GENEReviews

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Alström Syndrome

[*Alstrom Syndrome*]

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Summary

Disease characteristics. Alström syndrome is characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, dilated cardiomyopathy, the insulin resistance syndrome, and developmental delay. Wide clinical variability is observed among affected individuals, including sibs. Cone-rod dystrophy presents as progressive visual impairment, photophobia, and nystagmus starting between birth and age 15 months. Affected individuals have no light perception by age 20 years. Children usually have normal birth weight but become obese during their first year, resulting in childhood truncal obesity. Progressive sensorineural hearing loss presents in the first decade in as many as 70% of individuals. Hearing loss may progress to the severe or moderately severe range (40-70 db) by the end of the first to second decade. Insulin resistance/type 2 diabetes mellitus often presents in childhood and is typically accompanied by the skin changes of acanthosis nigricans. Other endocrine abnormalities can include hypothyroidism and male hypogonadotrophic hypogonadism. Over 60% of individuals with Alström syndrome develop cardiac failure as a result of dilated cardiomyopathy at some

stage of their lives. About 50% of individuals have delay in early developmental milestones. Urologic disorders of varying severity, characterized by detrusor-urethral dyssynergia, appear in females in their late teens. Severe renal disease is usually a late finding. The first signs of renal disease may be polyuria and polydipsia resulting from a concentrating defect secondary to interstitial fibrosis. End-stage renal disease (ESRD) can occur as early as the late teens.

Diagnosis/testing. The diagnosis of Alström syndrome is based on clinical findings. *ALMS1* is the only gene currently known to be associated with Alström syndrome. Molecular genetic testing of the *ALMS1* gene is estimated to detect mutations in 25%-40% of individuals. Such testing is available clinically on a limited basis.

Management. *Treatment of manifestations:* red-tinted prescription lenses for photodysphoria; instruction for the visually impaired; healthy diet and regular exercise; myringotomy tubes and/or hearing aids as needed for hearing impairment; anti-congestive measures as needed for cardiomyopathy; treatment of insulin resistance/type 2 diabetes as in the general population; consider high-dose statins for hyperlipidemia; consultation with an endocrinologist if pubertal development and/or menses are abnormal; urinary diversion or self-catheterization as needed for voiding difficulties; appropriate therapy of portal hypertension and esophageal varices; treatment of chronic obstructive pulmonary disease and associated infection per accepted guidelines. *Prevention of secondary complications:* routine pediatric immunizations; monitoring of cardiac status and oxygenation during acute illness and postoperatively. *Surveillance:* annual assessment of eyes; weight, height, and body mass index; hearing; heart (including echocardiography); plasma insulin concentration; lipid profile; plasma ALT, AST, and GGT concentrations; pulmonary function; thyroid function. Every two to three months, fasting plasma glucose concentration; closer follow-up if fasting or postprandial blood glucose concentrations are elevated. Twice-yearly urinalysis and plasma concentrations of electrolytes, uric acid, BUN, creatinine. Every one to two years, renal and bladder ultrasound examinations if symptomatic or if urinalysis is abnormal.

Genetic counseling. Alström syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Prenatal testing is available for at-risk pregnancies if the disease-causing mutations have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of Alström syndrome is based on cardinal clinical features that emerge throughout infancy, childhood, and young adulthood (see Figure1). Cardinal features are as follows [Marshall et al 2005]:

- **Cone-rod dystrophy** with secondary nystagmus and photodysphoria (light sensitivity/photophobia) occurs within the first year of life.
- **Obesity,** primarily truncal with a body mass index (BMI: kg/m^2) greater than 25 or greater than the 95th centile, develops in early childhood.
- **Progressive bilateral sensorineural hearing impairment** usually develops between ages one and ten years, but onset can be variable. The hearing impairment is initially in the high frequency range.
- **Dilated cardiomyopathy** with infantile or adolescent onset occurs in more than 60% of affected individuals.

- **Insulin resistance/type 2 diabetes mellitus.** Insulin resistance ranges from hyperinsulinemia to glucose intolerance to type 2 diabetes mellitus, depending on the age of the individual.
- **Hepatic disese** is variable, ranging from elevated transaminases to cirrhosis and liver failure.
- **Renal disease** is progressive; severity is highly variable.
- **Developmental delay** of fine and gross motor skills, and/or receptive or expressive language skills has been described in some individuals, and some school-age children experience academic difficulties.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *ALMS1* is the only gene currently known to be associated with Alström syndrome.

Clinical uses

- Confirmation of diagnosis
- Carrier testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** Sequence analysis of entire exons 10 and 16 and partial exon 8 detects mutations in 25%-40% of individuals with Alström syndrome [Collin et al 2002; Hearn et al 2002; Titomanilio et al 2004; JD Marshall, GB Collin, personal communication]. In a small study of a UK population, Minton et al (2006) sequenced the entire coding region of *ALMS1* and failed to identify a second mutated allele in two of 12 individuals; in two other persons (2/12) no disease-causing mutations were found [Minton et al 2006].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Alström Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis of exons 16, 10, and partial 8	*ALMS1* sequence variants	25%-40%	Clinical Testing
Sequence analysis of entire coding region		Unknown	Research only

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

Interpretation of test results. Given the current detection rate, failure to identify a disease-causing sequence variant does not preclude the diagnosis of Alström syndrome.

For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be caused by mutations in *ALMS1*.

Clinical Description

Natural History

A wide range of clinical variability is observed among individuals with Alström syndrome [Marshall et al 1997], including among sibs [Paisey et al 2000, Hoffman et al 2005]. The major clinical features of Alström syndrome (Table 2) are cone-rod dystrophy, resulting in childhood blindness; truncal obesity that manifests during the first year of life; progressive sensorineural hearing loss; infantile- or adolescent-onset dilated cardiomyopathy; insulin-resistant type 2 diabetes mellitus; and hepatic and renal dysfunction [Michaud et al 1996, Awazu et al 1997, Russell-Eggitt et al 1998].

Table 2. Age of Onset and Incidence of Common Features of Alström Syndrome

Feature	Age of Onset Range (Mean)	Incidence
Cone-rod dystrophy	Birth - 15 mos (5 mos)	100%
Obesity	Birth - 5 years (2.5 yrs)	98%
Progressive sensorineural hearing loss	2-25 yrs (9 yrs)	88%
Dilated cardiomyopathy	3 wks - 4 mos	42%
	Teens - late 30s	18%
Insulin resistance/type 2 diabetes mellitus	4-30 yrs/8-40 yrs (16 yrs)	92%/68%
Developmental delay	Birth-adolescence	25%-30%
Short stature	Puberty - adult	98%
Hypogonadotrophic hypogonadism	1-3 yrs	78% of males
Urologic disease	Adolescence - adult	48%
Renal disease	Adolescence - adult	Variably progressive with age in all individuals
Hepatic disease	8-30 yrs	23%-92%

Based on a study of 182 patients by Marshall et al (2005)

Cone-rod dystrophy. Visual problems present between birth and age 15 months as progressive cone dystrophy resulting in visual impairment, photophobia, and nystagmus. The retinal dystrophy progresses to include the rods, with visual acuity of 6/60 or less by age ten years, increasing constriction of visual fields, and no light perception by age 20 years [Russell-Eggitt et al 1998].

Electroretinography (ERG), required to establish the diagnosis of cone-rod dystrophy, is abnormal from birth, eventually with impairment of both cone and rod function. Rod function is preserved initially but deteriorates as the individual ages. Fundus examination in the first decade may be normal [Michaud et al 1996] or may show a pale optic disc and narrowing of the retinal vessels. Posterior subcapsular cataracts are common.

Obesity. Children with Alström syndrome have normal birth weight; hyperphagia and excessive weight gain begin during their first year, resulting in childhood truncal obesity. In some individuals body weight moderates, falling in the high-normal to normal range after adolescence.

Progressive bilateral sensorineural hearing loss. Hearing loss may be detected as early as age one year, initially in the high frequency range. Progressive sensorineural hearing loss

presents in the first decade in as many as 70% of individuals with Alström syndrome. Hearing loss may progress to the severe or moderately severe range (40-70 db) by the end of the first to second decade [van den Abeele et al 2001]. A high incidence of glue ear (long-standing sticky fluid in the middle ear) can lead to an additional conductive hearing loss [Marshall et al 2005].

Dilated cardiomyopathy. More than 60% of individuals with Alström syndrome develop congestive heart failure as a result of dilated cardiomyopathy at some stage of their lives. Onset, progression, and clinical outcome of the dilated cardiomyopathy vary, even within families [Makaryus et al 2003, Hoffman et al 2005].

More than 40% of affected individuals have a transient but severe dilated cardiomyopathy with onset between age three weeks and four months [Marshall et al 2005]. Most of these children survive and make an apparently full recovery in infancy. At a later age about 10%-15% of these have spontaneous recurrence of a progressive cardiomyopathy. Ascertainment bias of the infantile cardiomyopathy is possible because some infants who succumb early to infantile cardiomyopathy may have undiagnosed Alström syndrome.

About 20% have later-onset progressive cardiomyopathy occurring between the teens to late 30s. Postmortem myocardial fibrosis has been described [Marshall et al 2005].

Insulin resistance/type 2 diabetes mellitus. Diabetes mellitus in Alström syndrome is the result of tissue resistance to the actions of insulin, as demonstrated by an elevated plasma insulin concentration and glucose intolerance that usually present in childhood. The age at which type 2 diabetes mellitus develops varies; it may be as early as age five years. Type 2 diabetes mellitus and insulin resistance are typically accompanied by the skin changes of acanthosis nigricans, i.e., velvety hyperpigmented patches in intertriginous areas.

In a small study of 12 unrelated individuals with Alström syndrome, obesity (BMI and waist circumference) decreased with age, whereas insulin resistance increased with age [Minton et al 2006].

Hyperlipidemia. Hyperlipidemia is primarily hypertriglyceridemia, but can sometimes include high serum concentration of total cholesterol. Affected individuals are at risk for sudden increase in triglycerides precipitating life-threatening pancreatitis [Wu et al 2003].

Developmental delay. About 20% of affected individuals have delay in early developmental milestones including delays in gross and fine motor skills and in expressive and receptive language, and about 30% have a learning disability. Mental retardation (IQ<70) is very rare.

Short stature. Growth rates for young children are normal, but accelerated skeletal maturity (two to three years advanced bone age) and low-serum growth hormone concentrations result in adult stature that is typically less than the 25th centile. In about 98% of individuals over age 16 years height is below the fifth centile [Maffei et al 2007].

Scoliosis or kyphosis, beginning in puberty, is common [Maffei et al 2002].

Hypogonadotrophic hypogonadism. The onset of puberty is sometimes delayed in males but secondary sexual characteristics are usually normal. Male hypogonadotrophic hypogonadism results in low plasma testosterone concentration secondary to low plasma gonadotrophin concentration. Atrophic fibrotic seminiferous tubules are described [Marshall et al 2005]. Males with hypogonadotrophic hypogonadism often have a small penis at birth, and usually have small testes, often with gynecomastia in adolescence.

Endocrine disturbances in females include reduced plasma gonadotrophin concentrations, hirsutism, cystic ovaries, precocious puberty (pubertal onset before age eight years), endometriosis, irregular menses, or amenorrhea. External genitalia are normal in females.

No individuals with Alström syndrome are known to have reproduced.

Urologic disease. Urinary problems affect approximately 50% of individuals with Alström syndrome. Urologic disorders of varying severity, characterized by detrusor-urethral dyssynergia (lack of coordination of bladder and urethral muscle activity), have been described. The greatest problems appear to occur in females in their late teens. Minor symptoms include urgency and long intervals between voiding, which suggests a decrease in bladder sensation, hesitancy, and poor urinary flow. Moderate symptoms include urinary frequency, incontinence, and symptoms associated with recurrent infections. More severe urinary symptoms include worsening urinary incontinence or retention; these symptoms may alternate.

Lower abdominal and perineal pain is common and may relate to abnormal bladder/sphincter function [MacDermott 2001].

Renal disease. Renal disease is slowly progressive and highly variable. Onset can be in mid-childhood through adulthood. The first signs may be elevated serum concentrations of creatinine and blood urea nitrogen (BUN), followed by polyuria and polydipsia resulting from a concentrating defect due to interstitial fibrosis. End-stage renal disease (ESRD) can occur as early as the mid- to late teens.

Renal biopsy often shows interstitial fibrosis, glomerular hyalinosis, and tubular atrophy [Awazu et al 1997, Marshall et al 2005]

Hepatic disease. Elevated plasma concentration of liver enzymes is common in early childhood. Macrovesicular steatosis can be present or absent. Progression to hepatic failure can occur in the second to third decades. Hepatomegaly and its complications of portal hypertension, ascites, splenomegaly, and esophageal varices are also seen.

Liver biopsies and postmortem examination have revealed varying degrees of hepatic fibrosis, cirrhosis, chronic nonspecific active hepatitis with lymphocytic infiltration, patchy necrosis, and fatty liver [Awazu et al 1997, Quiros-Tejeira et al 2001, Marshall et al 2005].

Gastrointestinal disease. General GI disturbances such as epigastric pain and gastroesophageal reflux disease (GERD) are common.

Pulmonary involvement. Pulmonary symptoms include chronic bronchitis, frequent pneumonia, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension. Moderate to severe interstitial fibrosis has been reported [Marshall et al 2005]. In some cases, acute hypoxia, probably resulting from a combination of pulmonary fibrosis and severe scoliosis, has caused sudden death.

Other

- Scoliosis and kyphosis of varying severity are reported in one-third of individuals with Alström syndrome [van den Abeele et al 2001].
- Severe flat feet and dental abnormalities have been observed [Marshall 2005].
- Hypothyroidism has been reported in nearly 20% of individuals [Marshall et al 2005]; hyperthyroidism infrequently occurs [Satman, in press].

- Neurobehavioral manifestations such as absence seizures, excessive startle response, severe and unexplained peripheral pain, and mild autistic spectrum behaviors have been reported [Marshall et al 2005].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed [Minton et al 2006].

Prevalence

About 450 individuals diagnosed with Alström syndrome are known worldwide.

French-Acadians and other ethnically or geographically isolated populations have a higher-than-average frequency of Alström syndrome [Marshall et al 1997, Deeble et al 2000].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Bardet-Biedl syndrome shares some features of Alström syndrome. The major clinical features of Bardet-Biedl syndrome are rod-cone dystrophy, postaxial polydactyly, central obesity, cognitive impairment, hypogonadism, and renal dysfunction [Beales et al 1999]. A major difference between Alström syndrome and Bardet-Biedl syndrome is the timing of the onset of visual problems: in Alström syndrome, visual problems are usually apparent in the first two years of life; in Bardet-Biedl syndrome, the average age of onset of visual problems is 8.5 years. Polydactyly, which is common in Bardet-Biedl syndrome, has not been described in Alström syndrome. Mental retardation is well described in Bardet-Biedl syndrome, while intellectual dysfunction is less common and less well described in Alström syndrome. Other differences include the relative infrequency of hearing problems (~5%) and diabetes mellitus (5%-10%) in Bardet-Biedl syndrome compared with Alström syndrome. Mutations in at least 12 different genes are causative. Inheritance is autosomal recessive.

Achromatopsia, a disorder that affects only the retina, is characterized by reduced visual acuity, pendular nystagmus, increased sensitivity to light (photophobia), a small central scotoma, eccentric fixation, and reduced or complete loss of color discrimination. Most individuals have **complete achromatopsia** with total lack of function of all three types of cones [i.e., the long-wavelength-sensitive cones (red), the middle-wavelength-sensitive cones (green) and the short-wavelength-sensitive cones (blue)]. Rarely, individuals have **incomplete achromatopsia**, in which one or more cone types may be partially functioning resulting in symptoms similar to but less severe than those of complete achromatopsia. Nystagmus and increased sensitivity to bright light develop shortly after birth. Best visual acuity ranges from 20/200 or less in complete achromatopsia to as high as 20/80 in incomplete achromatopsia. Visual acuity is usually stable over time. The diagnosis of achromatopsia is based on case history, color vision testing, electrophysiologic examination, and absent or only minor fundus changes. The fundus is usually normal. Mutations in three genes, *CNGA3*, *CNGB3*, and *GNAT2*, are causative. Inheritance is autosomal recessive.

Leber congenital amaurosis (LCA), a severe dystrophy of the retina without other organ system involvement, typically becomes evident in the first year of life. Reduced vision is accompanied by nystagmus, sluggish pupillary responses, photophobia, hyperopia, and keratoconus. The electroretinogram (ERG) is characteristically "nondetectable" or severely subnormal. The oculo-digital sign (repeated eye rubbing, poking, and pressing of the eyes) is characteristic. Although the retina may appear normal in infancy, a pigmentary retinopathy reminiscent of retinitis pigmentosa is frequently observed later in childhood. Eight genes are

currently known to be associated with LCA: *CRX, CRB1, GUCY2D, AIPL1, RDH12, RPGRIP1, RPE65*, and *CEP290*. Depending on the survey, these genes together are estimated to account for from one-third to one-half of all LCA. Three other disease loci for LCA have been reported. Most often, Leber congenital amaurosis is inherited in an autosomal recessive manner. Rarely, LCA is inherited in an autosomal dominant manner as a result of mutations within the *CRX* gene.

Note: Individuals with Leber congenital amaurosis and dilated cardiomyopathy described by Russell-Eggitt et al (1989) were subsequently determined to have Alström syndrome [Russell-Eggitt et al 1998].

Early-onset dilated cardiomyopathy. Dilated cardiomyopathy, characterized by cardiac dilation and reduced systolic function, is the end stage of a number of inherited and acquired disorders. Familial dilated cardiomyopathy may be inherited in an autosomal dominant manner and less frequently in an autosomal recessive manner with ventricular dilatation and systolic dysfunction becoming apparent in the third and fourth decades.

Inherited mitochondrial disorders (see Mitochondrial Diseases Overview). These represent a heterogeneous group of complex disorders that may be caused by mutations in mitochondrial DNA or nuclear DNA. Clinical features common to mitochondrial disorders and Alström syndrome include cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus; however, central nervous system involvement and muscle weakness occur in individuals with mitochondrial disorders, while they are unusual in Alström syndrome. Generally, mitochondrial disorders present in late childhood or in adulthood, unlike Alström syndrome, which usually presents during the first year of life. The mitochondrial diseases similar to Alström syndrome include chronic progressive external ophthalmoplegia (CPEO), infantile myopathy and lactic acidosis, and Kearns-Sayre syndrome.

CPEO usually presents in young adulthood and is characterized by slowly progressive paralysis of the extraocular muscles leading to eventual ophthalmoparesis. It is usually associated with skeletal muscle weakness. In Kearns-Sayre syndrome, children are usually normal at birth and CPEO and pigmentary retinopathy appear in young adulthood. The retinal atrophy usually precedes the development of cardiac conduction disturbances.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Alström syndrome, a complete history of disease should direct detailed physical examination and investigations.

- **Cone-rod dystrophy.** Ophthalmologic evaluation, including electroretinogram and visual field testing
- **Obesity.** Measurement of weight and height; calculation of body mass index (BMI)
- **Progressive sensorineural hearing loss.** Audiometry to detect sensorineural or conductive hearing loss
- **Dilated cardiomyopathy.** A detailed cardiac history and examination, including echocardiography and ECGs. Echocardiography is required to demonstrate ventricular dilatation and decreased myocardial function.
- **Insulin resistance/type 2 diabetes mellitus**
  - Fasting plasma glucose, even in infancy
  - A glucose tolerance test as early as age six years

  - Plasma insulin concentration, as hyperinsulinism may be present from infancy

- **Hyperlipidemia.** A fasting lipid profile, including triglycerides
- **Urologic/renal disease**
  - History of urinary difficulties
  - Urinalysis and measurement of concentration of plasma urea, electrolytes, uric acid, and creatinine
  - If the individual is symptomatic or if urinalysis is abnormal, renal ultrasound examination to detect pelvi-calyceal dilatation and bladder ultrasound examination to measure post-voiding residual volumes
- **Hepatic disease**
  - Measurement of plasma ALT, AST, and GGT concentration
  - If plasma ALT, AST, and GGT concentration is high, liver ultrasonography to evaluate for possible hepatomegaly and portal hypertension
  - If clinically indicated, screening esophagogastroduodenoscopy for varices
- **Pulmonary disease.** Detailed assessment of pulmonary function by chest radiography, combined with pulmonary function tests
- **Other**
  - **Thyroid abnormalities.** Measure plasma TSH, T4, and T3 concentrations.
  - **Gastrointestinal.** If symptoms of **reflux esophagitis** are present, perform barium swallow or upper gastrointestinal endoscopy.
  - **Skin.** Note acanthosis nigricans (indication of insulin resistance/diabetes mellitus), alopecia, body hair, hirsutism on physical examination.
  - **Orthopedic abnormalities.** Note flat feet, scoliosis, barrel chest, kyphoscoliosis on physical examination.
  - **Neurologic manifestations.** Examine for absence seizures, autistic-spectrum behavioral abnormalities, excessive startle, partial unilateral paralysis, unexplained joint or muscle pain, muscle dystonia, or hyporeflexia.

Treatment of Manifestations

- **Rod-cone dystrophy**
  - Early on when photodysphoria is significant, the use of red-tinted prescription lenses may reduce symptoms.
  - Early instruction in the use of Braille, mobility training, adaptive living skills, and computing skills (including voice recognition and transcription software), and the use of large print reading materials while vision is still present are crucial.
- **Obesity.** A healthful diet and regular exercise, such as walking, hiking, biking, and swimming, are recommended.
- **Progresive sensorineural hearing loss**
  - Myringotomy has been helpful in individuals with recurrent "glue ear."

  - Digital hearing aids benefit some individuals.

- **Dilated cardiomyopathy.** Angiotensinogen-converting enzyme inhibitors, diuretics, digoxin, and possibly beta-blockers should be used in the treatment of cardiac failure.
- **Insulin resistance/type 2 diabetes** should be treated as in the general population unless heart failure and/or liver dysfunction are present. The diabetes mellitus is very insulin resistant, but some individuals respond to a low-sugar, low-fat diet; exercise; and metformin. Glitazones are added to further reduce insulin resistance but must be avoided in the presence of active or treated heart failure. These treatments should be discontinued when the serum creatinine concentration exceeds 200 µmol/L or if cardiomyopathy is evident.
- **Hypertriglyceridemia**
  - High-dose statins may reduce serum triglycerides, as can nicotinic acid, although the latter is not as well tolerated.
  - Fibrates have been ineffective in a few cases.
  - Pancreatitis should be treated as in the general population.
- **Hypogonadotrophic hypogonadism.** If abnormalities in pubertal development or menstrual abnormalities are present on physical examination, the affected individual should be referred to an endocrinologist with expertise in sexual developmental abnormalities.
- **Urologic/renal disease**
  - Some individuals have required urinary diversion or self-catheterization to manage voiding difficulties [MacDermott 2001].
  - The use of angiotensinogen-converting enzyme (ACE) inhibitors may be considered if proteinuria is detected.
- **Hepatic disease.** Portal hypertension may be treated with beta-blockade and sclerotherapy of the esophageal veins. Banding should be done in order to prevent upper GI hemorrhage from varices. Patients who fail to respond to medication and banding are candidates for a transjugular intrahepatic portosystemic shunt (TIPS) to decrease risk of variceal bleeding caused by portal hypertension. Patients with significant portal hypertension should be evaluated early for liver transplantation.
- **Pulmonary disease.** Chronic obstructive airway disease and associated infection should be managed in line with appropriate national guidelines.
- **Other**
  - If skeletal abnormalities are present, referral to an orthopedist is appropriate.
  - Thyroxine therapy should be initiated and monitored if the individual is hypothyroid.
  - Reflux esophagitis, skin manifestations, orthopedic abnormalities, and neurologic manifestations should be treated as in the general population.

Prevention of Secondary Complications

Routine pediatric immunizations should be given and administration of pneumococcal vaccination should be considered.

The combination of dilated cardiomyopathy, congestive heart failure, pulmonary hypertension, and pulmonary fibrosis can cause sudden severe hypoxia in a patient with infection or following surgery. Close monitoring of cardiac status and oxygenation are necessary until the patient is fully recovered.

Surveillance

- **Rod-cone dystrophy.** Annual ophthalmologic follow-up is indicated as long as the affected individual has vision.
- **Obesity.** Weight, height, and body mass index (BMI) should be recorded annually and plotted on growth curves.
- **Progressive sensorineural hearing loss.** Audiometry should be performed yearly.
- **Dilated cardiomyopathy**
  - A detailed cardiac history and examination including echocardiography annually even in the absence of symptoms related to left ventricular dysfunction (signs of cardiac failure, such as sweating, fatigue, lethargy, asthma, decreased physical activity)
  - ECGs in parallel with echocardiography and 24-hour ECG monitoring if indicated
  - In individuals who have had infantile cardiomyopathy, annual monitoring by a pediatric cardiologist even if the individual has recovered from cardiomyopathy and is asymptomatic
- **Insulin resistance/type 2 diabetes**
  - Annual measurement of plasma insulin concentration, as hyperinsulinemia may be present from early infancy.
  - Measurement of fasting plasma glucose concentration every two to three months
  - If fasting blood glucose is greater than 7 mmol/L, or postprandial blood glucose is greater than 11 mmol/L, measurement of HbA1c concentration and serum glucose concentration regularly (every six months, although glucose estimations may be performed more frequently as determined by the 'diabetic control' of the affected individual)
- **Hyperlipidemia.** Annual total lipid profile determination is appropriate unless hyperlipidemia is present, in which case more frequent monitoring may be indicated. When the affected individual is ill and/or dehydrated, pancreatitis precipitated by hyperlipidemia can be life threatening.
- **Renal disease**
  - Urinalysis and measurement of plasma concentrations of electrolytes, uric acid, BUN, and creatinine twice yearly
  - Renal and bladder ultrasound examinations every one to two years if the individual is symptomatic or if urinalysis is abnormal
- **Hepatic disease**
  - Annual measurement of plasma ALT, AST, and GGT concentration
  - If transaminases or GGT concentration is elevated, liver ultrasonography to evaluate for possible steatosis, hepatomegaly, and portal hypertension

- **Pulmonary disease.** Pulmonary function tests should be performed yearly to evaluate general lung function, even if symptoms of pulmonary fibrosis are not yet present.
- **Hypothyroidism.** Patients should be monitored annually for thyroid abnormalities.

Agents/Circumstances to Avoid

Therapy directed at one system may have adverse effects on other systems; for example, the use of glitazone therapy in diabetes mellitus is contraindicated in the presence of cardiac failure.

Testing 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 for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Alström syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.

Offspring of a proband. Individuals with Alström syndrome are not known to be fertile.

Other family members of a proband. Sibs of the proband's parents are at 50% risk of being carriers.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at 25% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed in menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Alstrom Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
ALMS1	2p13	Alstrom syndrome protein 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Alstrom Syndrome

203800	ALSTROM SYNDROME; ALMS
606844	ALMS1 GENE; ALMS1

Table C. Genomic Databases for Alstrom Syndrome

Gene Symbol	Entrez Gene	HGMD
ALMS1	7840 (MIM No. 606844)	ALMS1

For a description of the genomic databases listed, click here.

Normal allelic variants: *ALMS1* is a novel gene that does not share significant sequence homology with any other genes. There are 23 exons in *ALMS1*.

Pathologic allelic variants: To date, 24 mutations in *ALMS1* have been reported in Alström syndrome. The majority of these are nonsense and frameshift variations (insertions or deletions) that are predicted to cause premature protein truncation [Collin et al 2002, Hearn et al 2002, Kinoshita et al 2003, Titomanlio et al 2004, Bond et al 2005, Minton et al 2006].

Normal gene product: The 12.9 kb *ALMS1* transcript encodes a ubiquitously expressed protein of 4,169 amino acids of unknown function.

Abnormal gene product: Unknown

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Alstrom Syndrome International
14 Whitney Farm Rd
Mt Desert ME 04660
Phone: 800-371-3628
Fax: 207-288-6078
Email: jdm@jax.org
www.jax.org/alstrom

Alstrom Syndrome-UK
49 Southfield Avenue
Preston Paignton
South Devon TQ3 1LH
United Kingdom
Phone: 1803 524238

Email: info@alstrom.org.uk
www.alstrom.org.uk

National Library of Medicine Genetics Home Reference
Alstrom syndrome

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Revision History

- 25 June 2007 (me) Comprehensive update posted to live Web site
- 7 February 2005 (me) Comprehensive update posted to live Web site
- 11 May 2004 (ih) Revision: test availability
- 7 February 2003 (me) Review posted to live Web site
- 6 June 2002 (ih) Original submission

Age Range of Onset of Features in Alström Syndrome

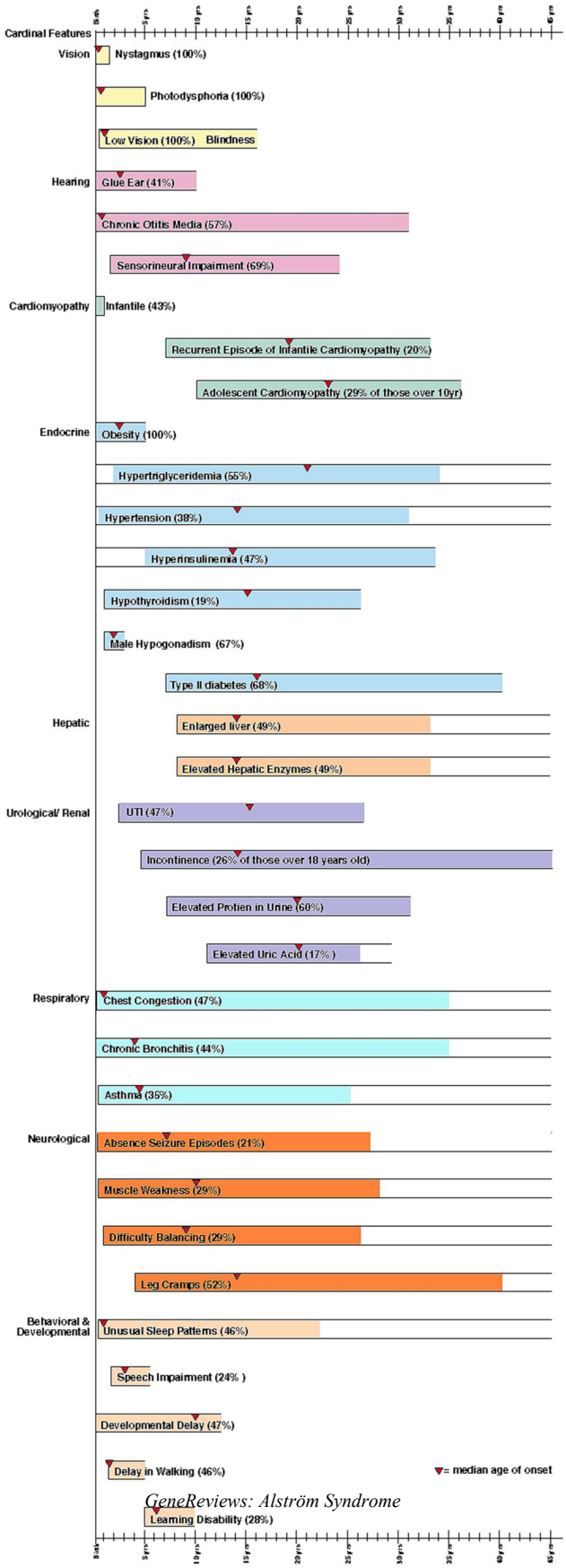

Figure 1. Age Range of Onset of Features in Alstrom Syndrome