DDX3X Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK561282/

SummaryClinical 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, 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.

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DiagnosisFormal diagnostic criteria for DDX3X-related neurodevelopmental disorder (DDX3X-NDD) have not been established.Suggestive FindingsDDX3X-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 aggressionLanguage impairment, often with significant verbal dyspraxiaBorderline microcephalyDysmorphic 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].Figure 1. Facial profiles of females heterozygous for a de novo DDX3X pathogenic variant

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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 ventriclesPolymicrogyriaOther. Decreased white matter volume, decreased cingulum bundle density, diminished anterior commissure, small pons and small inferior cerebellar vermisEstablishing the DiagnosisFemale 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 TestingBecause 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

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Clinical CharacteristicsClinical DescriptionDDX3X-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 DisorderView in own windowFindingReport 1 [Snijders Blok et al 2015]Report 2 [Wang et al 2018]Report 3 [Lennox et al 2020]DD/ID38/38 (100%)28/28 (100%)84/84 (100%)Behavior issues20/38 (53%)6/28 (21%)See footnote 1.Hypotonia29/38 (76%)19/28 (68%)66/83 (80%)Hypertonia alone or a mixture of hyper- & hypotoniaSee footnote 2.2/12 (17%)38/83 (46%)Epilepsy/seizures6/38 (16%)NA17/83 (20%)Movement disorders17/38 (45%) 217/28 (61%)18/83 (22%)Microcephaly12/38 (32%)7/28 (25%)25/74 (34%)Vision issues13/38 (34%)9/28 (32%)32/82 (39%)RespiratoryNA5/28 (18%)NACongenital heart abnormalitiesNA5/7 3 (71%)11/82 (13%)Skeletal (scoliosis)4/38 (11%)NA8/82 (10%)Hearing impairment3/38 (8%)NA4/78 (5%)Precocious puberty5/38 (13%)NA7/82 (9%)Cleft lip/palate/uvula3/38 (8%)NANANA = not applicableNote: 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 echocardiogramDDX3X-Related Neurodevelopmental Disorder in FemalesDevelopmental 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

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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].

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Genetically Related (Allelic) DisordersNo 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 DiagnosisBecause 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].

ManagementEvaluations Following Initial DiagnosisTo 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 DisorderView in own windowSystem/ConcernEvaluationComment

Constitutional

Assess height, weight, & head circumference.Check for evidence of FTT.

Neurodevelopment

Neurodevelopmental assessment to identify delaysTo 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 pathologistAssessment of speech, language, & communication abilities

Neurologic

Neurologic eval for hypotonia, movement disorder, spasticityIf 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 cardiologistEspecially those w/FTT & feeding difficultiesConsider autonomic instability in those w/syncope, tachycardia, &/or orthostatic hypotension

Respiratory

Eval by pulmonologistPatients w/apnea, tachypnea, other respiratory manifestations, &/or respiratory failure

Gastrointestinal/

Feeding

Gastroenterology / nutrition / feeding team evalIf feeding difficulties, GERD, &/or FTT are present: Swallowing, feeding, & nutritional status assessment to determine safety of oral vs gastrostomy feedingMgmt of constipation, if present

Musculoskeletal

Orthopedics / physiatry / PT & OT evalEval for scoliosis if referred by pediatricianDetermination of DME needs

Eyes/Vision

Ophthalmologic examExam for refractive errors, cortical visual impairment, optic atrophy, coloboma, nystagmus, & strabismus

Hearing loss

Audiologic evalFor SNHL, conductive HL, or both

Genetic counseling

By genetics professionals 1To inform affected persons & families re nature, MOI, &

implications of DDX3X-NDD in order 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.

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 loss1. Medical geneticist, certified genetic counselor, certified advanced genetic nurseTreatment of ManifestationsTreatment should be targeted to individual needs.Table 4. Treatment of Manifestations in Individuals with DDX3X-Related Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Educational Issues.

Speech &

language

By speech-language pathologistUse of augmentative & alternative communication strategies as needed

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & fallsFor 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 neurologistMany 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 constipationStool softeners, prokinetics, osmotic agents or laxatives as needed

Abnormal vision

Standard treatment(s) as recommended by ophthalmologistCommunity 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

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 nursingConsider involvement in adaptive sports.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability1. 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 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. 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 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 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.SurveillanceTable 5. Recommended Surveillance for Individuals with DDX3X-Related Neurodevelopmental DisorderView

in own windowSystem/ConcernEvaluationFrequency

Constitutional

Measure height, weight, BMI, & head circumference.Annually or more frequently if FTT

Eyes

Ophthalmologic evalAnnually or more frequently as needed

Hearing

Audiologic assessmentReevaluate 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 hypotoniaPT follow up for gait abnormality

If needs are present, PT assessment at least 1x/mo recommendedOnce stable, gradually ↓ frequency to 1x/yr.

Monitor for scoliosis.Annually or more frequently as needed

Neurologic

Follow up for possible seizures or for seizure mgmtMonitor 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 psychologistAs needed

Miscellaneous/

Other

Assess family need for social work support, other local resources.Annually or more frequently as neededFTT = failure to thrive; PT = physical therapyEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo 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 DisorderView in own windowSystem/ConcernEvaluationComment

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Cardiovascular

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Respiratory

Eval by pulmonologistPatients w/apnea, tachypnea, other respiratory manifestations, &/or respiratory failure

Gastrointestinal/

Feeding

Gastroenterology / nutrition / feeding team evalIf feeding difficulties, GERD, &/or FTT are present: Swallowing, feeding, & nutritional status assessment to determine safety of oral vs gastrostomy feedingMgmt of constipation, if present

Musculoskeletal

Orthopedics / physiatry / PT & OT evalEval for scoliosis if referred by pediatricianDetermination of DME needs

Eyes/Vision

Ophthalmologic examExam for refractive errors, cortical visual impairment, optic atrophy, coloboma, nystagmus, & strabismus

Hearing loss

Audiologic evalFor SNHL, conductive HL, or both

Genetic counseling

By genetics professionals 1To inform affected persons & families re nature, MOI, & implications of DDX3X-NDD in order 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.

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 loss1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

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Treatment of ManifestationsTreatment should be targeted to individual needs.Table 4. Treatment of Manifestations in Individuals with DDX3X-Related Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Educational Issues.

Speech &

language

By speech-language pathologistUse of augmentative & alternative communication strategies as needed

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & fallsFor 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 neurologistMany 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 constipationStool softeners, prokinetics, osmotic agents or laxatives as needed

Abnormal vision

Standard treatment(s) as recommended by ophthalmologistCommunity 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

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 nursingConsider involvement in adaptive sports.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability1. 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 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. 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

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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.

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.

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 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 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.

SurveillanceTable 5. Recommended Surveillance for Individuals with DDX3X-Related Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationFrequency

Constitutional

Measure height, weight, BMI, & head circumference.Annually or more frequently if FTT

Eyes

Ophthalmologic evalAnnually or more frequently as needed

Hearing

Audiologic assessmentReevaluate 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 hypotoniaPT follow up for gait abnormality

If needs are present, PT assessment at least 1x/mo recommendedOnce stable, gradually ↓ frequency to 1x/yr.

Monitor for scoliosis.Annually or more frequently as needed

Neurologic

Follow up for possible seizures or for seizure mgmtMonitor 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 psychologistAs needed

Miscellaneous/

Other

Assess family need for social work support, other local resources.Annually or more frequently as neededFTT = failure to thrive; PT = physical therapy

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

DisorderView in own windowSystem/ConcernEvaluationFrequency

Constitutional

Measure height, weight, BMI, & head circumference.Annually or more frequently if FTT

Eyes

Ophthalmologic evalAnnually or more frequently as needed

Hearing

Audiologic assessmentReevaluate 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 hypotoniaPT follow up for gait abnormality

If needs are present, PT assessment at least 1x/mo recommendedOnce stable, gradually ↓ frequency to 1x/yr.

Monitor for scoliosis.Annually or more frequently as needed

Neurologic

Follow up for possible seizures or for seizure mgmtMonitor 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 psychologistAs needed

Miscellaneous/

Other

Assess family need for social work support, other local resources.Annually or more frequently as neededFTT = failure to thrive; PT = physical therapy

Recommended Surveillance for Individuals with DDX3X-Related Neurodevelopmental Disorder

System/ConcernEvaluationFrequency

Constitutional

Measure height, weight, BMI, & head circumference.Annually or more frequently if FTT

Eyes

Ophthalmologic evalAnnually or more frequently as needed

Hearing

Audiologic assessmentReevaluate 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 hypotoniaPT follow up for gait abnormality

If needs are present, PT assessment at least 1x/mo recommendedOnce stable, gradually ↓ frequency to 1x/yr.

Monitor for scoliosis.Annually or more frequently as needed

Neurologic

Follow up for possible seizures or for seizure mgmtMonitor for abnormal movements.

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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 psychologistAs needed

Miscellaneous/

Other

Assess family need for social work support, other local resources.Annually or more frequently as needed

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.

Follow up for possible seizures or for seizure mgmt

Monitor for abnormal movements.

FTT = failure to thrive; PT = physical therapy

FTT = failure to thrive; PT = physical therapy

FTT = failure to thrive; PT = physical therapy

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

Therapies Under InvestigationSearch 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 InheritanceDDX3X-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 TestingOnce 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.

Mode of InheritanceDDX3X-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.

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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.

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.

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.

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.

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.

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Prenatal Testing and Preimplantation Genetic TestingOnce 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 StreetSuite 115Wilmington 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: 202-387-1968Fax: 202-387-2193

www.aaidd.org

CDC - Developmental Disabilities

Phone: 800-CDC-INFOEmail: 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 KingdomPhone: +44 (0) 1883 723356Email: info@rarechromo.org

www.rarechromo.org

VOR: Speaking out for people with intellectual and developmental disabilities

Phone: 877-399-4867Email: info@vor.net

www.vor.net

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

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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 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.DDX3X-Related Neurodevelopmental Disorder: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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)

View in own window

300160DEAD-BOX HELICASE 3, X-LINKED; DDX3X

300958INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, SNIJDERS BLOK TYPE; MRXSSBMolecular PathogenesisDDX3X 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 VariantsView in own windowReference SequencesDNA NucleotideChangePredictedProtein ChangeComment [Reference]

NM_001356.4

NP_001347.3

c.236G>Ap.Arg79LysObserved 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>Tp.Val300Phec.1052G>Ap.Arg351Glnc.898G>Tp.Arg362Cysc.1399G>Tp.Ala467Src.1127G>Ap.Arg376HisObserved in affected males w/de novo occurrence [Wang et al 2018, Nicola

et al

2019]c.1486G>Ap.Val496Metc.1702C>Tp.Pro568Serc.443+3A>Tp.?c.1126C>Tp.Arg376CysRecurrent variant, observed de novo in 3 female probands [Snijders Blok et al

2015]c.1535_1536delp.His512ArgfsTer5Recurrent 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.

Table A.DDX3X-Related Neurodevelopmental Disorder: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

DDX3X

Xp11.4

ATP-dependent RNA helicase DDX3X

DDX3X @ LOVD

DDX3X

DDX3X

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DDX3X-Related Neurodevelopmental Disorder: Genes and Databases

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Notable DDX3X Pathogenic Variants

Reference SequencesDNA NucleotideChangePredictedProtein ChangeComment [Reference]

NM_001356.4

NP_001347.3

c.236G>Ap.Arg79LysObserved 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>Tp.Val300Phec.1052G>Ap.Arg351Glnc.898G>Tp.Arg362Cysc.1399G>Tp.Ala467Serc.1127G>Ap.Arg376HisObserved in affected males w/de novo occurrence [Wang et al 2018, Nicola et al 2019]c.1486G>Ap.Val496Metc.1702C>Tp.Pro568Serc.443+3A>Tp.?c.1126C>Tp.Arg376CysRecurrent variant, observed de novo in 3 female probands [Snijders Blok et al 2015]c.1535_1536delp.His512ArgfsTer5Recurrent 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

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