradually ↓ frequency to 1x/yr.
	Monitor for scoliosis.	Annually or more frequently as needed
Neurologic	• Follow up for possible seizures or for seizure mgmt • Monitor for abnormal movements.	
Development	Monitor developmental progress & educational needs.	Every 6 mos, then annually when school aged
Endocrine	Monitor for evidence of precocious puberty.	Starting at age 8 yrs
Psychiatric/ Behavioral	Eval by developmental psychologist	As needed
Miscellaneous/ Other	Assess family need for social work support, other local resources.	Annually or more frequently as needed

FTT = failure to thrive; PT = physical therapy

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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

DDX3X-related neurodevelopmental disorder (*DDX3X*-NDD) is an X-linked disorder.

DDX3X-NDD in a Female Proband – Risk to Family Members

Parents of a female proband

- All female probands reported to date with *DDX3X*-NDD whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo DDX3X* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in a female proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a genetic alteration from a parent with germline mosaicism; presumed parental germline mosaicism has been reported in one family [Beal et al 2019].
- If parents have more than one affected child and if the *DDX3X* pathogenic variant cannot be detected in the leukocyte DNA of a parent, it can be presumed that the father or mother has germline mosaicism.

Sibs of a female proband. The risk to sibs of a female proband depends on the genetic status of the parents: if the proband represents a simplex case (i.e., a single occurrence in a family) and if the *DDX3X* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism [Beal et al 2019].

Offspring of a female proband. The effect of *DDX3X*-NDD on reproductive capability in affected women is not yet known; if a woman with *DDX3X*-NDD were to have children, the chance of transmitting a *DDX3X* pathogenic variant would be 50% in each pregnancy.

Other family members of a female proband. Given that almost all female probands with *DDX3X*-NDD reported to date have the disorder as the result of a *de novo* pathogenic variant, the risk to other family members is presumed to be low.

DDX3X-NDD in a Male Proband – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *DDX3X* pathogenic variant; therefore, he does not require further evaluation/testing.

- If a male is the only affected family member (i.e., a simplex case), the mother may be an asymptomatic heterozygote or the affected male may have a *de novo DDX3X* pathogenic variant, in which case the mother is not a heterozygote [Nicola et al 2019].
- If parents have more than one affected child and if the *DDX3X* pathogenic variant cannot be detected in the leukocyte DNA of the mother, it can be presumed that the mother has germline mosaicism.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of an affected male has a DDX3X pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and would not be expected to manifest a neurodevelopmental phenotype (see Clinical Description, *DDX3X*-NDD in Males).
- If a male proband represents a simplex case and if the *DDX3X* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a male proband. The effect of *DDX3X*-NDD on reproductive capability in affected men is not yet known; if a man with *DDX3X*-NDD were to have children, he would transmit the pathogenic variant to all of his daughters.

Other family members of a male proband. The risk to other family members depends on the genetic status of the proband's mother: if the mother has a *DDX3X* pathogenic variant, other (unaffected) females in her family may be at risk of being heterozygous for the *DDX3X* pathogenic variant.

Heterozygote detection. Molecular genetic testing of at-risk female relatives to determine their genetic status requires prior identification of the *DDX3X* pathogenic variant in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DDX3X* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **DDX3X Foundation**
  100 West 10th Street

Suite 115
Wilmington DE 19801
www.ddx3x.org

- **DDX3X Syndrome**
  Unique Rare Chromosome Disorder Support Group
  A guide for families on DDX3X disorder
- **Simons Searchlight**
  DDX3X
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **MedlinePlus**
  Intellectual Disability
- **National Organization for Disorders of the Corpus Callosum**
  Email: info@nodcc.org
  www.nodcc.org
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  www.rarechromo.org
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. DDX3X-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DDX3X	Xp11.4	ATP-dependent RNA helicase DDX3X	DDX3X @ LOVD	DDX3X	DDX3X

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 DDX3X-Related Neurodevelopmental Disorder (View All in OMIM)

300160	DEAD-BOX HELICASE 3, X-LINKED; DDX3X
300958	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, SNIJDERS BLOK TYPE; MRXSSB

Molecular Pathogenesis

DDX3X encodes a 662-amino acid conserved protein DDX3X (DEAD-box RNA helicase 3) that is important in diverse fundamental cellular processes, including translational regulation and mRNA metabolism [Shih et al 2008, Li et al 2014, Sharma & Jankowsky 2014]. *DDX3X*, which is on the X chromosome, is located in a chromosome region that can escape X-chromosome inactivation, although this is likely context specific [Carrel & Willard 2005, Garieri et al 2018]. DDX3X is a component of RNA-protein granules, including neuronal transport granules and cytoplasmic stress granules [Kanai et al 2004, Elvira et al 2006, Markmiller et al 2018]. DDX3X has two functional domains, a helicase ATP-binding domain and a helicase C-terminal domain.

Although two studies suggested that *DDX3X* missense variants may function via a haploinsufficient mechanism through Wnt signaling [Snijders Blok et al 2015, Kellaris et al 2018], more recent observations report a new mechanism in which some pathogenic variants induce the formation of cytoplasmic RNA-protein granules that, in a dominant-negative manner, disrupt translation in neuronal progenitors and neurons [Lennox et al 2020].

Mechanism of disease causation. The presence of many different truncating variants (nonsense and frameshift variants) throughout *DDX3X* suggests a disease-causing mechanism via haploinsufficiency. While missense variants could also have a loss-of-function effect, a dominant-negative mechanism may be operative. Of note, nearly all pathogenic missense variants are located within the helicase ATP-binding and helicase C-terminal domains.

Missense variants identified in male probands and unaffected heterozygous female relatives are thought to have a milder effect on protein function than the *de novo* variants found in female probands. To date, none of the *DDX3X de novo* pathogenic variants in females have been found in males, indicating that these variants may be lethal if present in the hemizygous state in a male.

Table 6. Notable *DDX3X* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001356.4 NP_001347.3	c.236G>A	p.Arg79Lys	Observed in the hemizygous state in an affected male & in the heterozygous state in an unaffected female relative [Snijders Blok et al 2015, Wang et al 2018, Lennox et al 2020]
	c.1084C>T	p.Val300Phe	
	c.1052G>A	p.Arg351Gln	
	c.898G>T	p.Arg362Cys	
	c.1399G>T	p.Ala467Ser	
	c.1127G>A	p.Arg376His	Observed in affected males w/*de novo* occurrence [Wang et al 2018, Nicola et al 2019]
	c.1486G>A	p.Val496Met	
	c.1702C>T	p.Pro568Ser	
	c.443+3A>T	p.?	
	c.1126C>T	p.Arg376Cys	Recurrent variant, observed *de novo* in 3 female probands [Snijders Blok et al 2015]
	c.1535_1536del	p.His512ArgfsTer5	Recurrent variant, observed *de novo* in 2 female probands [Snijders Blok et al 2015]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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