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Ataxia-Telangiectasia

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Summary

Clinical characteristics

The phenotypic spectrum of ataxia-telangiectasia (A-T), a multisystem disorder, is a continuum ranging from classic A-T at the severe end and variant A-T at the milder end. Nonetheless, distinguishing between classic A-T and variant A-T on this spectrum helps understand differences in disease course, rate of progression, and life expectancy.

Classic A-T is characterized by childhood onset of progressive neurologic manifestations (initially cerebellar ataxia, followed typically by extrapyramidal involvement and peripheral sensorimotor neuropathy), immunodeficiency (variably associated with abnormalities of humoral immunity, cellular immunity, or combined immune deficiency), pulmonary disease (resulting from recurrent infections, immune deficiency, aspiration, interstitial lung disease, and neurologic abnormalities), and increased risk of malignancy. Although it is generally accepted that intellectual disability is not common in A-T, disturbances in cerebellar as well as non-cerebellar brain areas and networks may result in cognitive deficits. Increased sensitivity to ionizing radiation (x-ray and gamma ray) can result in severe side effects from such treatments. Life expectancy is significantly reduced due to cancer, pulmonary disease, and infections.

Variant A-T has a significantly milder disease course. While cerebellar ataxia can be absent, extrapyramidal movement disorders are common (typically dystonia and dystonic tremor) and most individuals have manifestations of axonal sensorimotor polyneuropathy. In contrast to classic A-T, immune function is generally normal, respiratory infections are not increased, and pulmonary disease is not a major feature. However, risk of developing malignancies is increased, particularly in premenopausal females who have an increased risk of developing breast cancer and hematologic malignancies.

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Diagnosis/testing

The diagnosis of A-T is established in a proband with suggestive findings and biallelic pathogenic variants in *ATM* identified by molecular genetic testing. Of note, newborn screening (NBS) for severe combined immunodeficiency (SCID) that relies on the identification of reduced T-cell receptor excision circle (TREC) levels in blood spots most likely identifies about 50% of children with classic A-T, who require immediate subspecialty evaluation at a center with expertise in the diagnosis of SCID, its causes, and its treatment.

Management

Treatment of manifestations: Supportive care to improve quality of life, maximize function, and reduce complications ideally involves multidisciplinary care by specialists in (pediatric) neurology, pulmonology, immunology, pediatrics (for children) and internal medicine (for adults), rehabilitation medicine, and professionals in physical therapy, speech-language therapy, occupational therapy, and nutrition. For specific issues care may be provided by specialists in oncology, medical genetics, endocrinology, orthopedics, dermatology, mental health, and social work.

Surveillance: Routine evaluations by treating clinicians is necessary to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations. Recommended surveillance is the same for individuals with classic A-T and variant A-T, with the exception that individuals who do not have evidence of lung disease at the time of initial diagnosis do not require annual screening for pulmonary disease.

Agents/circumstances to avoid: Rubella vaccination should be avoided in individuals with severe immunodeficiency as it can possibly increase the risk for granulomas; ionizing radiation (x-ray and gamma ray) is contraindicated, due to increased sensitivity; and radiation therapy is contraindicated because increased radiosensitivity may lead to very severe complications.

Evaluation of relatives at risk: It is appropriate to offer molecular genetic testing for the familial *ATM* pathogenic variants to apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible sibs with biallelic *ATM* pathogenic variants who would benefit from prompt initiation of treatment of manifestations of A-T, surveillance for malignancy, and awareness of agents/circumstances to avoid; and family members who are heterozygous for an *ATM* pathogenic variant and who would benefit from age-appropriate intensified surveillance for breast cancer.

Therapies under investigation: Use of intra-erythrocyte dexamethasone; the effects of nicotinamide riboside (a form of vitamin B_3) on ataxia scores and immunoglobulin levels; gene therapy with antisense oligonucleotides in a single case study; effect of allogenic hematopoietic stem cell transplantation on neurologic functioning.

Genetic counseling

A-T is caused by biallelic pathogenic variants in *ATM* and inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ATM* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and having A-T, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial *ATM* pathogenic variants. Although individuals heterozygous for an *ATM* pathogenic variant are not at risk for A-T, their risk of developing cancer is increased compared to that of the general population (in particular, heterozygous females have an increased risk of developing breast cancer). Once the *ATM* pathogenic variants have been identified in an affected family member, heterozygote testing for at-risk relatives and prenatal and preimplantation genetic testing for A-T are possible.

GeneReview Scope

Ataxia-Telangiectasia: Phenotypic Spectrum

Severity	Key Differences In:			
	Neurologic decline	Immunodeficiency & pulmonary disease	Age at typical first occurrence of malignancy	Life expectancy
Classic A-T	Childhood onset	Usually present	Childhood (median age: 12.5 yrs)	Significantly reduced due to cancer, pulmonary disease, & infections
Variant A-T	Less progressive	Typically absent	Adulthood	Longer than in classic A-T

A-T = ataxia-telangiectasia

Diagnosis

No consensus clinical diagnostic criteria for ataxia-telangiectasia (A-T) have been published.

The two scenarios in which A-T may be considered are abnormal newborn screening for severe combined immunodeficiency and a symptomatic proband.

Scenario 1: Abnormal Newborn Screening for Severe Combined Immunodeficiency

Newborn screening (NBS) for severe combined immunodeficiency (SCID), a severe but treatable immunologic disorder, relies on the identification of reduced T-cell receptor excision circle (TREC) levels in blood spots.

Classic A-T. Newborns with classic A-T (who are still asymptomatic and undiagnosed) may have low TREC levels comparable to the TREC levels of newborns with SCID and, thus, may have a positive NBS. NBS for SCID most likely identifies about 50% of children with classic A-T [Mallott et al 2013]. Note: Infants with classic A-T who have an abnormal NBS result also demonstrate the laboratory findings suggestive of classic A-T.

Variant A-T. Since variant A-T is not associated with immunodeficiencies, NBS for SCID does not detect variant A-T.

Note: This chapter specifically focuses on A-T; for potential causes of decreased TREC levels in NBS other than classic A-T and SCID, see Puck [2019].

Newborns with an abnormal NBS for SCID **require immediate subspecialty immunology evaluation** at a center with expertise in the diagnosis of SCID, its genetic causes, and its treatment protocols, including hematopoietic stem cell transplantation (HSCT). (See Management, Evaluations Following Initial Diagnosis.)

Scenario 2: Symptomatic Proband with Findings Suggestive of A-T

Classic A-T

Clinical findings

- Cerebellar ataxia (the presenting feature in most individuals)
- Extrapyramidal movement disorders (chorea, myoclonus, dystonia, tremor)
- Dysarthria
- Eye movement disorders (gaze-evoked nystagmus, oculomotor apraxia *)
- Oculocutaneous telangiectasias *

* In most individuals with classic A-T, abnormal eye movements and telangiectasias only occur some years after disease onset. Motor and sensory neuropathy generally develop at the end of the first decade of life.

Laboratory findings

- **Serum concentration of alpha-fetoprotein (AFP)** is the most important blood biomarker in individuals with classic A-T. In all individuals with classic A-T, serum AFP is elevated (>10 ng/mL, range: 200-1,000 ng/mL) [Waldmann & Mcintire 1972, Stray-Pedersen et al 2007]. Note: Because serum AFP concentrations are high at birth in all persons and only reach normal values around age two years, it is unreliable as a diagnostic marker in young children [Schieving et al 2014].
- **Immunologic**
  - **Serum levels of immunoglobulins.** Especially IgA, IgG, and IgG subclasses (in particular IgG2 and IgG4) are decreased [Nowak-Wegrzyn et al 2004]. Approximately 10% of individuals with classic A-T have IgA and IgG deficiency with normal or raised IgM concentration, the so-called hyper IgM phenotype [Noordzij et al 2009].
  - **Immunophenotype.** Numbers of B and T cells, in particular naïve $CD4^+$ and CD8 cells, may be decreased [Nowak-Wegrzyn et al 2004, Driessen et al 2013].
  - **Lymphocyte functional tests.** Impairment of lymphocyte function can be present in individuals with A-T. In particular, a restricted response to antigens and abnormal B-cell class switching may be found [Staples et al 2008].

Brain MRI findings. The classic finding, cerebellar atrophy affecting both the cerebellar vermis and the hemispheres [Tavani et al 2003], is usually not present when the first clinical manifestations occur [Lin et al 2014].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). A history of cancer in a sib or parent (particularly of breast cancer in the mother of the proband and/or a severe reaction to chemotherapy and/or radiation in the mother) may suggest the diagnosis of A-T. Absence of a known family history of A-T or cancer does not preclude the diagnosis.

Variant A-T

Clinical findings

- Cerebellar ataxia
- Extrapyramidal movement disorders (dystonia, chorea, myoclonus, tremor)
- Dysarthria
- Peripheral neuropathy; anterior horn disease in a minority of individuals
- Cancer in a young individual with an apparently static neurologic (motor) disorder ("cerebral palsy")

Laboratory findings

- **Serum concentration of AFP.** Although serum AFP levels are generally increased in variant A-T [Waldmann & Mcintire 1972], they are not as high as those observed in classic A-T and can eventually become normal [van Os et al 2019b].
- **Immunologic.** No suggestive immunologic findings

Brain MRI findings. Although brain MRI shows atrophy of both the cerebellar vermis and hemispheres in most individuals with variant A-T [Tavani et al 2003], it can also be normal [Schon et al 2019].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). A history of cancer in a sib or parent (particularly of breast cancer in the mother of the proband

and/or a severe reaction to chemotherapy and/or radiation in the mother) may suggest the diagnosis of A-T. Absence of a known family history of A-T or cancer does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of A-T **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ATM* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of biallelic *ATM* variants of uncertain significance (or of one known *ATM* pathogenic variant and one *ATM* variant of uncertain significance) itself does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ATM* is performed first to detect small missense, nonsense, and splice site variants and intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel (e.g., for ataxias, immunodeficiency, or cancer predisposition) that includes *ATM* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of incidental findings (such as 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*. (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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Note: Unlike exome sequencing, genome sequencing can identify variants outside of the coding region. Although most confirmed pathogenic *ATM* variants are within exons [Taylor et al 2015], several pathogenic variants have been detected in the noncoding region of *ATM* [McConville et al 1996, Castellví-Bel et al 1999, Fiévet et al 2019, Schon et al 2019, Cremin et al 2020, Klee et al 2021].

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 Ataxia-Telangiectasia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ATM	Sequence analysis [3]	90%-95% [4, 5]
	Deletion/duplication analysis [6]	5%-10%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/duplications/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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Several deep intronic variants outside of the exon and splice junction regions typically included by standard sequencing have been observed, including a deep intronic founder variant detected in the United Kingdom (c.5763-1050A>G, formerly known as 5762ins137) [McConville et al 1996].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Alternatively, deletion/duplication analysis by using read depth or detecting breakpoints in exome and genome sequencing data is also possible.

Clinical Characteristics

Clinical Description

Ataxia-telangiectasia (A-T) is often described has having a "classic A-T" phenotype and a "variant A-T" phenotype; however, these phenotypes are more of a continuum ranging from classic A-T at the severe end to variant A-T at the milder end. Nonetheless, distinguishing between classic A-T and variant- A-T on this phenotypic spectrum helps understand differences in disease course, rate of progression, and life expectancy (see Table 2) [van Os et al 2017b, Levy & Lang 2018, Amirifar et al 2019, Schon et al 2019, van Os et al 2020b, Veenhuis et al 2021b].

Table 2. Ataxia-Telangiectasia: Comparison of Classic A-T and Variant A-T by Select Features

Feature		Classic A-T	Variant A-T
Neurologic	**Cerebellar ataxia**	++	+, ±, –
	Extrapyramidal movement disorder	++	+, ±, –
	Peripheral neuropathy	+	+, ±, –
	Dysarthria	++	++
	Dysphagia/feeding/nutrition issues	++	±
	Oculomotor apraxia	++	+, ±, –
Increased susceptibility to malignancy		++	++
Abnormal cognition & behavior		±	?
Immunodeficiency		+	Ab
Infection		±	Ab
Pulmonary disease		+	Ab
Endocrine abnormalities	**Growth failure**	++	?
	Abnormal puberty	+	±, –
	Insulin resistance	+	±

Table 2. continued from previous page.

Feature	Classic A-T	Variant A-T
Telangiectasias	+	+, ±, –

Based on Hoche et al [2014], van Os et al [2017a], Levy & Lang [2018], Amirifar et al [2019], Hoche et al [2019], Schon et al [2019], van Os et al [2020b], Veenhuis et al [2021b]
++ = always present; + = usually present; ± = sometimes present; – rarely present; Ab = absent; ? = although this feature has not been systematically studied in individuals with variant A-T, the authors feel that this is very uncommon in these individuals

Classic A-T

Neurologic. In most children with classic A-T, cerebellar ataxia is the presenting manifestation observed after the child starts to sit and walk [Boder & Sedgwick 1958]. Infants show postural instability when sitting or standing. Although children start to walk at a normal age, their gait does not improve and remains wobbly.

During the first years after disease onset, motor abnormalities may appear to be stable because the natural acquisition of motor milestones in young children may appear to "compensate" for the (progressive) disease course [Levy & Lang 2018].

Children have balance problems when they walk and show a rapid broad-based gait, with backward posturing of the arms and hands as a finding of dystonia.

In addition, most children with classic A-T have extrapyramidal involvement such as dystonia, choreoathetosis, myoclonic jerks, and tremor. In the second or third decade, parkinsonism can occur [Levy & Lang 2018].

After about age eight years children begin to show clinical signs of peripheral neuropathy, manifesting as a progressive sensorimotor neuropathy, decreased or loss of deep tendon reflexes, distal muscle weakness and atrophy, and impaired vibration sense [Verhagen et al 2007].

After about age ten years most children with classic A-T require use a wheelchair to compensate for the cerebellar ataxia and extrapyramidal and peripheral nervous manifestations.

With disease progression, speech problems occur in all individuals. Despite dysarthria, oral communication generally remains possible [Veenhuis et al 2021b].

Dysphagia, which is common in young adults, makes eating frustrating and exhausting [Lefton-Greif et al 2000]. For this reason, affected individuals and their caregivers may tend to reduce their meals, potentially leading to insufficient caloric intake [Rothblum-Oviatt et al 2016].

Oculomotor apraxia in individuals with classic A-T include gaze-evoked nystagmus, hypometric saccades, saccadic intrusions, convergence/accommodation, and vestibulo-ocular reflex abnormalities [Lewis et al 1999, Tang & Shaikh 2019]. These abnormalities progress over time.

As the result of the complex eye movement disorders, visual fixation can be difficult and can, for example, affect reading [Lewis et al 1999].

Increased susceptibility to malignancy. As result of the DNA repair defect that characterizes A-T, the risk of developing malignancies is increased (25%), with a median age at diagnosis of 12.5 years [Suarez et al 2015].

- **Children** are prone to developing lymphomas (B-cell non-Hodgkin lymphoma and Hodgkin lymphoma) and leukemias (most notably T-cell acute lymphoblastic leukemias and T-cell prolymphocytic leukemia) [Taylor et al 1996, Bakhtiar et al 2021].
- **Adults**. In addition to hematologic malignancies, adults are prone to developing solid tumors including breast cancer, ovarian cancer, gastric cancer, liver cancer, esophageal carcinomas, melanomas, leiomyomas, and sarcomas [Rothblum-Oviatt et al 2016].

Abnormal cognition and behavior. Only a limited number of studies have investigated cognition in individuals with A-T. Although it is generally accepted that intellectual disability is not a common finding in A-T [Vinck et al 2011, Hoche et al 2014], disturbances in cerebellar as well as non-cerebellar brain areas and networks may result in cognitive deficits [Hoche et al 2014]. Noted deficits include problems with intellectual functioning, nonverbal memory, verbal abstract reasoning and calculation, and executive function [Rothblum-Oviatt et al 2016] that overlap with the so-called cerebellar cognitive affective syndrome [Hoche et al 2019]. The first manifestations start at the end of the first decade of life.

Immunodeficiency is highly variable with abnormalities of humoral immunity, cellular immunity, or combined immune deficiency [Nowak-Wegrzyn et al 2004, Driessen et al 2013, Chopra et al 2014]. In most individuals, the immunodeficiency remains stable over time [Chopra et al 2014].

- **Humoral immunity.** Impaired antigen receptor recombination and class-switch recombination result in a suboptimal production of a diverse repertoire of B cells [Driessen et al 2013]. The most common deficiencies in humoral immunity are low levels of immunoglobulins, particularly selective IgA deficiency, hypogammaglobulinemia, and IgG subclass deficiency (most commonly involving IgG2 and IgG4) [Nowak-Wegrzyn et al 2004].

  About 10% of individuals with IgA and IgG deficiency have normal or elevated levels of IgM, the so-called hyper IgM phenotype [Noordzij et al 2009]. Due to severe immune deficiency, life span in individuals with hyper IgM is shorter than life span in individuals with classic A-T without hyper IgM [van Os et al 2017b]. Respiratory failure is a common cause of death in these individuals.

  A reduced selective polysaccharide antibody response can also occur, mostly in individuals with deficiencies of both IgA and IgG2 [Sanal et al 1999, Nowak-Wegrzyn et al 2004].

- **Cellular immunity.** Thymic hypoplasia causes T-cell deficiency. The most common deficiency in cellular immunity is lymphopenia with reduced numbers of $CD4^+$ and $CD8^+$ cells [Nowak-Wegrzyn et al 2004, Driessen et al 2013].

Infection. Despite the known immunodeficiencies in individuals with classic A-T, severe infections (bacterial, viral, and opportunistic) are uncommon [Nowak-Wegrzyn et al 2004].

In contrast, mild sinopulmonary infections occur quite frequently and may aggravate pulmonary disease [McGrath-Morrow et al 2010]. These recurrent upper respiratory tract infections occur at all ages, unlike lower respiratory infections, which are more common in older individuals [Nowak-Wegrzyn et al 2004].

Viruses are the most common cause of respiratory tract infections during the first two years of life in both healthy children and children with A-T.

Bacterial causes of respiratory tract infections are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* in children under age 15 years [Davies 2009, Bhatt & Bush 2014, Schroeder & Zielen 2014]; *Pseudomonas aeruginosa* is more common in older individuals [Schroeder & Zielen 2014].

Pulmonary disease, present in a majority of individuals with A-T, causes significant morbidity and mortality. Pulmonary disease can be attributed to a combination of recurrent infections, immune deficiency, aspiration, interstitial lung disease, and neurologic abnormalities [Lefton-Greif et al 2000, Bott et al 2007, McGrath-Morrow et al 2010, McGrath-Morrow et al 2021].

Recurrent respiratory tract infections can result in bronchiectasis and pleural abnormalities [Schroeder & Zielen 2014, McGrath-Morrow et al 2021].

Interstitial lung disease, which commonly manifests as dry cough, tachypnea, hypoxemia, and dyspnea (in the absence of viral or bacterial infections), usually occurs in adolescence.

Neuromuscular and central nervous system involvement can lead to dysphagia (commonly evident in the second decade) and chronic aspiration, aggravating existing lung disease [Lefton-Greif et al 2000, McGrath-Morrow et al 2021].

Pulmonary disease progresses with increasing age and neurologic involvement.

Endocrine abnormalities include growth impairment, gonadal dysfunction, and insulin resistance [Pommerening et al 2015].

- **Poor linear growth,** due to underlying nutritional problems, recurrent infections, and suboptimal serum growth hormone levels, is common [Ehlayel et al 2014, Voss et al 2014]. In addition, it is thought that growth failure is a primary A-T-related issue, being more prominent in females than males [Nissenkorn et al 2016].
- **Abnormal puberty**
  - **Males**. Although the levels of follicle-stimulation hormone (FSH), luteinizing hormone (LH), and testosterone are typically within the normal range, gonadal failure and abnormal spermatogenesis have also been described [Sedgwick 1972, Nissenkorn et al 2016].
  - **Females**. Elevated LH and FSH levels are common in adolescent females with A-T, indicating ovarian failure. When gonadotropin levels are elevated, clinical findings range from complete absence of pubertal development to normal sexual development and normal menstruation [Nissenkorn et al 2016].
- **Insulin resistance,** present in some adults, typically manifests as hyperglycemia, hyperinsulinemia, and peripheral insulin resistance. Diabetes is rarely associated with glycosuria or ketosis [Schalch et al 1970].
- **Other.** Thyroid and adrenal function are generally normal [Ammann et al 1970, Nissenkorn et al 2016].

Telangiectasias, vascular abnormalities occurring in the conjunctiva and sun-exposed skin (e.g., ears, face, neck, hands), are usually evident by age six years, but not at disease onset [Greenberger et al 2013]. Overtime, telangiectasias can occur in other organs such as the bladder (described after treatment with intravenous cyclophosphamide) [Cohen et al 2008], gastrointestinal tract, and brain [Habek et al 2008, Schoenaker et al 2018]. Telangiectasias in the brain usually need no therapeutic intervention. When telangiectasias occur in other organs, no standard therapeutic recommendations are available.

Other findings

- **Premature aging** (resulting from the genomic instability caused by the DNA repair defect that characterizes A-T) can manifest as: (1) graying hair and skin abnormalities, such as hypopigmentation and café au lait spots; and (2) adolescent onset of age-related diseases such as diabetes mellitus and liver disease [Shiloh & Lederman 2017].
- **Radiation sensitivity.** Due to impairment of repair of DNA double-strand breaks, individuals with A-T have an increased sensitivity to ionizing radiation (x-ray and gamma ray) [Lavin & Khanna 1999] and radiomimetic drugs. Severe side effects from these treatments have been reported [Perlman et al 2003].
- **Cutaneous granulomas,** described in some individuals [Chiam et al 2011], are thought to be related to vaccine-derived rubella virus [Bodemer et al 2014, Buchbinder et al 2019].
- **Elevated serum liver enzymes and hepatic steatosis** are often seen in adults [van Os et al 2020b].

Intrafamilial variability. Although family members with A-T may show some differences in clinical presentation and laboratory findings (including immunologic abnormalities), the phenotype within a family tends to be similar [Taylor et al 2015].

Life expectancy in classic A-T is significantly reduced due to cancer, pulmonary disease, and infections. Most affected individuals do not live longer than age 30 years [Crawford et al 2006, Micol et al 2011].

Individuals with the hyper IgM phenotype of classic A-T have a poorer prognosis than individuals with classic A-T, and most die before age 15 years due to respiratory failure [van Os et al 2017b].

Variant A-T

Neurologic manifestations vary.

The first manifestations of variant A-T can occur in childhood to adulthood. Most individuals have their first manifestations by age ten years.

Cerebellar ataxia can be absent in variant A-T, in contrast to classic A-T.

Extrapyramidal movement disorders are common, the most predominant of which are dystonia and dystonic tremor. Most individuals who have a purely extrapyramidal presentation tend to have a milder disease course [van Os et al 2019b].

Chorea and parkinsonism are rare in variant A-T.

Most individuals with variant A-T have, in addition to central motor manifestations, signs and symptoms of an axonal sensorimotor polyneuropathy [Schon et al 2019].

Rarely, individuals with variant A-T have anterior horn cell disease, which can either be one of the presenting features or can manifest during the disease course [van Os et al 2019b].

Oculomotor apraxia. Although abnormal eye movements can include nystagmus, jerky ocular pursuit, and hypo- and hypermetric saccades, individuals with variant A-T can have normal eye movements [Schon et al 2019].

Feeding/nutrition. Occasionally, nutritional problems can occur in individuals with variant A-T due to neurologic decline [Schon et al 2019].

Increased susceptibility to malignancy. Individuals with variant A-T have an increased risk of developing malignancies (29.5%) [van Os et al 2019b]. In particular, premenopausal females are at increased risk to develop breast cancer and hematologic malignancies [Schon et al 2019].

Abnormal cognition and behavior. No information is available on these findings in variant A-T.

Immunodeficiency. Serum immunoglobulin levels and T- and B-cell counts are generally normal [Verhagen et al 2009a].

Infection. Respiratory infections do not occur at a frequency greater than that in the general population [Verhagen et al 2009a].

Pulmonary disease is not a major feature in variant A-T [Schon et al 2019].

Endocrine abnormalities. Th prevalence of endocrine abnormalities like diabetes mellitus, growth impairment, and gonadal dysfunction in individuals with variant A-T seems to be similar to that in the general population [Verhagen et al 2009a, Schon et al 2019].

Telangiectasias have been reported in about 55% of individuals with variant A-T [van Os et al 2019b].

Other findings

- **Premature aging,** from a clinical perspective, is not a clearly recognizable feature of variant A-T; however, no studies have investigated the lifelong risks of common age-related disorders such diabetes mellitus, cardiovascular disease, and neurodegenerative disorders like Parkinson disease.

- **Radiation sensitivity.** Individuals with variant A-T have an increased sensitivity to ionizing radiation (x-ray and gamma ray) and radiomimetic drugs [Verhagen et al 2009a, Schon et al 2019].

Intrafamilial variability. In a study of 57 individuals with variant A-T that included five sets of sibs, the neurologic phenotypes of sibs were similar [Schon et al 2019].

Life expectancy in variant A-T. The longer life expectancy in variant A-T than in classic A-T can be attributed to less progressive neurologic decline, typical absence of respiratory and immunologic features, and older age of occurrence of malignancies [van Os et al 2017b].

Heterozygotes

Although individuals heterozygous for a pathogenic *ATM* variant are not at risk for A-T, their risk of developing cancer is increased compared to that of the general population. In particular, heterozygous females younger than age 50 years have an increased risk of developing breast cancer [Olsen et al 2005, van Os et al 2016].

In addition to this increased cancer risk, heterozygotes may also have an increased risk of developing cardiovascular disease, diabetes mellitus, and neurodegenerative disorders; however, systematic population studies to (quantitatively) investigate this issue are lacking [van Os et al 2016].

Genotype-Phenotype Correlations

In general, nonsense and/or frameshift variants lead to the classic A-T phenotype, whereas missense and splice site variants are more typically associated with variant A-T. Within families, phenotypes of affected individuals are generally similar [Verhagen et al 2012, Taylor et al 2015].

Specific *ATM* variants with genotype-phenotype correlations include the following (see Table 6):

- **c.3576G>A.** Individuals who are either homozygous or compound heterozygous for this splice site variant have milder classic A-T with prolonged survival and lower susceptibility to immunodeficiency, respiratory disease, and cancer [van Os et al 2019a].
- **c.5763-1050A>G.** This splice site variant, associated with the A-T variant phenotype, is a founder variant in the United Kingdom [McConville et al 1996, Stewart et al 2001].
- Compound heterozygosity for **c.6154G>A** (a missense variant) and **c.7886_7890delTATTA** (a frameshift variant) result in the variant A-T phenotype with dopa-responsive dystonia [Charlesworth et al 2013].
- **c.6200C>A.** This missense variant in Canadian Mennonites is associated with a dystonia-predominant variant A-T phenotype [Saunders-Pullman et al 2012].
- **c.7271T>G.** Four of six individuals homozygous for this missense variant had variant A-T and normal serum alpha-fetoprotein levels [Schon et al 2019]. This variant is associated with a high risk of breast cancer [Stankovic et al 1998].
- **c.8147T>C.** All individuals who are compound heterozygous for this missense variant have variant A-T [van Os et al 2020b].

Nomenclature

Ataxia-telangiectasia was previously referred to as Louis-Bar syndrome.

Prevalence

The reported incidence of A-T, a rare disorder, varies between 1:300,000 and 1:40,000. The estimated prevalence is 1-9:100,000 [Swift et al 1986, Rothblum-Oviatt et al 2016].

In the United States approximately 350 children with A-T are known to the patient organization A-T Children's Project (see www.atcp.org).

Based on the incidence of A-T in the United States, the heterozygote frequency is estimated to be one in 200 persons [Swift et al 1986].

Increased heterozygote frequencies have been reported in the following populations due to founder variants (see Table 6):

- One in three to one in 15 in the Druze population in northern Israel [Fares et al 2004]
- One in 81 in the Moroccan and Tunisian Jewish population [Gilad et al 1996]
- One in 36 in the Romani population in Spain [Mancebo et al 2007, Carranza et al 2017]

Genetically Related (Allelic) Disorders

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

Sporadic tumors occurring as single tumors in the absence of any other findings of ataxia-telangiectasia frequently contain a somatic pathogenic variant in *ATM* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Genetic disorders associated with eye findings and ataxia in the differential diagnosis of ataxia-telangiectasia (A-T) are listed in Table 3. Notably, none of these disorders is associated with immunologic abnormalities. For review of the differential diagnosis of cerebellar ataxia, see Hereditary Ataxia Overview.

Table 3. Genes of Interest in the Differential Diagnosis of Ataxia-Telangiectasia

Gene	Disorder [1]	Onset (in yrs)	Additional Features of This Disorder Not Observed in A-T
APTX	Ataxia w/oculomotor apraxia type 1	2-10	• Hypoalbuminemia • ↑ serum total cholesterol • Generally normal serum AFP
FXN	Friedreich ataxia	10-15	• Pyramidal & sensory signs • Optic atrophy • Cardiomyopathy • Normal serum AFP
PIK3R5	Ataxia w/oculomotor apraxia type 3 (OMIM 615217)	12-18	
PNKP	Ataxia w/oculomotor apraxia type 4 (OMIM 616267)	<10	• Hypoalbuminemia • ↑ cholesterol
SETX	Ataxia w/oculomotor apraxia type 2	3-30	Pyramidal signs
TTPA	Ataxia w/vitamin E deficiency	5-15	• Low plasma levels of vitamin E • Pyramidal signs • ↓ visual acuity • Normal serum AFP

Based on van Os et al [2020a]
AFP = alpha-fetoprotein; A-T = ataxia-telangiectasia
1. The disorders listed in this table are inherited in an autosomal recessive manner.

Management

Most of the guidelines recommended for the management of health-related problems in individuals with ataxia-telangiectasia (A-T) are expert and evidence based, due to a lack of clinical trials; see Rothblum-Oviatt et al

[2016] (full text), Schoenaker et al [2016], van Os et al [2017b] (full text), Amirifar et al [2020], and McGrath-Morrow et al [2021] (full text).

Evaluations Following Initial Diagnosis

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

Table 4. Ataxia-Telangiectasia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment	
		Classic A-T	Variant A-T
Neurologic	By neurologist familiar w/A-T, when possible	Assess for ataxia (w/SARA [1] &/or ICARS) & extrapyramidal movement disorders such as dystonia, chorea, parkinsonism, myoclonus & tremor. Consider using specific scales for A-T such as A-T NEST [2] or ATFS	
Rehabilitation	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures & scoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)	
Dysarthria	By speech-language pathologist	Evaluate speech production & language.	
Dysphagia/Feeding/ Nutrition	Nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement if nutritional status is poor &/or if there is dysphagia &/or ↑ risk of aspiration.	Usually not a concern early in disease course
Oculomotor problems	Exam by neurologist	Specific eval by ophthalmologist or eye specialist not regularly required; only if indicated	
Cognition/Behavior	By neurologist or OT familiar w/A-T, when possible	Usually not a concern. Because (moderate to) severe ID is not a hallmark of A-T, if there are such concerns, an additional cause should be sought.	Usually not a concern
Increased susceptibility to malignancy	Assessment by doctor of internal medicine / pediatrician	In all persons: • Eval for clinical manifestations of malignancy (e.g., lymphadenopathy) • Laboratory tests to assess for hematologic malignancies (per annual screening; see Table 5) In adults: breast MRI (in females) & abdominal echo (per annual screening; see Table 5)	
Immunodeficiency	Assessment by immunologist	Evaluate: • For humoral & cellular immune defects; • Whether immunoglobulin substitution therapy is indicated; • Vaccination status.	Usually not a concern

Table 4. continued from previous page.

System/Concern	Evaluation	Comment	
		Classic A-T	Variant A-T
Infection	Assessment by primary care clinician / pulmonologist	• Assess for sinopulmonary infection. • Determine need for prophylactic antibiotic treatment.	Usually not a concern
Pulmonary disease	Assessment by immunologist / pulmonologist / doctor of internal medicine / pediatrician	• Assess for pulmonary function [3] & common causes of pulmonary disease. • Assess lung function when possible (often age >4 yrs).	Usually not a concern
Endocrine abnormalities	Assessment by doctor of internal medicine / pediatrician	• Assess length/height in children (using standard growth charts). • Assess age-appropriate pubertal development. • Screening for diabetes, cardiovascular disease, & hepatic disease in adolescents & adults	Usually not a concern
Genetic counseling	By genetics professionals [4]	To inform affected persons & their families re nature, MOI, & implications of A-T (& heterozygosity for an *ATM* pathogenic variant) 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; • Palliative care involvement &/or home nursing referral.	For difficult life-prolonging decisions or for clarification of treatment options, consider further consultation w/independent clinical teams. [5]	

ADL = activities of daily living; ATFS = Ataxia Telangiectasia Functioning Scale; A-T NEST = Ataxia-Telangiectasia Neurological Examination Scale Toolkit; ICARS = International Cooperative Ataxia Rating Scale; ID = intellectual disability; ILD = interstitial lung disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia

1. Schmitz-Hübsch et al [2006]

2. Jackson et al [2016]

3. Regarding interstitial lung disease (ILD), spirometry can detect restrictive lung disease. Decreased forced vital capacity (FVC) is possibly the result of abnormalities in respiratory muscle coordination or scoliosis. Helium dilution measurements can help discriminate between true restrictive lung disease and an inability to expire to residual volume. Although a lung biopsy can help confirm the diagnosis of ILD, the diagnostic benefits should be weighed against the risks of the procedure [McGrath-Morrow et al 2010, McGrath-Morrow et al 2021].

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

5. Linney et al [2019]

Treatment of Manifestations

There is no cure for ataxia-telangiectasia.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in (pediatric) neurology, pulmonology, immunology, pediatrics (for children) and internal medicine (for adults), rehabilitation medicine, and professionals in physical

therapy, speech-language therapy, occupational therapy, and nutrition. For specific issues care may be provided by specialists in oncology, medical genetics, endocrinology, orthopedics, dermatology, mental health, and social work [van Os et al 2017a] (full text).

The following discussion takes into consideration that distinctions between the findings in classic A-T and variant A-T are not always possible; thus, clinicians need to focus on the issues that are most relevant to each affected individual.

Ataxia. Nicotinamide riboside, a form of vitamin B_3, at 25 mg/kg/day (maximum dose of 900 mg/day), has significantly reduced ataxia scores (i.e., improved the motor disorder) in a single trial with 24 individuals with both classic and variant A-T [Veenhuis et al 2021a].

Extrapyramidal movement disorders. The effectiveness of pharmacotherapy in movement disorders in A-T is low to moderate. Only a few non-randomized studies have investigated the treatment of movement disorders in individuals with A-T specifically [Zannolli et al 2012, Nissenkorn et al 2013, Shaikh et al 2013, Leuzzi et al 2015, Veenhuis et al 2021a].

Dystonia, the most troublesome movement disorder in A-T, can vary in distribution and severity and varies among affected individuals.

- **Focal dystonia.** As in individuals with torticollis, botulinum toxin A is the treatment of first choice.
- **Generalized dystonia.** Anticholinergic drugs and GABA mimetics can be helpful.
- **Generalized, dopa-responsive dystonia.** A trial with levodopa may be useful in some individuals [Charlesworth et al 2013].
- **Deep brain stimulation (DBS)** of the globus pallidus pars interna, described to date in two individuals with A-T and dystonia, had conflicting results [Georgiev et al 2016].

For recommendations on the treatment of ataxia, chorea, myoclonus, and tremor, see van Os et al [2017b].

Rehabilitation / activities of daily living. The main goal of supportive treatment by a rehabilitation specialist (physiatrist), physical therapists, occupational therapists, and allied health care workers is the maintenance of physical function and condition and prevention of complications such as contractures. A multidisciplinary approach is the cornerstone of the treatment of motor disability.

Physical therapists can provide exercises to maintain muscle strength, overall condition, and activity and to prevent joint contractures. Necessary aids can include:

- Foot orthoses;
- A (wheel)chair to provide a good upright sitting position to reduce scoliosis and prevent choking;
- Standing frames.

Occupational therapists can provide aids and devices for activities of daily living.

Dysarthria. A speech-language therapist can help address dysarthria and provide practical advice to improve speech intelligibility and support families [Veenhuis et al 2021b]. In most individuals with A-T, oral communication is possible. When dysarthria is severe, a speech-language therapist can suggest use of communication aids (e.g., augmentative and alternative communication [AAC]) and equipment.

Dysphagia/feeding/nutrition. Management of dysphagia may involve feeding teams that include speech-language therapists, nutritionists (regarding thickened liquids and caloric intake), and gastroenterologists (who recommend gastrostomy feeding when appropriate).

Good nutritional status is required for optimal effectiveness of all other treatments in A-T. Individuals with A-T are often malnourished, as a result of the combination of physical difficulties with eating (i.e., oral-motor

problems affecting chewing and swallowing), easy fatigability, and endocrine abnormalities that affect growth [Lefton-Greif et al 2000, Lefton-Greif et al 2011, Ehlayel et al 2014, Ross et al 2015, Nissenkorn et al 2016, Natale et al 2021]. In addition to these secondary factors, the underlying molecular defect itself seems to make affected individuals prone to have poor linear growth.

Practical tips such as attention to a good sitting position, use of a straw, thickening of thin liquids, and giving children easily chewable foods may help [Ross et al 2015, van Os et al 2017a].

Gastrostomy placement early in the disease course can improve clinical outcomes [Lefton-Greif et al 2011, Ross et al 2015].

Oculomotor problems. Ophthalmologists can advise regarding visual aids that may be helpful (e.g., for reading) in the context of eye movement abnormalities.

Nystagmus and oculomotor apraxia generally do not require drug treatment.

- 4-aminopyridine did improve oculomotor and vestibular function in a small case series [Shaikh et al 2013].
- Acetyl-DL-leucine was shown to have an effect on downbeat nystagmus in a small study [Brueggemann et al 2022].

Malignancy. To date, there are no specific consensus treatment protocols for malignancies in A-T [Machida et al 2013, Pérez-Villena et al 2013, Schoenaker et al 2016, van Os et al 2017a].

Treatment protocols for an individual with A-T with a malignancy should be individualized based on patient-related factors (such as mobility, lung function) and malignancy-related factors (such as type of malignancy and alternative treatment options).

Chemotherapy in general can be initiated with dose-adjusted protocols; doses can be increased when chemotherapy is tolerated.

Radiation therapy is contraindicated in individuals with classic A-T and variant A-T because increased radiosensitivity may lead to very severe complications.

Allogenic stem cell transplantation, described in several individuals with A-T and a malignancy, has had differing outcomes. There seems to be a serious risk of adverse events when this therapy is given without an adjusted conditioning regime [Ghosh et al 2012, Ussowicz et al 2013, Beier et al 2016, Bakhtiar et al 2018, Slack et al 2018].

Cognition. When there are concerns about cognition, 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:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - 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.

Behavior. Over time individuals with A-T are prone to develop cerebellar cognitive affective syndrome [Hoche et al 2014, Hoche et al 2019], for which monitoring is warranted (see Surveillance).

As individuals with A-T have a severe disorder, attention should be paid to their emotional well-being [van Os et al 2020b].

Prophylactic antibiotic treatment should be considered early in the disease course in individuals with recurrent or severe infections and in those with immunoglobulin G deficiency or specific polysaccharide antibody deficiency [van Os et al 2017a].

Immunoglobulin replacement therapy is indicated in individuals with severe IgG deficiency and in those with the hyper IgM phenotype. It may be considered in individuals with recurrent infections, mild humoral immune defects, or low antibody responses despite booster immunizations [Davies 2009].

Immunizations. Most children have had their immunizations before the diagnosis of A-T is established; generally, this goes without any complications. Inactivated vaccines are safe in all persons with A-T. Flu vaccines, 13-valent pneumococcal conjugate, and 23-valent pneumococcal polysaccharide vaccines should be given to all individuals with A-T.

Of note, in individuals with severe immunodeficiency, rubella vaccination should be avoided, as it can possibly increase the risk for granulomas [Bodemer et al 2014, Buchbinder et al 2019].

Respiratory. The European Respiratory Society (ERS) has prepared extensive guidelines for the multidisciplinary respiratory management of A-T, emphasizing the need for monitoring of immune function, recurrent infection, pulmonary function, swallowing, nutrition, and scoliosis, all of which could contribute to increased respiratory morbidity and mortality in A-T [Bhatt et al 2015] (full text).

Anesthetic and perioperative risk. Due to pulmonary problems and often poor nutritional status, individuals with A-T are at increased risk of developing complications during and shortly after anesthesia [McGrath-Morrow et al 2008, Verhagen et al 2009b, McGrath-Morrow et al 2010, Lockman et al 2012]. Therefore, individuals with A-T should be operated on in a hospital with specialists with expertise in A-T. Forced weaning and early extubation can improve outcomes, specifically in individuals with severe restrictive pulmonary dysfunction [Verhagen et al 2009b].

Endocrinology. Young adults with A-T may develop insulin-resistant diabetes mellitus and hypercholesterolemia [Andrade et al 2015, Donath et al 2020], which can be treated following protocols for the general population. However, the shortened life expectancy of individuals with classic A-T can result in the decision not to treat high cholesterol levels, since treatment will not have any expected clinical consequences.

In females with gonadal failure (in case of primary or secondary amenorrhea), estrogen supplementation can prevent osteoporosis [Ehlayel et al 2014].

Growth hormone treatment may be an option for children with severe growth failure [Woelke et al 2017].

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Note the recommended surveillance is the same for individuals with classic A-T and variant A-T, with the exception that individuals who do not have evidence of lung disease at the time of the initial diagnosis do not require annual screening for pulmonary disease.

Table 5. Ataxia-Telangiectasia: Recommended Surveillance

System/Concern	Evaluation	Frequency/Timing
Neurologic	• Eval by neurologist for response to therapy for existing findings & development of new findings • If child has severe/profound ID, seek additional cause.	• Annually • More frequently if problems are present or suspected
Educational needs	Screening for cognitive functioning & any speech-language issues	• Before becoming school age; once school age, annually • More frequently if problems are present or suspected
Behavior	Monitoring for social-emotional development	When starting kindergarten & again when entering secondary school
ADL/Musculoskeletal	By PT, OT, &/or rehab specialist	Per rehab team
Dysarthria/Communication	By SLP	Per treating SLP
Oculomotor problems	By ophthalmologist	Only if indicated
Immunodeficiency	By immunologist (immunoglobulin levels, white blood cell count)	• Annually • More frequently if problems are present or suspected
Infection	By immunologist	
Pulmonary disease	• By pulmonologist • Lung function testing (by spirometry)	• Annually for persons w/evidence of disease at time of initial diagnosis • More frequently if problems are present or suspected
Increased susceptibility to malignancy	Clinical assessment for signs/symptoms of leukemia &/or lymphoma incl for lymphadenopathy & unexplained fever	Annually
	Blood count & smear, immunoglobulin levels, M protein, LDH, IgM	• Annually • More frequently if problems are present or suspected • Immediate referral to oncologist if malignancy is diagnosed or suspected
	Ultrasound exam of abdomen in adulthood	Annually
	Breast MRI in females	• Annually starting at age 25 yrs • More frequently if problems are present or suspected

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency/Timing
Endocrine abnormalities	Assess length/height in children.	• Annually in childhood • More frequently if problems are present or suspected
	Assess age-appropriate pubertal development.	• Annually • More frequently if problems are present or suspected
	Diabetes screening: urinalysis, fasting blood glucose concentration, Hgb A1c	• Annually in adults • More frequently if problems are present or suspected
Feeding/Nutrition	By SLP/nutritionist	• Annually • More frequently if problems are present or suspected
Family support & resources	All health care providers should pay attention to the well-being of persons w/A-T & their families.	At each visit

Hgb = hemoglobin; ID = intellectual disability; LDH = lactate dehydrogenase; SLP = speech-language pathologist

Heterozygotes

Females who are suspected heterozygotes for an *ATM* pathogenic variant (such as mothers of children with A-T) should have molecular genetic testing to confirm the presence of an *ATM* pathogenic variant and determine which *ATM* pathogenic variant is present in the mother to clarify her risk of breast cancer.

- Females heterozygous for the *ATM* variant c.7271T>G have a breast cancer risk that is similar to that of females with a *BRCA1* or *BRCA2* pathogenic variant; thus, more intensive breast screening is recommended from age 25 years (see *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer, Surveillance). To date, there is limited data on medical or surgical prophylactic treatments to decrease the risk of breast cancer in *ATM* heterozygotes [Cragun et al 2020].
- Females heterozygous for any other *ATM* pathogenic variant should have an annual mammogram beginning at age 40 years [van Os et al 2016]. Breast MRI can be considered based on additional factors including family history, age, and breast density.
- Radiation therapy at conventional doses is not contraindicated in females heterozygous for an *ATM* pathogenic variant [van Os et al 2016].

Males and females heterozygous for a pathogenic *ATM* variant are at increased risk of developing other types of tumors such as malignancies of the gastrointestinal tract as well as increased risk of cardiovascular disease [van Os et al 2016].

- To date, intensified screening for other types of cancer have not been recommended.
- To date, it is not recommended that heterozygotes avoid radiation therapy at conventional doses or diagnostic x-rays or CT scans.

Heterozygotes should be made aware of lifestyle factors that contribute to cardiovascular diseases, but no specific screening has been recommended [van Os et al 2016].

Agents/Circumstances to Avoid

Affected individuals

- Rubella vaccination should be avoided in individuals with severe immunodeficiency as it can possibly increase the risk for granulomas [Bodemer et al 2014, Buchbinder et al 2019].

- Ionizing radiation (x-ray and gamma ray) is contraindicated, due to increased sensitivity [Lavin & Khanna 1999].
- Radiation therapy is contraindicated because increased radiosensitivity may lead to very severe complications [Perlman et al 2003].

Heterozygotes. There are no agents/circumstances to avoid.

Evaluation of Relatives at Risk

It is appropriate to offer molecular genetic testing for the *ATM* pathogenic variants identified in the proband to apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible:

- Sibs with biallelic *ATM* pathogenic variants who would benefit from prompt initiation of treatment of manifestations of A-T, surveillance for malignancy, and awareness of agents/circumstances to avoid;
- Family members who are heterozygous for an *ATM* pathogenic variant and who would benefit from age-appropriate intensified surveillance for breast cancer (see Clinical Description, Heterozygotes and Surveillance, Heterozygotes).

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

Therapies Under Investigation

Currently, a multicenter randomized controlled trial with **intra-erythrocyte dexamethasone** in patients with A-T is being conducted (see NCT03563053).

Nicotinamide riboside (a form of vitamin B_3) was shown to have a positive effect on ataxia scores and immunoglobulin levels in a proof-of-concept study [Veenhuis et al 2021a]. A second study on the same topic is being conducted (see NCT04870866).

Gene therapy with antisense oligonucleotides in A-T is currently being studied in a single case study in the United States (see www.atcp.org). To date, no toxic side effects have been reported, but the clinical effects are not available yet.

Allogenic hematopoietic stem cell transplantation in A-T has been conducted in single cases and small case series, with divergent results regarding effect on neurologic functioning [Broccoletti et al 2008, Ghosh et al 2012, Ussowicz et al 2013, Beier et al 2016, Bakhtiar et al 2018, Slack et al 2018, Duecker et al 2019].

Treatment studies with steroids in individuals with A-T. Although such studies have shown promising results for neurologic manifestations [Buoni et al 2006, Broccoletti et al 2008, Zannolli et al 2012, Hasegawa et al 2019], long-term use of steroids may potentially cause severe side effects.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Ataxia-telangiectasia (A-T) is caused by biallelic pathogenic variants in *ATM* and inherited an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ATM* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ATM* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Although individuals heterozygous for an *ATM* pathogenic variant are not at risk for A-T, their risk of developing cancer is increased compared to that of the general population. In particular, heterozygous females younger than age 50 years have an increased risk of developing breast cancer (see Clinical Description, Heterozygotes); intensified breast cancer screening is recommended for heterozygous females (see Surveillance, Heterozygotes).

Sibs of a proband

- If both parents are known to be heterozygous for an *ATM* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and having A-T, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial *ATM* pathogenic variants.
- Sibs with biallelic *ATM* pathogenic variants may show some differences in clinical presentation and laboratory findings (including immunologic abnormalities); however, the phenotype within families tends to be similar [Taylor et al 2015].
- Although individuals heterozygous for an *ATM* pathogenic variant are not at risk for A-T, their risk of developing cancer is increased compared to that of the general population. In particular, heterozygous females younger than age 50 years have an increased risk of developing breast cancer (see Clinical Description, Heterozygotes); intensified breast cancer screening is recommended for heterozygous females (see Surveillance, Heterozygotes).

Offspring of a proband

- Although most individuals with A-T do not reproduce, exceptions have been reported [Stankovic et al 1998; Byrd et al 2012; Dawson et al 2015; Blancato et al, unpublished data]. Reproduction has been reported in several women with variant A-T [Schon et al 2019].
- The offspring of an individual with A-T are obligate heterozygotes for a pathogenic variant in *ATM* and are at increased risk for cancer (see Surveillance, Heterozygotes).

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for an *ATM* pathogenic variant and at increased risk for cancer (see Surveillance, Heterozygotes).

Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the *ATM* pathogenic variants in the family.

Although individuals with a heterozygous *ATM* pathogenic variant are not at risk for A-T, their risk of developing cancer is increased compared to that of the general population (see Clinical Description, Heterozygotes). In particular, heterozygous females have an increased risk of developing breast cancer, and intensified breast cancer screening is recommended [van Os et al 2016] (see Surveillance, Heterozygotes).

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 young adults who are affected, are heterozygous, or are at risk of being heterozygous.
- *ATM* genetic testing should be considered for the reproductive partners of individuals known to be heterozygous for an *ATM* pathogenic variant, particularly if both partners are of the same ancestral background. Increased heterozygote frequencies have been reported in the following populations due to founder variants: the Druze population in northern Israel, the Moroccan and Tunisian Jewish population, and the Romani population in Spain (see Table 6).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ATM* pathogenic variants have 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.

- **A-T Children's Project**
  Ataxia-Telangiectasia Children's Project
  Phone: 800.5.HELP.A-T (800.543.5728); 954-481-6611
  www.atcp.org
- **A-T Society**
  United Kingdom
  Phone: 44 (0) 1582 760733
  Email: info@atsociety.org.uk
  www.atsociety.org.uk

- **Ataxia-Telangiectasia in Children**
  Guidance on diagnosis and clinical care
- **MedlinePlus**
  Ataxia-telangiectasia
- **NCBI Genes and Disease**
  Ataxia-telangiectasia
- **NIH-NCATS Genetic and Rare Diseases Information Center (GARD)**
  PO Box 8126
  Gaithersburg MD 20898-8126
  Phone: 888-205-2311 (toll-free)
  Ataxia-Telangiectasia
- **Twan Foundation**
  Netherlands
  www.twanfoundation.nl
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state
- **European Society for Immunodeficiencies (ESID) Registry**
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  ESID Registry

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. Ataxia-Telangiectasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATM	11q22.3	Serine-protein kinase ATM	Ataxia Telangiectasia Mutated (ATM) @ LOVD	ATM	ATM

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 Ataxia-Telangiectasia (View All in OMIM)

208900	ATAXIA-TELANGIECTASIA; AT
607585	ATM SERINE/THREONINE KINASE; ATM

Molecular Pathogenesis

ATM encodes a serine/threonine kinase, serine-protein kinase ATM, that is a member of the family of phosphoinositide 3-kinases. Some of these kinases, including ATM, are involved in DNA damage response and

repair. Double-strand DNA breaks activate ATM, which in turn phosphorylates many substrates involved in DNA repair, cell cycle checkpoints, and apoptosis. ATM is also involved in RNA metabolism and transcription regulation that affect redox and calcium homeostasis. As such, the absence of ATM leads to disruption of multiple pathways in the cell's nucleus, cytoplasm, as well as other cellular compartments such as the mitochondria and peroxisomes, resulting in widespread consequences. In the nervous system of individuals with ataxia-telangiectasia (A-T), abnormalities are most prominent in the cerebellum. However, many other cell types and organs are affected. Knowledge of the underlying disease mechanisms in each of these organs is still evolving [Lee & Paull 2021].

Individuals with classic A-T have no ATM kinase activity, whereas individuals with variant A-T have residual ATM kinase activity, and – compared to classic A-T – have a less severe disease course [Verhagen et al 2012].

Mechanism of disease causation. Loss of function

- **Classic A-T.** Many *ATM* variants associated with classic A-T (i.e., out-of-frame deletions or start codon, nonsense, frameshift, or splice site variants) cause loss of function, and most will lead to nonsense-mediated mRNA decay and absence of the ATM protein. Other variants (i.e., missense or in-frame deletions) may encode stable but inactive proteins.
- **Variant A-T** often involves variants with residual protein function. These are mainly missense variants or variants where a part of the transcript is spliced normally, despite the presence of a splice site variant.

***ATM*-specific laboratory technical considerations.** Multiple deep intronic *ATM* pathogenic variants have been identified that would not be detected by standard exome sequencing [McConville et al 1996, Castellví-Bel et al 1999, Fiévet et al 2019, Schon et al 2019, Cremin et al 2020, Klee et al 2021].

If a variant of uncertain significance (VUS) is identified, additional testing such as immunoblotting for ATM and/or functional analysis of ATM kinase activity is recommended.

Table 6. *ATM* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000051.4 NP_000042.3	c.103C>T	p.Arg35Ter	Founder variant in persons of Moroccan & Tunisian Jewish ancestry [Gilad et al 1996]
	c.1339C>T	p.Arg447Ter	Founder variant in northern Israel Druze population originally from central Lebanon & Jordan [Fares et al 2004]
	c.1564_1565delAG	p.Glu522IlefsTer43	Founder variant in persons of Amish ancestry [Telatar et al 1998]
	c.3576G>A	--	Splice site variant assoc w/milder classic A-T w/prolonged survival & lower susceptibility to immunodeficiency, respiratory disease, & cancer [van Os et al 2019a]
	c.4507C>T	p.Gln1503Ter	Founder variant in Costa Rican population [Telatar et al 1998]
	c.5763-1050A>G	--	• Intronic variant causing a pseudo-exon inclusion • Founder variant in UK assoc w/ variant A-T [McConville et al [1996]

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.5908C>T	p.Gln1970Ter	Founder variant in Costa Rican population [Telatar et al 1998]
	c.6154G>A	p.Glu2052Lys	Compound heterozygosity for this variant & p.Ile2629SerfsTer25 is reported in variant A-T w/dopa-responsive dystonia [Charlesworth et al 2013].
	c.6200C>A	p.Ala2067Asp	Founder variant in Canadian Mennonites assoc w/dystonia-predominant variant A-T [Saunders-Pullman et al 2012]
	c.6672_6680delGGCTCTACGinsCTC	p.Met2224_Arg2227delinsIleSer	Founder variant in northern Israel Druze population originally from central Lebanon & Jordan [Fares et al 2004]
	c.7271T>G	p.Val2424Gly	• 4/6 persons homozygous for this variant had variant A-T & normal serum AFP levels [Schon et al 2019]. • Assoc w/high risk of breast cancer in homozygotes & heterozygotes [Stankovic et al 1998, van Os et al 2016] (See Surveillance, Heterozygotes.)
	c.7449G>A	--	Splice site founder variant in Costa Rican population [Telatar et al 1998]
	c.7886_7890delTATTA	p.Ile2629SerfsTer25	Compound heterozygosity for this variant & p.Glu2052Lys is reported in variant A-T w/dopa-responsive dystonia [Charlesworth et al 2013].
	c.8147T>C	p.Val2716Ala	All persons who are compound heterozygous for this missense variant have variant A-T [van Os et al 2020b].
	c.9007_9034del28	p.Asn3003AspfsTer6	Founder variant in Romani population in Spain [Mancebo et al 2007, Carranza et al 2017]

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.
AFP = alpha-fetoprotein; A-T = ataxia-telangiectasia

Chapter Notes

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