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# *ATN1*-Related Neurodevelopmental Disorder

Synonyms: *ATN1*-Related Neurodevelopmental Condition; CHEDDA (Congenital Hypotonia, Epilepsy, Developmental Delay, Digit Abnormalities)

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## Summary

### Clinical characteristics

*ATN1*-related neurodevelopmental disorder (*ATN1*-NDD) is characterized by developmental delay / intellectual disability. Other neurologic findings can include infantile hypotonia, brain malformations, epilepsy, cortical visual impairment, and hearing loss. Feeding difficulties, present in some individuals, may require gastrostomy support when severe; similarly, respiratory issues, present in some, may require respiratory support after the neonatal period. Distinctive facial features and hand and foot differences are common. Other variable findings can include cardiac malformations and congenital anomalies of the kidney and urinary tract (CAKUT). To date, 18 individuals with *ATN1*-NDD have been identified.

### Diagnosis/testing

The diagnosis of *ATN1*-NDD is established in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in a 16-amino-acid sequence of exon 7 in *ATN1* in which histidine is in every other position (His-X; HX motif), identified by molecular genetic testing.

### Management

*Treatment of manifestations:* There is no cure for *ATN1*-NDD. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in clinical genetics, neurology, ophthalmology, gastroenterology, cardiology, and general pediatrics.

*Surveillance:* Regular clinic visits are recommended due to the complexity of the medical and developmental issues. The frequency of visits should be decided on a person-by-person basis, but may need to be greater (e.g.,

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every 3-6 months) in the first two years of life, then stretching to visits every six months to one year when the child is stable.

*Agents/circumstances to avoid:* In individuals with MRI-confirmed stenosis of the craniocervical junction, caution is required when manipulating the head and neck for airway management.

## Genetic counseling

*ATN1-NDD* is an autosomal dominant condition typically caused by a *de novo* pathogenic variant. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo ATN1* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism. Given this risk, prenatal and preimplantation genetic testing may be considered.

# Diagnosis

No consensus clinical diagnostic criteria for *ATN1*-related neurodevelopmental disorder (*ATN1*-NDD) have been published.

## Suggestive Findings

*ATN1*-related neurodevelopmental disorder (*ATN1*-NDD) **should be considered** in individuals with the following clinical and brain MRI findings.

### Clinical Findings

**Common**

- Developmental delay (DD) or intellectual disability (ID) that is typically profound and rarely mild AND
- Any of the following presenting in infancy or childhood:
  - Generalized hypotonia of infancy
  - Severe feeding difficulties
  - Respiratory complications such as obstructive and/or central apnea
  - Epilepsy that is often consistent with a severe developmental and epileptic encephalopathy, and is either responsive or nonresponsive to anti-seizure medication
  - Central vision impairment, strabismus, and/or hypermetropia
  - Hearing impairment that is usually conductive, secondary to recurrent otitis media with effusions commonly requiring tympanostomy tubes; however, mild sensorineural hearing impairment has also been described
  - Hand and foot anomalies, most frequently overlapping toes, camptodactyly, and persistent fetal fingertip pads

**Less common**

- Congenital heart defects including atrial septal defects, patent foramen ovale, patent ductus arteriosus, and left or bilateral superior vena cava
- Congenital anomalies of the kidney and urinary tract (CAKUT), including renal hypoplasia or agenesis
- Genital anomalies such as bilateral or unilateral undescended testes
- Distinctive facial features including temporal alopecia (i.e., sparse hairline bitemporally), prominent ears, and a thin upper lip; see Figure 1 in Palmer et al [2019] (full text)

### Brain MRI

Structural brain anomalies are common, including cerebellar hypoplasia, abnormalities of the corpus callosum, perisylvian polymicrogyria, and absent falx cerebri. For more details see Table 3.

### Family History

Because *ATN1*-NDD is typically caused by a *de novo* pathogenic variant, all probands to date represent simplex cases (i.e., a single occurrence in a family).

## Establishing the Diagnosis

The diagnosis of *ATN1*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in a 16-amino-acid sequence of exon 7 in *ATN1* in which histidine is in every other position (His-X; HX motif), 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 *ATN1* variant of uncertain significance does not establish or rule out the diagnosis of this condition.

**Molecular genetic testing** in a child with developmental delay or an older individual with intellectual disability may begin with **chromosomal microarray analysis** (CMA). Other options include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *ATN1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability (ID) multigene panel** that includes *ATN1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of *ATN1*-NDD, some panels for intellectual disability may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID, whereas some multigene panels may not.

  **Genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 1.** Molecular Genetic Testing Used in *ATN1*-Related Neurodevelopmental Disorder

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *ATN1* | Sequence analysis [3] | All variants reported to date [4] |
| | Gene-targeted deletion/duplication analysis [5] | None reported to date |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on allelic variants detected in this gene.
*3.* 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.* All variants reported to date are *de novo ATN1* missense or in-frame deletions/duplications within a 16-amino-acid sequence in exon 7 in which histidine is in every other position (His-X; HX motif) [Palmer et al 2019, Palmer et al 2021].
*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.

# Clinical Characteristics

## Clinical Description

*ATN1*-related neurodevelopmental disorder (*ATN1*-NDD) is characterized by developmental delay / intellectual disability. Other neurologic findings can include brain malformations, epilepsy, cortical visual impairment, infantile hypotonia, and hearing loss. Feeding difficulties, present in some individuals, may require gastrostomy support when severe; similarly, respiratory issues, present in some, may require respiratory support after the neonatal period. Distinctive facial and limb features are commonly reported. Other variable findings can include cardiac malformations and congenital anomalies of the kidney and urinary tract (CAKUT).

To date, 18 individuals have been identified with *ATN1*-NDD [Palmer et al 2019, Palmer et al 2021, Shiyue et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

**Table 2.** Select Features of *ATN1*-Related Neurodevelopmental Disorder

| Feature | | # of Persons w/Feature | Comment |
|---|---|---|---|
| **DD/ID** | **Mild** | 1/18 | |
| | **Moderate** | 0/18 | |
| | **Profound** | 17/18 | |
| **Hypotonia** | | 17/18 | |
| **Respiratory difficulties** | | 13/18 | 9/18: Obstructive sleep apnea<br>3/18: Central sleep apnea |
| **Feeding difficulties** | | 12/18 | 9/18: Gastrostomy feeding<br>8/18: Dysphagia<br>9/18: GERD |
| **Epilepsy** | | 9/18 | |
| **Cortical visual impairment** | | 9/18 | |
| **Hearing loss** | | 9/18 | |
| **Ophthalmologic involvement** | | 7/18 | Strabismus, hypermetropia, microphthalmia |

*Table 2. continued from previous page.*

| Feature | # of Persons w/Feature | Comment |
|---|---|---|
| **Cardiac malformation** | 8/18 | |
| **Genital anomalies** | 4/18 | Cryptorchidism |
| **CAKUT** | 2/18 | Renal hypoplasia or agenesis |

Based on Palmer et al [2019], Palmer et al [2021], and Shiyue et al [2022]
CAKUT= congenital anomalies of the kidney and urinary tract; DD/ID = developmental delay / intellectual disability; GERD = gastroesophageal reflux disease

**Developmental delay (DD) and intellectual disability (ID).** Most individuals with *ATN1*-NDD have profound developmental delay. Most individuals have significant gross motor delay, ranging from lack of head control to the ability to walk a few steps unaided. The exception is one girl (age 26 months) with mild developmental delay [Palmer et al 2021].

Fine motor skills range from inability to grasp toys / small objects or bring hands to the midline to the ability to finger feed. In contrast, the girl with milder features has fine motor skills that are just below average.

While some affected individuals can speak one or two words and communicate in gestures, most are nonverbal with no clear words. To date communication devices have not been reported to be particularly helpful, consistent with a profound developmental delay; however, caregivers thought that two individuals had more advanced receptive skills, and the girl with milder developmental delay was able to talk in short sentences at the age of 26 months.

**Hypotonia.** The majority (11/18) had persistent global hypotonia. Over time, six developed appendicular hypertonia/spasticity in the presence of central hypotonia. Only one child, the girl with mild developmental delay, has continued to have normal tone over time.

**Feeding difficulties** appear to be secondary to a combination of gastroesophageal reflux disease, low tone, and dysphagia. Eight individuals required gastrostomy feeds as a result of both poor feeding and increased risk of aspiration. Two of the eight were able to start oral feeding, and one other was preparing to try oral feeding. One individual relied on total parenteral nutrition at age one year because of severe gut motility issues.

**Cortical visual impairment** was present in eight individuals.

**Sensorineural hearing loss** was present in four of the 16 of individuals evaluated for this finding.

**Epilepsy.** In its most severe form, *ATN1*-NDD can be described as a neonatal- or infantile-onset developmental and epileptic encephalopathy characterized by seizures resistant to multiple anti-seizure medications (ASMs) associated with developmental delay and intellectual disability.

One individual had Lennox-Gastaut syndrome.

While seizures were controlled in many individuals with a single ASM, others required two or more ASMs to achieve seizure control.

**Respiratory/sleep difficulties** can require respiratory support after the neonatal period. Of the 18 individuals who experienced respiratory difficulties, nine had obstructive sleep apnea; of these, three also had central sleep apnea. Three individuals with obstructive sleep apnea required tracheostomy.

Other findings contributing to respiratory difficulty in some individuals included Pierre Robin sequence, micrognathia, laryngomalacia, and asthma.

**Neuroimaging.** While some individuals have a normal brain MRI, major structural brain abnormalities are common (see Table 3).

Normal brain imaging findings appear to correlate with better neurodevelopmental outcome. In the five individuals with no major structural abnormalities, motor skills in four ranged from crawling, pulling to stand, taking a few steps, or, in one instance, walking unassisted, and at least four were able to grasp objects. Three individuals had no clear words, one had single words, and one speaks in short sentences.

By contrast, of the 13 individuals with major structural abnormalities, two could stand with support, whereas the others had minimal motor skills (range: lack of head control to inability to roll to sitting with support); 12 individuals were nonverbal and one had a few single words.

**Table 3.** *ATN1*-Related Neurodevelopmental Disorder: Literature Review of Brain Imaging and Developmental Features

| Individual [Reference] | Imaging Findings | Age at Last Review | Development | Epilepsy (Seizure Control) |
|---|---|---|---|---|
| 1 [Palmer et al 2019] | Parenchymal atrophy, unilateral periventricular leukomalacia, left cerebellar hyperintensity | 3 yrs | No head control, cannot roll; nonverbal | Lennox Gastaut syndrome, onset age 12 mos |
| 2 [Palmer et al 2019] | Perisylvian polymicrogyria, parenchymal atrophy, thin corpus callosum, absent falx cerebri | 1 yr | Rolls to side, coos | No seizures |
| 3 [Palmer et al 2019] | Normal | 5 yrs | Walks a few steps unaided, holds small objects, speaks single words | No seizures |
| 4 [Palmer et al 2019] | Normal | 7 yrs | Sits w/support, grasps objects; nonverbal | Infantile spasms (control w/2 ASMs) |
| 5 [Palmer et al 2019] | Perisylvian polymicrogyria, thin corpus callosum, partially absent falx cerebri, parenchymal atrophy | 9 yrs | Immobile, nonverbal | (control w/ monotherapy) |
| 6 [Palmer et al 2019] | Vermian hypoplasia | 4 yrs | Sits w/support; nonverbal | Neonatal-onset DEE (intractable to ASM) |
| 7 [Palmer et al 2019] | Perisylvian polymicrogyria, thin corpus callosum, absent falx cerebri | 5 yrs | Sits w/support, grasps objects, babbles | DEE, onset age 7 mos (control w/ monotherapy) |
| 8 [Palmer et al 2019] | Polymicrogyria of right sylvian fissure, vermian hypoplasia, thin corpus callosum | 2 mos | No motor ability; nonverbal | No seizures |
| 9 [Palmer et al 2021] | Normal | 3 yrs, 6 mos | Crawls & pulls to stand, no clear words | No seizures |
| 10 [Palmer et al 2021] | Normal (mild prominence of subarachnoid fluid compartment) | 3 yrs, 6 mos | Sits w/minimal support, commando crawls, able to finger feed; no clear words but will yell to get parents' attn | Diagnosed at 3 yrs, 6 mos (control w/ monotherapy) |
| 11 [Palmer et al 2021] | Malformations consistent w/ Dandy-Walker spectrum (mild) | 2 yrs, 6 mos | Sits unassisted, good head control, stands w/support, uses wheelchair for mobility; babbles & coos | Infantile spasms (control w/ monotherapy) |
| 12 [Palmer et al 2021] | Normal | 2 yrs, 2 mos | Walking independently, fine motor improved to just below avg w/early intervention; mild expressive language delay | No seizures |

*Table 3. continued from previous page.*

| Individual [Reference] | Imaging Findings | Age at Last Review | Development | Epilepsy (Seizure Control) |
|---|---|---|---|---|
| 13 [Palmer et al 2021] | Cerebral parenchymal atrophy, cerebellar vermian hypoplasia, thin corpus callosum | 17 yrs | Head control but unable to sit w/o support; nonverbal | No seizures |
| 14 [Palmer et al 2021] | Pontine hypoplasia, dysplastic tectum, thin corpus callosum, global cerebral brain atrophy, prominent subarachnoid spaces & ventricles | 2 yrs | Does not have independent head control against gravity; no grasping or holding toys; nonverbal, can make whimpering sounds when upset | Diagnosed as neonate |
| 15 [Palmer et al 2021] | Generalized parenchymal volume loss, thin corpus callosum, enlargement of prepontine & suprasellar cisterns, small hippocampi, & other abnormalities | 3 yrs, 3 mos | Can roll over, unable to sit w/o support, limited fine motor skills; nonspecific verbalizations | Onset 6 mos, → DEE by 16 mos (control w/ multiple ASMs) |
| 16 [Palmer et al 2021] | Dysgenesis of corpus callosum, callosal lipoma, hypoplasia of inferior vermis of cerebellum, dysmorphic brain stem w/small pons | 6 mos | Cannot roll, limited head control, can bring hands to midline; nonverbal | No seizures |
| 17 [Palmer et al 2021] | Asymmetric cerebral hemisphere, large lateral ventricle, atrophy | 13 yrs, 6 mos | Sitting, stands w/aid, uses wheelchair for mobility, grasps objects; few words, communicates w/gestures | One seizure w/febrile illness at age 12 yrs |
| 18 [Shiyue et al 2022] | Hypoplasia of left cerebellar hemisphere & delayed myelination | 7 mos, 16 days | Can raise head, unable to sit independently or grasp objects; no words or clear babble | No seizures |

ASM = anti-seizure medication; DEE = developmental and epileptic encephalopathy

### Other associated features

- **Behavioral problems.** Sleep disturbances, which likely are multifactorial, are the only behavioral issues reported.
- **Growth.** While weight gain is suboptimal secondary to feeding issues in some individuals, growth parameters are usually within the normal range.
- **Ophthalmologic involvement** includes strabismus, hypermetropia, microphthalmia, corneal leukoma, and optic nerve hypoplasia.
- **Hearing impairment** includes both sensorineural hearing loss and conductive hearing loss. Recurrent otitis media with effusions commonly requires tympanostomy tubes. Hearing impairment ranges from mild/moderate to profound.
- **Constipation**, a significant issue in six of 18 individuals, has required medical management (see Table 5).
- **Musculoskeletal**
  - Scoliosis was reported in six of 18 individuals attributed to neuromuscular involvement rather than vertebral anomalies; however, no information is available on need for specific intervention.
  - Hip dysplasia was reported in five of 18 individuals; no information is available on the need for specific intervention.
  - Cervical stenosis was reported in two of six individuals on cervical spine MRI; no information is available on the need for specific intervention other than caution when manipulating the head and neck for airway management (see Agents/Circumstances to Avoid).

- Orofacial clefting: cleft palate (2 individuals); Pierre Robin sequence (1 individual), micrognathia (1 individual)
- Arthrogryposis (1 individual)

- **Other congenital anomalies**
  - Cardiac anomalies, including atrial and ventricular septal defects, anomalous drainage of the great veins, coarctation of the aorta, patent ductus arteriosus and foramen ovale
  - Urogenital anomalies, including unilateral renal hypoplasia or agenesis, vesicoureteric reflux, and cryptorchidism
  - Anorectal anomalies, including anteriorly placed anus

**Prognosis.** It is unknown whether life span in *ATN1*-NDD is abnormal. One individual is alive at age 18 years, demonstrating that survival into adulthood is possible [Palmer et al 2021]. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

## Genotype-Phenotype Correlations

No consistent genotype-phenotype correlations have been identified.

Although more data are required, it is notable that the unique *ATN1* variant observed in one individual with a milder phenotype (see Clinical Description) caused a duplication of the amino acids histidine and leucine within the HX repeat motif rather than the typically observed indel or single-nucleotide variant [Palmer et al 2021].

## Nomenclature

*ATN1*-NDD is also referred to as *ATN1*-related neurodevelopmental condition [Author, personal communication].

## Prevalence

To date 18 individuals have been reported with *ATN1*-NDD. The actual prevalence is unknown. While it is thought to be rare, it is probably underrecognized and underreported, as it has only recently been described and the clinical findings are nonspecific.

# Genetically Related (Allelic) Conditions

**Pallister-Killian syndrome (PKS)** (OMIM 601803). Tissue-limited mosaicism of tetrasomy of the short arm of chromosome 12, including *ATN1*, is associated with PKS.

- Similar to *ATN1*-related neurodevelopmental disorder (*ATN1*-NDD), PKS is associated with temporal alopecia, severe developmental delay and cognitive impairment, epilepsy, hypotonia, and multiple congenital anomalies (including high arched or cleft palate, polymicrogyria, limb and genitourinary anomalies, and congenital heart defects).
- Unlike *ATN1*-NDD, PKS is not associated with skin pigmentation differences, diaphragmatic hernia, or overlapping toes/fingers.

Of note, the identification of mosaic tetrasomy of 12p requires chromosome analysis of specific tissues; thus, routine molecular genetic testing of a blood sample would not be expected to suggest a diagnosis of PKS.

**Dentatorubral-pallidoluysian atrophy (DRPLA).** Heterozygous pathogenic CAG expansions in exon 5 of *ATN1* are associated with DRPLA. DRPLA is a progressive condition of ataxia, myoclonus, epilepsy, and progressive intellectual deterioration in children and ataxia, choreoathetosis, and dementia or character changes in adults. Onset ranges from before age one year to age 72 years; mean age of onset is 31.5 years. The clinical

presentation varies depending on the age of onset. The cardinal features in adults are ataxia, choreoathetosis, and dementia. Cardinal features in children are progressive intellectual deterioration, behavioral changes, myoclonus, and epilepsy.

# Differential Diagnosis

**Molecular genetic testing.** Because the phenotypic features associated with *ATN1*-related neurodevelopmental disorder (*ATN1*-NDD) are not sufficient to diagnose this condition, all genes associated with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

**Genomic testing.** Pallister-Killian syndrome – a chromosomal condition associated with mosaic tetrasomy of the 12p region that includes *ATN1* – has phenotypic overlap with *ATN1*-NDD and should be considered in the differential diagnosis (see Genetically Related Conditions).

# Management

Although no clinical practice guidelines for *ATN1*-related neurodevelopmental disorder (*ATN1*-NDD) have been published, Palmer et al [2021] have proposed management recommendations.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ATN1*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with *ATN1*-Related Neurodevelopmental Disorder

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Constitutional** | Assess length, weight, head circumference. | |
| **Development** | Developmental assessment | • To incl motor, adaptive, cognitive, & speech/language eval<br>• Eval for early intervention program / IEP |
| **Neurologic** | Neurologic eval | • To incl brain MRI if not performed at time of diagnosis<br>• Consider EEG if seizures are a concern.<br>• Assess for cortical visual impairment. |
| **Speech/Language** | By speech-language pathologist | To assess need for speech therapy &/or alternative means of communication |
| **Respiratory** | Pediatric assessment | • Screening for central & obstructive apnea in neonatal period<br>• Consider referral to sleep specialist &/or respiratory physician if respiratory &/or sleep symptoms occur. |
| **Feeding** | Gastroenterology / nutrition / feeding team eval | • To incl eval of aspiration risk & nutritional status<br>• Consider eval for gastric tube placement in persons w/dysphagia &/or aspiration risk. |
| **Cardiovascular** | Pediatric assessment | • To incl EKG & echocardiogram<br>• Refer to cardiologist if concerns are identified. |
| **Orthopedics** | Eval by orthopedist | To incl assessment for:<br>• Craniocervical junction stenosis, preferably by spine MRI<br>• Scoliosis, hip dislocation |

*Table 4. continued from previous page.*

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Activities of daily living** | Physical medicine & rehab / PT & OT eval | To incl assessment of:<br>• Gross motor & fine motor skills<br>• Mobility, activities of daily living, & need for adaptive devices<br>• Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) |
| **Craniofacial** | Pediatric assessment | To screen for orofacial clefting / micrognathia in neonatal period & refer to maxillofacial specialist if there are concerns |
| **Genitourinary** | Pediatric assessment | • To incl renal/abdominal ultrasound to assess for renal agenesis or hypoplasia<br>• Assess for cryptorchidism. |
| **Vision** | Ophthalmologic eval | To assess for ↓ vision, abnormal ocular movement, best corrected visual acuity, refractive errors, & strabismus |
| **Hearing** | Audiologic eval | Assess for hearing loss. |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & their families re nature, MOI, & implications of *ATN1-NDD* to facilitate medical & personal decision making |
| **Family support & resources** | | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support;<br>• Home nursing referral. |

IEP = individualized education plan; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

There is no cure for *ATN1*-NDD.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in clinical genetics, neurology, ophthalmology, gastroenterology, cardiology, and general pediatrics (see Table 5).

**Table 5.** Treatment of Manifestations in Individuals with *ATN1*-Related Neurodevelopmental Disorder

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **DD/ID** | See Developmental Delay / Intellectual Disability Management Issues. | |
| **Epilepsy** | Standardized treatment w/ASM by experienced neurologist | • Many ASMs may be effective; none has been demonstrated effective specifically for this condition.<br>• Education of parents/caregivers [1] |
| **Speech/Language** | By speech-language pathologist | Early intervention |
| **Respiratory** | • May require respiratory support, esp in neonatal period.<br>• Consider jaw distraction surgery if micrognathia is a component of obstructive sleep apnea. | Use caution when manipulating head & neck for airway management (e.g., intubation) if cervical spine stenosis has not yet been evaluated. |
| **Feeding** | • Feeding therapy<br>• Gastrostomy tube placement may be required for persistent feeding issues & aspiration risk. | Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia |

*Table 5. continued from previous page.*

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Bowel dysfunction** | For constipation: stool softeners, prokinetics, osmotic agents, &/or laxatives as needed | |
| **Cardiovascular** | • May not require treatment<br>• Cardiology referral if structural heart defects detected or if otherwise indicated | Consider need for / risks & benefits of surgery. |
| **Musculoskeletal** | • Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls<br>• For severe stenosis of the craniocervical junction: mgmt by neurosurgery &/or orthopedic specialists w/special attn during general anesthesia | Consider need for positioning & mobility devices, disability parking placard. |
| **Ophthalmologic involvement** | By ophthalmologist | Treatment of refractive errors &/or strabismus |
| **Central visual impairment** | No specific treatment | Early intervention program to stimulate visual development |
| **Hearing** | Hearing aids may be helpful; per otolaryngologist. | Community hearing services through early intervention or school district |
| **Family/Community** | • Ensure appropriate social work involvement to connect families w/local resources, respite, & support.<br>• Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. | • Ongoing assessment of need for palliative care involvement &/or home nursing<br>• Consider involvement in adaptive sports or Special Olympics. |

ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy

*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 Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

**Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

**Ages 3-5 years.** In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:

- An IEP provides specially designed instruction and related services to children who qualify.
- IEP services will be reviewed annually to determine whether any changes are needed.
- Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

## Surveillance

Regular clinic visits are recommended because of the complexity of the medical and developmental issues associated with *ATN1*-NDD. The frequency of visits should be decided on a person-by-person basis, but may need to be greater (e.g., every 3-6 months) in the first two years of life, then stretching to visits every six months to one year when the child is stable.

**Table 6.** Recommended Surveillance for Individuals with *ATN1*-Related Neurodevelopmental Disorder

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Development** | Monitor developmental progress & educational needs. | At each visit |
| **Epilepsy** | Monitor those w/seizures as clinically indicated. | |
| **Respiratory** | Monitor for evidence of aspiration, respiratory insufficiency. | |
| **Feeding** | • Measurement of growth parameters<br>• Eval of nutritional status & safety of oral intake | |
| **Gastrointestinal** | Monitor for constipation. | |
| **Cardiovascular** | Per treating cardiologist | Per treating cardiologist |
| **Musculoskeletal** | • Orthopedics /PT & OT eval for development &/or progression of contractures &/or need for additional adaptive devices<br>• Screening for craniocervical junction stenosis & referral to neurosurgical team for advice on surveillance & mgmt | At each visit |
| **Craniofacial** | Eval of cleft lip/palate by treating craniofacial team | Per treating craniofacial team |
| **Genitourinary** | Monitor for signs/symptoms of urinary tract infections. | At each visit |
| | Other monitoring per treating urologist | Per treating urologist |

*Table 6. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Vision** | Per treating ophthalmologist or intervention program | Individualized depending on health needs |
| **Hearing** | Per treating audiologist or intervention program | |
| **Family/Community** | Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning). | At each visit |

OT = occupational therapy; PT = physical therapy

## Agents/Circumstances to Avoid

In individuals with MRI-confirmed stenosis of the craniocervical junction, caution is required when manipulating the head and neck for airway management.

## 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 condition.

# 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

*ATN1*-related neurodevelopmental disorder (*ATN1-NDD*) is an autosomal dominant condition typically caused by a *de novo* pathogenic variant.

## Risk to Family Members

**Parents of a proband**

- All probands reported to date with *ATN1*-NDD whose parents have undergone molecular genetic testing have the condition as a result of a *de novo ATN1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the *ATN1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *ATN1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

**Offspring of a proband**

- To date, individuals with *ATN1*-NDD are not known to have had children; however, many are not yet of reproductive age.
- Each child of an individual with *ATN1*-NDD would have a 50% chance of inheriting the *ATN1* pathogenic variant.

**Other family members.** Given that all probands with *ATN1*-NDD reported to date have the condition as a result of a *de novo ATN1* pathogenic variant, the risk to other family members is presumed to be low.

## Related Genetic Counseling Issues

**Family planning**

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

## Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo ATN1* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

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

# Resources

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

- **American Epilepsy Society**

  www.aesnet.org

- **Canadian Epilepsy Alliance**

  Canada

  **Phone:** 1-866-EPILEPSY (1-866-374-5377)

  www.canadianepilepsyalliance.org

- **Epilepsy Canada**

Canada

**Phone:** 877-734-0873

**Email:** epilepsy@epilepsy.ca

www.epilepsy.ca

- **Epilepsy Foundation**

  **Phone:** 301-459-3700

  **Fax:** 301-577-2684

  www.epilepsy.com

- **Human Disease Gene Website Series - Registry**

  ATN1

- **Simons Searchlight Registry**

  *Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.*

  **Phone:** 855-329-5638

  **Fax:** 570-214-7327

  **Email:** coordinator@simonssearchlight.org

  www.simonssearchlight.org

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** ATN1-Related Neurodevelopmental Disorder: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *ATN1* | 12p13.31 | Atrophin-1 | ATN1 database | ATN1 | ATN1 |

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 ATN1-Related Neurodevelopmental Disorder (View All in OMIM)

| | |
|---|---|
| 607462 | ATROPHIN 1; ATN1 |
| 618494 | CONGENITAL HYPOTONIA, EPILEPSY, DEVELOPMENTAL DELAY, AND DIGITAL ANOMALIES; CHEDDA |

## Molecular Pathogenesis

*ATN1* encodes the protein atrophin-1 (ATN1), a member of a class of evolutionarily conserved transcriptional corepressors involved in nuclear signaling [Palmer et al 2019]. *ATN1*-related neurodevelopmental disorder (*ATN1*-NDD) is caused by heterozygous *ATN1* pathogenic variants in an evolutionarily conserved region of exon 7 that codes for a histidine-rich amino acid motif of eight HX repeats (in which H represents histidine and X represents any other amino acid). This motif is thought to have specific zinc-binding properties that are disrupted by *ATN1* pathogenic variants that affect the spacing of these repeats.

Although the role of ATN1 is incompletely understood, it appears to be a key nuclear transcriptional regulator involved in organ development in which the HX repeat motif plays a critical role [Palmer et al 2019].

**Mechanism of disease causation.** It is unlikely that *ATN1* pathogenic variants cause simple haploinsufficiency of *ATN1* given that the databases gnomAD and BRAVO (which exclude individuals with severe childhood-onset conditions) have reports of healthy individuals with heterozygous stop-gain, frameshift, and canonic splice *ATN1* variants. Given that the pathogenic variants causing *ATN1*-NDD cluster in the 16-amino-acid His-X repeat in exon 7, it is likely that disruption of this motif affects critical functioning of the protein.

***ATN1*-specific laboratory technical considerations.** To date, pathogenic variants causing *ATN1*-NDD have only been reported to affect the 16-amino-acid repeat in exon 7 (His-X).

# Chapter Notes

## Author Notes

Dr Elizabeth Palmer (elizabeth.palmer@unsw.edu.au) and Professor Fowzan Alkuraya (falkuraya@kfshrc.edu.sa) are actively involved in clinical research regarding individuals with *ATN1*-NDD. They would be happy to communicate with persons who have any questions regarding diagnosis of *ATN1*-NDD or other considerations.

Contact Dr Elizabeth Palmer and Professor Fowzan Alkuraya to inquire about review of *ATN1* variants of uncertain significance in patients who do not have the typical features of DRPLA.

Dr Elizabeth Palmer and Professor Alkuraya are also interested in hearing from clinicians treating families affected by CHEDDA (*c*ongenital *h*ypotonia, *e*pilepsy, *d*evelopmental delay, *d*igit *a*bnormalities) in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this condition.

## Acknowledgments

We would like to thank the patients, families, and clinicians who have participated in our previous publications delineating this condition.

## Revision History

- 25 August 2022 (bp) Review posted live
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