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Alström Syndrome

Richard B Paisey, MD, FRCP,[1] Rick Steeds, MD,[2] Tim Barrett, MD,[3] Denise Williams, MD,[4] Tarekegn Geberhiwot, MD,[5] and Meral Gunay-Aygun, MD[6,7]

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Summary

Clinical characteristics

Alström syndrome is characterized by cone-rod dystrophy, obesity, progressive bilateral sensorineural hearing impairment, acute infantile-onset cardiomyopathy and/or adolescent- or adult-onset restrictive cardiomyopathy, insulin resistance / type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), and chronic progressive kidney disease. Cone-rod dystrophy presents as progressive visual impairment, photophobia, and nystagmus usually starting between birth and age 15 months. Many individuals lose all perception of light by the end of the second decade, but a minority retain the ability to read large print into the third decade. Children usually have normal birth weight but develop truncal obesity during their first year. Sensorineural hearing loss presents in the first decade in as many as 70% of individuals and may progress to the severe or moderately severe range (40-70 db) by the end of the first to second decade. Insulin resistance is typically accompanied by the skin changes of acanthosis nigricans, and proceeds to T2DM in the majority by the third decade. Nearly all demonstrate hypertriglyceridemia.

Other findings can include endocrine abnormalities (hypothyroidism, hypogonadotropic hypogonadism in males, and hyperandrogenism in females), urologic dysfunction / detrusor instability, progressive decrease in renal function, and hepatic disease (ranging from elevated transaminases to steatohepatitis/NAFLD). Approximately 20% of affected individuals have delay in early developmental milestones, most commonly in gross and fine motor skills. About 30% have a learning disability. Cognitive impairment (IQ <70) is very rare.

Wide clinical variability is observed among affected individuals, even within the same family.

Author Affiliations: 1 Consultant Endocrinologist, Torbay Hospital Torquay, Devon, United Kingdom; Email: richard.paisey@nhs.net. 2 Consultant Cardiologist, University Hospitals Birmingham, United Kingdom; Email: rick.steeds@uhb.nhs.uk. 3 Pediatric Endocrinologist, University of Birmingham Birmingham, United Kingdom; Email: t.g.barrett@bham.ac.uk. 4 Consultant Clinical Geneticist, Birmingham Women's Hospital Birmingham, United Kingdom; Email: denise.williams21@nhsnet; denise.williams@bwhct.nhs.uk. 5 Consultant in Inherited Metabolic Disorders, University Hospitals Birmingham, United Kingdom; Email: tarekegn.geberhiwot@uhb.nhs.uk; t.g.hiwot@bham.ac.uk. 6 Professor, Departments of Pediatrics and Genetics Johns Hopkins University School of Medicine Baltimore, Maryland; Email: mgunaya1@jhu.edu. 7 National Human Genome Research Institute Medical Genetics Branch Section on Human Biochemical Genetics Intramural Office of Rare Diseases National Institutes of Health Bethesda, Maryland; Email: mgunaya1@jhu.edu.

Diagnosis/testing

The clinical diagnosis of Alström syndrome is based on cardinal clinical features that emerge throughout infancy, childhood, and young adulthood. The molecular diagnosis of Alström syndrome is established in individuals of all ages by identification of biallelic pathogenic variants in *ALMS1* on molecular genetic testing.

Management

Treatment of manifestations: No therapy exists to prevent the progressive organ involvement of Alström syndrome. Individuals with Alström syndrome require coordinated multidisciplinary care to formulate management and therapeutic interventions. Red-orange tinted prescription lenses may reduce symptoms of photodysphoria; early educational planning should be based on the certainty of blindness. Obesity and insulin resistance are managed by a healthful, reduced-calorie diet with restricted simple carbohydrate intake and regular aerobic exercise. Myringotomy and/or hearing aids as needed for hearing impairment. Standard therapy for heart failure / cardiomyopathy. Standard treatment of insulin resistance / T2DM as in the general population. Consider nicotinic acid derivatives for hyperlipidemia; consultation with an endocrinologist if pubertal development and/or menses are abnormal; urinary diversion or self-catheterization in those with voiding difficulties; renal transplantation has been successful in a number of cases; appropriate therapy for portal hypertension and esophageal varices.

Surveillance: Routine assessment of vision and hearing; weight, height, and body mass index; heart (including echocardiography and EKG in all individuals, and MRI in those age >18 years); postprandial c-peptide and glucose and HbA1C starting at age four years; lipid profile; plasma ALT, AST, and GGT concentrations; thyroid function. Twice-yearly CBC, electrolytes, BUN, creatinine, cystatin-C, uric acid, urinalysis. Renal and bladder ultrasound examinations every one to two years if symptomatic and/or if urinalysis is abnormal.

Agents/circumstances to avoid: Any substance contraindicated in persons with renal, hepatic, and/or myocardial disease. 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.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an individual with Alström syndrome in order to identify as early as possible those who would benefit from prompt evaluation for manifestations of Alström syndrome, initiation of treatment, and/or surveillance for age-related manifestations.

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. When the *ALMS1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Alström syndrome **should be suspected** in individuals with the following clinical findings that evolve as affected individuals age [Marshall et al 2005]:

- Cone-rod dystrophy with decreased vision and secondary nystagmus and photodysphoria (light sensitivity / photophobia) usually within the first year of life. Full-field electroretinography, required to

establish the diagnosis of cone-rod dystrophy, is abnormal from birth, eventually with impairment of both cone and rod function. Fundus examination in the first decade may be normal or may show a pale optic disc and narrowing of the retinal vessels.

- Early childhood-onset obesity, primarily truncal with a body mass index (BMI: kg/m^2) greater than 25 (for adults) or greater than the 95th centile on age- and sex-appropriate growth charts
- Progressive bilateral sensorineural hearing impairment (initially in the high-frequency range), usually diagnosed between ages one and ten years, although onset can vary
- Acute infantile-onset cardiomyopathy and/or adolescent- or adult-onset restrictive cardiomyopathy
- Insulin resistance / type 2 diabetes mellitus (T2DM), the result of tissue resistance to the actions of insulin, usually present in childhood and manifest as elevated plasma insulin concentration and glucose intolerance. Insulin resistance ranges from hyperinsulinemia to glucose intolerance to T2DM, depending on the age of the individual. T2DM can develop in childhood or adolescence.
- Normal stature in childhood; short stature in adulthood
- Hypogonadism, non-autoimmune hypothyroidism, and female hyperandrogenism
- Urologic dysfunction / detrusor instability
- Progressive decrease in renal function
- Hepatic disease that is variable and ranges from elevated transaminases to steatohepatitis / nonalcoholic fatty liver disease (NAFLD). The liver and spleen may be enlarged. Extensive fibrosis, cirrhosis, portal hypertension, and liver failure have been described.
- Hypertriglyceridemia
- Hypertension
- Gradual thickening of subcutaneous tissues (e.g., thick ears)
- Alopecia

Establishing the Diagnosis

The clinical diagnosis of Alström syndrome is based on cardinal clinical features that emerge throughout infancy, childhood, and young adulthood (Table 1 and Figure 1); therefore, the accuracy of the proposed clinical diagnostic criteria is low in children before age five years, especially in the absence of infantile cardiomyopathy [Marshall et al 2013, Louw et al 2014, Khan et al 2015, Long et al 2015, Xu et al 2016, Nerakh & Ranganath 2019, Weiss et al 2019].

Table 1. Alström Syndrome Diagnostic Criteria by Age

Age Range	Diagnostic Criteria		Minimum Required
	Major	Minor	
Birth - 2 yrs [1]	• 1 *ALMS1* pathogenic variant OR family history of Alström syndrome • Nystagmus / photophobia / impaired vision • Infantile cardiomyopathy	• Obesity • SNHL	2 major criteria OR 1 major + 2 minor criteria
3-14 yrs [1]	• 1 *ALMS1* pathogenic variant OR family history of Alström syndrome • Nystagmus / photophobia / impaired vision (if old enough for testing: cone dystrophy by ERG) • History of infantile cardiomyopathy	• SNHL • Obesity &/OR its complications (e.g., insulin resistance, T2DM, liver steatosis, hypertriglyceridemia) • Restrictive cardiomyopathy • ↓ renal function	2 major criteria OR 1 major + 3 minor criteria

Table 1. continued from previous page.

Age Range	Diagnostic Criteria		Minimum Required
	Major	Minor	
15 yrs - adult	• 1 *ALMS1* pathogenic variant OR family history of Alström syndrome • Vision (history of nystagmus in infancy/childhood, impaired vision, legal blindness, cone & rod dystrophy by ERG)	• SNHL • Restrictive cardiomyopathy &/OR history of infantile cardiomyopathy • Obesity &/OR its complications (e.g., insulin resistance, T2DM, liver steatosis, hypertriglyceridemia) • CKD Stage ≥III	2 major + 2 minor criteria OR 1 major + 4 minor criteria

Adapted from Marshall et al [2007]; reprinted with permission of Nature Publishing Group
CKD = chronic kidney disease; ERG = electroretinogram; SNHL = sensorineural hearing loss; T2DM = type 2 diabetes mellitus
1. Children in these age groups should be reevaluated for the presence of major and minor criteria as they age.

The molecular diagnosis of Alström syndrome is established in individuals of all ages by identification of biallelic pathogenic variants in *ALMS1* on molecular genetic testing (see Table 2). Because atypical clinical presentations of Alström syndrome are increasingly recognized [Taşdemir et al 2013, Casey et al 2014, Sanyoura et al 2014, Bronson et al 2015, Yang et al 2017, Maltese et al 2018], molecular genetic testing is recommended in individuals with suggestive clinical features.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Alström syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Alström syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ALMS1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

A multigene panel that includes *ALMS1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) In infants with apparently isolated dilated cardiomyopathy a multigene panel for cardiomyopathy may lead to the diagnosis of Alström syndrome. Similarly, a multigene panel for retinopathy may be diagnostic in apparently isolated infantile retinal dystrophy or in suspected misdiagnosis of Usher syndrome in the setting of retinal degeneration associated with hearing loss. Rare atypical cases with milder retinal disease may be diagnosed by multigene panels for obesity. Note: (2) 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. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (4) 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. (5) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

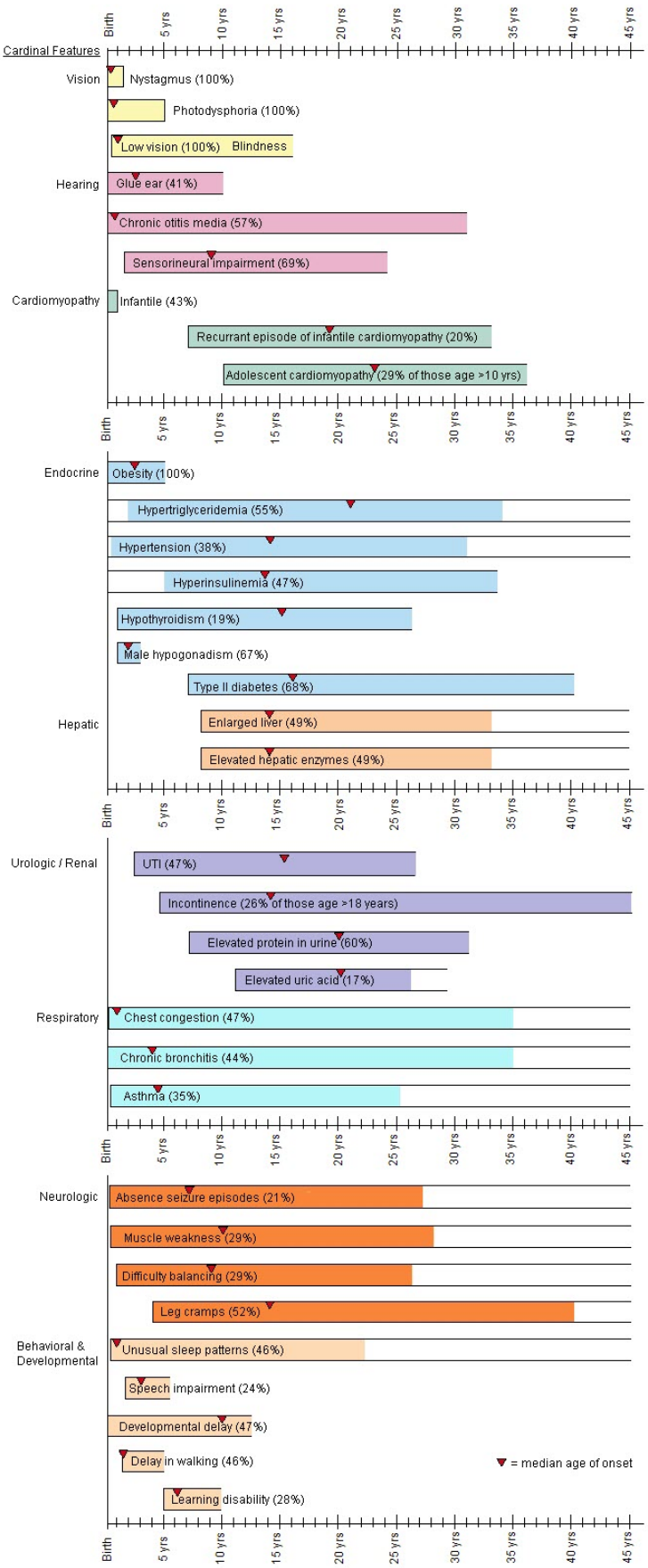

Figure 1. Age range of onset of features in Alström syndrome

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

Option 2

When the diagnosis of Alström syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

Table 2. Molecular Genetic Testing Used in Alström Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method [3]
ALMS1 [4]	Sequence analysis [4]	85%-90% [5]
	Gene-targeted deletion/duplication analysis [6]	~5% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Because approximately 10% of families with Alström syndrome have no identified *ALMS1* pathogenic variant [Marshall et al 2015], a ciliopathy multigene panel should be performed in individuals with mild/atypical Alström syndrome and only missense or no variants in *ALMS1*.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Marshall et al [2015]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. The following have been reported: a gross deletion [Bond et al 2005], insertion of a Ya5 *Alu* retrotransposon in the *ALMS1* coding sequence [Taşkesen et al 2012], a balanced translocation [Hearn et al 2002], and several other intragenic large deletions [Marshall et al 2015, Astuti et al 2017].

Clinical Characteristics

Clinical Description

The first clinical manifestation of Alström syndrome (Table 3) is usually nystagmus caused by cone-rod dystrophy and/or infantile-onset cardiomyopathy. Later-onset findings include obesity that manifests during the first years of life, progressive sensorineural hearing loss (SNHL), insulin resistance / T2DM, adolescent- or adult-onset restrictive cardiomyopathy, hepatic steatosis, and progressive renal dysfunction. Wide clinical variability is observed among individuals with Alström syndrome, including among sibs [Hoffman et al 2005].

Table 3. Age of Onset and Incidence of Common Features of Alström Syndrome

Feature	Age of Onset Range (Mean)	Incidence [1]
Cone-rod dystrophy	Birth - 15 mos (5 mos) [2]	100%

Table 3. continued from previous page.

Feature		Age of Onset Range (Mean)	Incidence [1]
Obesity		Birth - 5 years (2.5 yrs)	98%
Progressive SNHL		2-25 yrs (9 yrs)	88%
Cardiomyopathy	Infantile	2 wks - 4 mos	42% [3]
	Restrictive	Juvenile - late 30s	18%
Insulin resistance / T2DM		4-30 yrs / 8-40 yrs (16 yrs)	92% / 68%
Short stature		Puberty - adult	98%
Hypogonadism (central or primary)		10+ yrs	78% of males
Urologic disease (bladder dysfunction)		Adolescence - adult	48%
Progressive renal disease		Adolescence - adult	Variably progressive in all individuals
Hepatic disease		8-30 yrs	23%-100%

Based on a study of 182 patients by Marshall et al [2005]
SNHL = sensorineural hearing loss; T2DM = type 2 diabetes mellitus
1. Given the age-dependent nature of many features of Alström syndrome, percentages are not exact and may be underestimates.
2. Rare individuals with atypical later onset and milder retinal dystrophy are reported.
3. The proportion of infants with Alström syndrome who develop infantile-onset cardiomyopathy is probably underestimated because some infants succumb to heart failure before the diagnosis of Alström syndrome is made.

Cone-rod dystrophy. In most affected individuals, visual problems present as progressive cone dystrophy resulting in visual impairment, photophobia, and nystagmus between birth and age 15 months. Rod function is preserved initially but deteriorates as the individual ages, with visual acuity of 6/60 or less by age ten years, increasing constriction of visual fields, and no light perception by age 35 years [Nasser et al 2018].

Optical coherence tomography (OCT) reveals central macular changes that are mild during early childhood but slowly progress, resulting in loss of photoreceptors and retinal pigment epithelium. Severe retinal wrinkling, intraretinal opacities, foveal contour abnormalities, optic nerve drusen, vitreoretinal separation, and hyperreflectivities in all retinal layers are observed. The severity of the macular changes on OCT correlates with vision [Dotan et al 2017]. The severity and age of onset of the retinal degeneration vary among affected individuals [Malm et al 2008]. While many individuals lose all perception of light by the end of the second decade, a minority retain the ability to read large print into the third decade. Posterior subcapsular cataracts are common, even in the absence of diabetes.

Obesity. Children with Alström syndrome have normal birth weight. Hyperphagia and excessive weight gain begin during the first years, resulting in childhood obesity. In some individuals body weight tends to normalize, decreasing into the high-normal to normal range after adolescence.

Progressive bilateral SNHL presents in the first decade in as many as 70% of individuals with Alström syndrome; average age at detection of hearing loss is seven years [Marshall et al 2005, Ozantürk et al 2015, Lindsey et al 2017]. A majority of affected infants pass newborn screening for hearing loss [Lindsey et al 2017]. Hearing loss may be detected as early as age one year. Initially in the high frequency range, 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].

In 33 individuals with Alström syndrome, the average rate of progression of hearing loss was 10-15 db/decade [Lindsey et al 2017]. The auditory defect in Alström syndrome is mapped to the outer hair cells of cochlea based on absent otoacoustic emissions, intact speech discrimination, and disproportionately normal auditory brain

stem responses [Lindsey et al 2017]. Therefore, individuals with Alström syndrome are good candidates for aural amplification or cochlear implantation in cases of severe-to-profound hearing loss [Florentzson et al 2010, Lindsey et al 2017].

A high incidence of adhesive otitis media (glue ear) due to long-standing fluid in the middle ear can lead to an additional conductive hearing loss [Marshall et al 2005].

Cardiomyopathy. More than 60% of individuals with Alström syndrome develop congestive heart failure at some stage of their lives as a result of infantile-, adolescent-, or adult-onset cardiomyopathy. Onset, progression, and clinical outcome of cardiomyopathy can vary, even within families [Hoffman et al 2005, Mahamid et al 2013, Brofferio et al 2017].

More than 40% of infants with Alström syndrome present with a transient but severe cardiomyopathy with onset between ages three weeks and four months [Marshall et al 2005, Brofferio et al 2017]. Of note, the proportion of those with Alström syndrome who develop infantile-onset cardiomyopathy may be underestimated because some infants may succumb before the diagnosis of Alström syndrome [Louw et al 2014]. Most infants with severe cardiomyopathy develop irreversible heart failure, leading to death within the first weeks to months of life. Autopsy findings in these neonates show dramatically increased mitotic activity in the cardiomyocytes (i.e., mitogenic cardiomyopathy) [Louw et al 2014, Shenje et al 2014]. Most infants who survive make an apparently full recovery by age two years.

About 20% of individuals with Alström syndrome develop a later-onset progressive restrictive cardiomyopathy identified between the teens and late 30s. A characteristic feature of these individuals appears to be myocardial fibrosis documented at postmortem [Marshall et al 2005] and on cardiovascular MRI in asymptomatic and clinically affected individuals [Loudon et al 2009, Corbetti et al 2013, Edwards et al 2015]. Strain echocardiography suggests that some degree of myocardial fibrosis is probably present in almost all individuals with Alström syndrome including asymptomatic children [Brofferio et al 2017].

Flow-limiting coronary artery disease occurs in approximately 10% but does not appear to be related to progression of myocardial fibrosis.

Severe insulin resistance / type 2 diabetes mellitus (T2DM) are hallmarks of Alström syndrome. The age at which T2DM develops varies; it has been reported at as early as age five years. Insulin resistance proceeds to T2DM in the majority by the third decade. Insulin resistance results in the skin changes of acanthosis nigricans; i.e., velvety hyperpigmented patches in intertriginous areas [Akdeniz et al 2011, Han et al 2018]. An obesity-related contrast in the incidence of T2DM has been described in Canadian versus Italian cohort studies of children with Alström syndrome followed from childhood through to adolescence, with much lower diabetes rates in the leaner Italian children [Mokashi & Cummings 2011, Bettini et al 2012].

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]. The hyperinsulinism was out of proportion to the degree of obesity. Consistently, in a recent study comparing 38 individuals with Alström syndrome to 76 age-, sex-, and BMI-matched controls, the severity of insulin resistance in individuals with Alström syndrome was documented to be more than five times that of equally obese controls [Han et al 2018], and metabolic syndrome (defined as ≥3 of the following: abdominal obesity, hypertriglyceridemia, low HDL-cholesterol, hypertension, impaired glucose tolerance) was ten times more common in Alström syndrome compared to controls.

Coronary artery disease as a result of insulin resistance, diabetes, dyslipidemia, and renal failure was reported in one affected individual [Jatti et al 2012]. A more recent cohort study of individuals from the UK has shown that duration of diabetes is linked with increased carotid-femoral pulse wave velocity and that this in turn predicts

occurrence of atherosclerosis [Paisey et al 2015]. The authors' unpublished data show coronary artery disease to be increasingly common in adults with Alström syndrome (observed in up to 10%).

Diabetic peripheral neuropathy with risk of foot ulceration occurs rarely if at all in Alström syndrome [Paisey et al 2009] in contrast to patients with adolescent-onset T2DM without Alström syndrome, in whom 30% had severe peripheral neuropathy.

Hyperlipidemia. Insulin resistance is associated with hypertriglyceridemia in >90% of individuals with Alström syndrome [Paisey et al 2004, Paisey et al 2009, Han et al 2018]. Serum triglyceride levels commonly range from 2 to 5 mmol/L (177 to 443 mg/dL) with HDL cholesterol <1 mmol/L (39 mg/dL) and total cholesterol levels from 5 to 7 mmol/L (193 to 271 mg/dL). In some cases serum triglyceride levels can increase to well above 20 mmol/L (1,770 mg/dL). Affected individuals are at risk for sudden increase in triglycerides, precipitating life-threatening pancreatitis [Marshall et al 2005].

Short stature. Growth rates for young children are normal, but accelerated skeletal maturity (2-3 years advanced bone age) and low-serum growth hormone concentrations result in adult stature that is typically below the 25th centile. In about 98% of individuals older than age 16 years height is below the fifth centile [Maffei et al 2007].

Male pubertal development. A variable combination of hypogonadotropic hypogonadism and testicular fibrosis can result in delayed or arrested puberty in males, resulting in normal or immature secondary sexual characteristics; gynecomastia may be present [Marshall et al 2005]. Male fertility, which has not been systematically studied, has not been reported in males with biallelic *ALMS1* pathogenic variants.

Female pubertal development. Endocrine disturbances in females include reduced plasma gonadotropin concentrations, hirsutism, polycystic ovarian syndrome associated with insulin resistance, precocious puberty, irregular menses, or amenorrhea. External genitalia are normal in females, though breast development is often poor.

Fertility in females has not been systematically studied. Although a molecular diagnosis was not confirmed, one clinical report describes two unrelated females with late presentation of the syndrome, each of whom had healthy children [Iannello et al 2004].

Urologic disorders of varying severity, which affect approximately 50% of affected individuals, can include detrusor-urethral dyssynergia (lack of coordination of bladder and urethral muscle activity). The greatest problems appear to occur in females in their late teens. Minor manifestations include urgency and long intervals between voiding, suggesting decreased bladder sensation, hesitancy, and poor urinary flow. Moderate manifestations include urinary frequency, incontinence, and symptoms associated with recurrent infections. More severe manifestations are rare (<2%) and 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 is common, slowly progressive, and highly variable [Waldman et al 2018]. Onset can be in mid-childhood through adulthood. End-stage renal disease can occur as early as the mid- to late teens.

Renal ultrasonography and MRI may reveal abnormalities [Waldman et al 2018]. The most common ultrasonography finding is renal parenchymal hyperechogenicity often limited to the medulla. Renal cysts are identified in a small number of patients [Waldman et al 2018, Baig et al 2020].

Renal biopsy often shows interstitial fibrosis, glomerular hyalinosis, and tubular atrophy but absence of histopathologic features of diabetic or reflux nephropathy [Marshall et al 2005, Baig et al 2020]. In addition, glomerular function in Alström syndrome does not show significant association with T2DM, hyperlipidemia, cardiomyopathy, or hypertension, suggesting that kidney disease is a primary manifestation of the syndrome. Diabetes and hypertension may have an additive effect on the progression of renal disease.

Obstructive uropathy is rare.

Hepatic disease. Individuals with Alström syndrome have disproportionately high liver fat in comparison to equally obese controls [Han et al 2018]. Their risk of advanced NAFLD and cirrhosis is disproportionately increased for their age, BMI, and duration of diabetes [Gathercole et al 2016]. Plasma concentration of liver enzymes is often elevated starting in early childhood. Hepatomegaly is common. In some affected individuals liver disease progresses to cirrhosis and hepatic failure in the second to third decade. Portal hypertension associated with splenomegaly, esophageal varices, ascites, and hepatic encephalopathy may occur.

Liver biopsies and postmortem examination have revealed varying degrees of steatohepatitis, hepatic fibrosis, cirrhosis, chronic nonspecific active hepatitis with lymphocytic infiltration, and patchy necrosis [Quiros-Tejeira et al 2001, Marshall et al 2005]. Early stages of steatohepatitis can remit and relapse with significant improvements in exercise tolerance, insulin resistance, and blood sugar [Paisey et al 2014].

Gastrointestinal disease. General gastrointestinal disturbances such as epigastric pain and gastroesophageal reflux disease are common.

Pulmonary involvement ranges in severity from frequent upper and lower respiratory infections to pulmonary fibrosis and pulmonary hypertension. Recurrent upper and lower respiratory infections are common at all ages. Evaluation of pulmonary function is problematic because individuals with Alström syndrome have difficulty with deep inspiration / forced expiration. Most frequently there is restrictive lung disease due to kyphoscoliosis, sometimes in combination with pulmonary fibrosis, which has been confirmed in postmortem tissue. This may progress (with the added effects of cardiomyopathy) to pulmonary hypertension. The resulting susceptibility to severe hypoxia postoperatively or during episodes of pneumonia has been reported [Khoo et al 2009, Florentzson et al 2010].

A study of the burden of otosinopulmonary disease in 38 individuals with Alström syndrome revealed that recurrent otitis media was ubiquitous (92%), with 50% requiring pressure-equalization tube placement [Boerwinkle et al 2017]. A history of bronchitis/pneumonia and sinusitis was reported in 61% and 50% of individuals, respectively. However, manifestations of primary ciliary dyskinesia (PCD) (laterality defects, unexplained neonatal respiratory distress, year-round nasal congestion, and wet cough) were far less prevalent in individuals with Alström syndrome compared to those with PCD. In addition, the average nasal nitric oxide production in this cohort was 232 ± 57.1 nL/min compared to <77 nL/min required for a diagnosis of PCD.

Other findings include the following [Marshall et al 2005]:

- Scoliosis and kyphosis of varying severity (30%-70%) [Van den Abeele et al 2001] beginning in puberty [Maffei et al 2002]
- Severe flat feet (*pes planus*)
- Dental abnormalities
- Hypothyroidism (20%-30%) [Han et al 2018]
- Hypertension, often beginning in childhood (30%)
- Delay in early developmental milestones in ~20% of affected individuals, most commonly in gross and fine motor skills; ~30% have a learning disability. Cognitive impairment (IQ <70) is very rare.

Genotype-Phenotype Correlations

Genotype-phenotype correlations are challenging because almost all *ALMS1* pathogenic variants are null variants and the majority of affected individuals are compound heterozygous for rare variants reported in only a few families [Marshall et al 2015].

Prevalence

The prevalence of Alström syndrome is difficult to estimate; it is possible that individuals with attenuated forms of Alström syndrome may be underdiagnosed [Paisey et al 2011]. Estimates of the prevalence range from 1:100,000 [Minton et al 2006] to 1:1,000,000 [Marshall et al 2011b, Orphanet].

About 950 individuals diagnosed with Alström syndrome have been identified worldwide (Orphanet, accessed 4-8-19).

Ethnically or geographically isolated populations have a higher-than-average frequency of Alström syndrome [Deeble et al 2000, Ozantürk et al 2015].

Genetically Related (Allelic) Disorders

Currently no phenotypes other than Alström syndrome are known to be caused by biallelic *ALMS1* pathogenic variants. However, it is possible that increasing use of non-targeted genetic testing (e.g., whole-exome sequencing) may identify partial or atypical forms of Alström syndrome or other *ALMS1*-related phenotypes.

Differential Diagnosis

Polydactyly, cognitive impairment, and structural heart and genitourinary defects are not typical in Alström syndrome; these features should prompt evaluation for alternative diagnosis such as Bardet-Biedl syndrome (see Table 4).

Table 4. Disorders to Consider in the Differential Diagnosis of Alström Syndrome

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/Alström syndrome	Distinguishing from Alström syndrome (AS)
Bardet-Biedl syndrome (BBS)	>21 genes [1]	AR [2]	• Rod-cone dystrophy • Central obesity • Hypogonadism • Renal dysfunction	• Older mean age of onset of visual problems in BBS (8.5 yrs in BBS vs birth - 2 yrs in AS) • Polydactyly is common in BBS (not described in AS). • Cognitive impairment is common in BBS (normal intelligence in most persons w/AS). • Hearing problems are infrequent (~5%) in BBS. • Diabetes mellitus is less frequent (5%-10%) in BBS.

Table 4. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/Alström syndrome	Distinguishing from Alström syndrome (AS)
Achromatopsia (ACH)	*ATF6* *CNGA3* *CNGB3* *GNAT2* *PDE6C* *PDE6H*	AR	• Infantile nystagmus • Photophobia • Severely ↓ visual acuity • Poor or no color discrimination	• Only the retina is affected in ACH. [3] Retinal findings: • Common in ACH; not reported in AS: central outer retinal atrophy/ cavitation • Common in AS; less common in ACH: retention of central inner retinal layers (foveal immaturity) Absent in ACH: • Cardiomyopathy, obesity, SNHL, T2DM, liver disease, & renal dysfunction
Leber congenital amaurosis / early-onset severe retinal dystrophy (LCA/EOSRD)	>30 genes [4]	AR AD	• Retinal degeneration • ↓ visual acuity • Onset typically in 1st yr of life • Nystagmus • Photophobia	• Absence of other organ system involvement in LCA/EOSRD • Characteristic oculo-digital sign (repeated eye rubbing, poking, & pressing of eyes) in LCA/EOSRD
Early-onset dilated cardiomyopathy (DCM) (See Dilated Cardiomyopathy Overview.)	>25		• Dilated cardiomyopathy • Renal dysfunction (in syndromic forms due to mt defect)	Skeletal muscle disease w/↑ creatine kinase in most syndromic forms of DCM (not observed in AS)
Mitochondrial disorders [5]	See footnote 5.	AR AD Mat	• Cardiomyopathy • Sensorineural deafness • Optic atrophy • Pigmentary retinopathy • Diabetes mellitus	• CNS involvement & muscle weakness may occur in mt disorders (not reported in AS). • Late-childhood or adulthood presentation in mt disorders (vs AS, which usually presents in 1st yr of life)

AD = autosomal dominant; AR = autosomal recessive; AS = Alström syndrome; MOI = mode of inheritance; Mat = maternal; mt = mitochondrial; SNHL = sensorineural hearing loss

1. At least 21 genes are associated with BBS: *BBS1*, *BBS2*, *ARL6*, *BBS4*, *BBS5*, *MKKS*, *BBS7*, *TTC8*, *BBS9*, *BBS10*, *TRIM32*, *BBS12*, *MKS1*, *CEP290*, *WDPCP*, *SDCCAG8*, *LZTFL1*, *BBIP1*, and *IFT27*.

2. In some families, pathogenic variants in more than one BBS-related gene may result in a clinical phenotype of BBS. However, such families are difficult to identify and by previous estimations may account for less than 10% of all BBS.

3. Khan et al [2015]

4. To date, variants in 24 genes account for 70%-80% of individuals with LCA/EOSRD (see Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview: Table 2).

5. Mitochondrial disorders are a heterogeneous group of complex disorders that may be caused by pathogenic variants in mitochondrial DNA or nuclear DNA (see Mitochondrial Disorders Overview).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Alström syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Alström Syndrome

System/Concern	Evaluation	Comment
Constitutional	• Measure height, weight, head & waist circumference. • Detailed dietary history: caloric intake & dietary components • Assess daily physical activity level.	• Assess for obesity (check weight for height or calculate BMI). • Assess for short stature, check IGF-1.
Eyes	Ophthalmologic consultation	• Infants / young children: assess for photophobia, nystagmus, & impaired visual acuity. • Older children / adults: assess for cataracts; impaired vision; perform visual field testing, electroretinography.
Ears/Hearing	Audiologic evaluation [1]	• Assess for high-frequency SNHL. • Perform auditory brain stem response & otoacustic emissions.
	Otolaryngology consultation	Assess for chronic otitis media / adhesive otitis media that could contribute to hearing loss.
Insulin resistance / Type 2 diabetes mellitus	Endocrinology-metabolism consultation	Evaluate for: • Hyperinsulinemia (check skin for acanthosis nigricans from age 5 yrs on) • Pre-diabetes from age 4 yrs on (HbA1C, postprandial C-peptide & blood glucose, oral glucose tolerance test) • Dyslipidemia from age 5 yrs on
		Evaluate gonadal function from age 10 yrs on.
Hypothyroidism	Refer to endocrinologist as needed.	Check thyroid gland function.
Hypogonadism/ Hyperandrogenism	Refer to endocrinologist as needed.	• Assess pubertal development; check levels of FSH, LH, estrogen, & testosterone as needed. • Males: evidence of delayed or arrested puberty secondary to hypogonadotropic hypogonadism &/or testicular fibrosis • Females: hirsutism, polycystic ovarian syndrome, precocious puberty, irregular menses, amenorrhea
Cardiovascular	Assess for cardiomyopathy & refer to cardiologist as needed.	• Ages 3 wks to 4 mos: assess for infantile cardiomyopathy; order baseline echocardiogram. • Teens to late 30s: assess for restrictive cardiomyopathy incl EKG & cardiac MRI to detect myocardial fibrosis.
Respiratory	Assess pulmonary function & refer to pulmonologist as needed.	Seek evidence of restrictive lung disease.
Urologic	• Assess for detrusor-urethral dyssynergia. • Refer to urologist as needed.	Especially in females in late teens

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	• Assess fine & gross motor, speech/language, general cognitive, & vocational skills. • Evaluate special considerations in school setting for those w/impaired vision & hearing
Psychiatric/ Behavioral	Neuropsychiatric evaluation based on sensory loss present (i.e., deafness, blindness, deaf-blindness)	For individuals age >12 mos: screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Sleep	Assess for sleep apnea.	Refer to sleep study if loud snoring, gasping for air during sleep
Renal	• Assess renal function. • Refer to nephrologist as needed.	• Check CBC, serum electrolytes, creatinine, cystatin C, BUN • Check blood pressure, 24-hr blood pressure monitoring as needed
Liver	• Assess for nonalcoholic fatty liver disease. • Refer to hepatologist as needed.	• Assess for liver disease by ultrasonography, FibroScan®, hepatic enzymes, & liver synthetic function (prothrombin time) • In patients w/advanced liver disease: assess need for upper endoscopy to evaluate for esophageal varices.
Musculoskeletal	Refer to orthopedist as needed.	Assess for scoliosis/kyphosis & flat foot.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	Genetic counseling
	Family supports/resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; SNHL = sensorineural hearing loss
1. See Hereditary Hearing Loss and Deafness Overview for details about audiologic evaluations.

Treatment of Manifestations

Medical Issues

No therapy exists to prevent the progressive organ involvement of Alström syndrome. Individuals with Alström syndrome require coordinated multidisciplinary care to formulate and coordinate management and therapeutic interventions.

Rod-cone dystrophy

- Early on when photodysphoria is significant, the use of red-orange tinted prescription lenses may reduce symptoms.
- Early educational planning should be based on the certainty of blindness. 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, reduced-calorie diet with restricted simple carbohydrate intake and regular aerobic exercise, such as walking, hiking, biking, and swimming with adaptations for the blind, are recommended to control weight gain. Employment of a helper/partner to encourage exercise and appropriate diet may be beneficial.

Progressive sensorineural hearing loss

- Myringotomy has been helpful in individuals with recurrent otitis media.
- Hearing can be maximized with bilateral digital hearing aids.
- Cochlear implantation has benefited some patients [Florentzson et al 2010].

Cardiomyopathy. Standard therapy for heart failure includes angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, and beta-blockers as well as cardiac resynchronization and implantable cardio-defibrillators in accordance with current guidelines. Cardiac transplantation has been successful in rare cases [Goerler et al 2007]. Attention should be paid to asymptomatic coronary artery disease given the adverse metabolic profile of these patients, with secondary prevention therapy required when atheromata are significant.

Insulin resistance / type 2 diabetes (T2DM) should be treated as in the general population with T2DM including the accepted caveats where heart failure and/or liver dysfunction is present. The diabetes mellitus is characterized by insulin resistance, and all patients will benefit from lifestyle modifications (e.g., weight loss programs, exercise) and metformin [Paisey & Leeson-Beevers 2016].

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 (2.6 mg/dL) or if cardiomyopathy is evident. Incretin analogs given subcutaneously, as in nonsyndromic T2DM, are successful in two thirds of patients in whom diabetes is suboptimally controlled on good nutrition, exercise, and metformin [Paisey et al 2008, Paisey et al 2009]. Second-line agents include GLP-1 agonists and insulin.

The progression to diabetes mellitus and the severity of hyperglycemia can be mitigated by lifestyle changes and reduction of severe obesity.

Hypertriglyceridemia

- Nicotinic acid derivatives can be helpful in long-term reduction of severe hypertriglyceridemia (>20 mmol/L or 1,770 mg/dL) especially if pancreatitis has occurred and diabetes is absent or well controlled [Paisey et al 2004, Paisey et al 2009]. Statins may not be fully effective but can be considered for long-term prevention of atherosclerosis in adults with low HDL, high LDL, and diabetes.
- Pancreatitis should be treated as in the general population. In order to reduce serum triglyceride levels, a 48-hour fast with intravenous saline will allow excess circulating triglyceride to be metabolized, thus resetting lipid trafficking. Subsequent healthy diet, exercise, and optimal treatment of diabetes will then sustain lower triglyceride levels [Paisey et al 2009].

Other endocrine issues

- As children approach puberty, gonadotropin and pituitary hormones should be assessed to determine if hormone replacement is necessary.
- Male hypogonadism should be treated with testosterone according to local endocrine guidelines to preserve sexuality, muscle strength, and bone health.
- Thyroxine therapy should be initiated and monitored if the individual is hypothyroid. Free T4 and TSH monitoring is recommended as many people with Alström syndrome have secondary hypothyroidism.

Urologic. Urologic signs and symptoms should be evaluated by a urologist. Some individuals have required urinary diversion or self-catheterization to manage voiding difficulties [MacDermott 2001].

Renal disease

- The use of enzyme ACE inhibitors is recommended if proteinuria is detected. As in the general population, intense inhibition of the renin-angiotensin-aldosterone axis with ACE inhibition, A2

blockade, and aldosterone blockade (spironolactone or eplenerone) is likely to result in hyperkalemia and potentially renal failure [Harel et al 2012].
- Although successful renal transplantation has occurred in increasing numbers of individuals [Poli et al 2017], it can be problematic in the presence of other complications including morbid obesity, uncontrolled diabetes, and cardiomyopathy.

Hepatic disease. Advanced NAFLD is common in adults with Alström syndrome, who need careful monitoring using liver ultrasound, FibroScan®, enhanced liver fibrosis score, and liver enzymes. As appropriate, upper gastrointestinal endoscopy should be performed to assess for esophageal and gastric varices. Portal hypertension may be treated with beta-blockade. Banding or sclerotherapy of the esophageal varices may be needed in order to prevent upper gastrointestinal hemorrhage from varices. Patients who fail to respond to these treatments may be candidates for a transjugular intrahepatic portosystemic shunt. Patients with advanced liver disease / portal hypertension should be evaluated early for liver transplantation.

Pulmonary disease. Regular physical activity, including breathing exercises, can reduce chronic hypoxia and improve well-being. Patients should be encouraged to have seasonal flu and pneumonia vaccines as per national guidelines. Coaching by an exercise expert may be necessary to achieve adequate spirometry.

Other

- If skeletal abnormalities are present, referral to an orthopedist is appropriate. Kyphoscoliosis may require surgical treatment. Characteristic stoop can be countered by exercise.
- Reflux esophagitis, skin manifestations, orthopedic abnormalities, and neurologic manifestations should be treated as in the general population.
- Routine pediatric immunizations including annual flu shots should be given and administration of pneumococcal vaccination considered.
- Care must be taken during sedation or operative procedures. The combination of decreased myocardial function, pulmonary hypertension, and pulmonary fibrosis can cause sudden severe hypoxia in an affected individual following surgery or even during a minor infection. Close monitoring of cardiac status and oxygenation are necessary until the individual is fully recovered.

Developmental Delay Management Issues

A study on aspects of learning from the perspective of people with Alström syndrome revealed that individuals with Alström syndrome have an image of themselves as capable people willing to learn, but in constant need of support to continue learning throughout their lives to be as independent as possible [Rönnåsen et al 2016]. People with Alström syndrome should be allowed to be their own advocates, as they know best how they learn, and what type of sensory material (tactile, auditory, visual) and modalities are most effective for them. The tactile modality for learning should be emphasized early as it will continue throughout life.

An overview of the current holistic approach to families of persons with Alström syndrome emphasizes the possibilities for better integration in society and attainment of educational and employment opportunities [Paisey & Leeson-Beevers 2016].

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

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or

cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center-based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restricted environment at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters teen years, a transition plan should be discussed and incorporated into the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., scoliosis).

Communication issues. Consider evaluation for alternative means of communication (e.g., Augmentative and Alternative Communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

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

Concerns about depression, anxiety, and nihilism are common in the late teens as young persons with Alström syndrome realize the severity of its effects. These issues can be addressed by a pediatric psychiatrist.

Surveillance

A suggested plan for annual evaluations for patients with Alström syndrome may be found at www.alstrom.org.uk [Paisey & Leeson-Beevers 2016].

Table 6. Recommended Surveillance for Individuals with Alström Syndrome

System/Concern	Evaluation	Age/Frequency [1]
Constitutional	Measure height, weight, & waist circumference for evidence of linear growth failure & obesity.	• Every 3-6 mos in 1st 2 yrs • Every 6-12 mos after age 2 yrs
	Assess diet & exercise regimen.	Every 6-12 mos after age 2 yrs
Eyes	Complete eye exam specifically for retinopathy & cataracts	Annually (incl after complete loss of vision to assess overall health of the eye)
Hearing	Audiologic reexam to determine type & extent of hearing loss & success w/hearing habilitation	Annually
Communication	Eval of needs for alternative means of communication	
Insulin resistance/ Type 2 diabetes mellitus	Measurement of postprandial c-peptide & glucose & HbA1C	Starting at age 4 yrs: • Annually if normal • Every 3 mos if abnormal
Hyperlipidemia	Measurement of plasma triglyceride, LDL, HDL, & total cholesterol	• Annually if normal • More frequently if abnormal
Cardiomyopathy	Those w/history of infantile cardiomyopathy (even if asymptomatic): follow up w/pediatric cardiologist	Every 6 mos
	Detailed cardiac history & exam incl echocardiography even in absence of symptoms related to left-ventricular dysfunction (shortness of breath, chest discomfort, sweating, fatigue, lethargy, ↓ physical activity, swelling)	Annually
	Echocardiogram & EKG	Every 12 mos
	Cardiovascular MRI	Every 3 yrs starting at age 18 yrs or w/any change in clinical status
	Noninvasive CT coronary angiography	If symptoms or unheralded asymptomatic ↓ in LV function
Other endocrine	Children: evaluate timing of development of secondary sex characteristics for evidence of delayed puberty.	Annually
	• Adult males: evaluate for hypogonadism; measure serum testosterone & gonadotropins. • Adult females: evaluate for hyperandrogenism.	Annually starting at age 13 yrs
	Evaluate for hypothyroidism.	Annually

Table 6. continued from previous page.

System/Concern	Evaluation	Age/Frequency [1]
Renal	All patients: CBC, electrolytes, BUN, creatinine, cystatin-C, uric acid, urinalysis	Every 6 mos
	In addition to above: • All patients w/renal disease should be followed by nephrologist & have urine protein/creatinine ratio. • Evaluate all patients w/CKD Stage ≥III for bone disease (PTH, calcium, phosphorus, bone density).	Every 6-12 mos
	Renal & bladder US	Every 1-2 yrs
Liver	ALT, AST, AP, GGT, total protein, albumin, total bilirubin, direct bilirubin, prothrombin time	Annually
	Abdominal US to evaluate for hepatic steatosis, hepatomegaly, splenomegaly, & ascites	
	Those w/significant liver disease should be followed by hepatologist & have upper endoscopies to assess & treat esophageal varices.	Every 6-12 mos
Musculoskeletal	Spine exams & x-rays as needed for evidence of scoliosis/ kyphosis	Annually
Development	Monitor developmental progress & educational needs.	At each visit in young children, annually in school-age children
Behavioral/ Psychiatric	Assessment for evidence of behavioral & psychiatric problems	Annually
Family needs	Eval by social worker for needs in home environment	

Based on Monitoring Guidelines from Alström Syndrome International (www.alstrom.org/professionals/monitoring-guidelines/) (last modified: 1-13-17)

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CKD = chronic kidney disease; CT = computerized tomography; GGT = gama glutamil transferase; HDL = high density lipoproteins; LDL = low density lipoproteins; LV = left ventricular; MRI = magnetic resonance imaging; PTH = parathyroid hormone; US = ultrasound

1. Recommended frequencies shown are for stable well-controlled patients. In many patients more frequent evaluations are needed.

Agents/Circumstances to Avoid

Substances contraindicated in persons with renal, hepatic, and/or myocardial disease should be avoided.

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.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an individual with Alström syndrome in order to identify as early as possible those who would benefit from prompt evaluation for manifestations of Alström syndrome (Table 5), initiation of treatment, or surveillance for age-related manifestations (Table 6).

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

Therapies Under Investigation

A treatment trial with the antifibrotic agent PBI-4050 is currently under way [Baig et al 2018].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Mode of Inheritance

Alström syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ALMS1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. No males with molecularly confirmed Alström syndrome are known to have fathered children and no females are known to have become pregnant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ALMS1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ALMS1* pathogenic variants in the family.

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, clarification of carrier status, 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 carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ALMS1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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.

- **Alstrom Syndrome International (ASI)**
  14 Whitney Farm Road
  Mount Desert ME 04660
  Phone: 888-745-8356 (toll-free)
  Email: info@alstrom.org
  www.alstrom.org
- **Alstrom Syndrome UK Support Group**
  4 St Kitts Close
  Torquay Devon TQ2 7GD
  United Kingdom
  Phone: 07517 278 946; 01709 210151
  Email: info@alstrom.org.uk; liz.loughery@alstrom.org.uk
  www.alstrom.org.uk
- **EURO-WABB Project**
  Patient information sheet for Alström syndrome
- **National Library of Medicine Genetics Home Reference**
  Alstrom syndrome
- **Ciliopathy Alliance**
  United Kingdom
  ciliopathyalliance.org
- **EURO-WABB Project Registry**
  EU rare diseases registry for Wolfram syndrome, Alström syndrome and Bardet-Biedl syndrome (see Farmer et al [2013])

ww.registry.euro-wabb.org

Molecular Genetics

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

Table A. Alstrom Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ALMS1	2p13.1	Centrosome-associated protein ALMS1	ALMS1 database	ALMS1	ALMS1

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 Alstrom Syndrome (View All in OMIM)

203800	ALSTROM SYNDROME; ALMS
606844	ALMS1 CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN; ALMS1

Molecular Pathogenesis

ALMS1 encodes ALMS1, a large (>4,000-amino acid) protein that localizes to the proximal ends of centrioles / basal bodies as well as non-centrosomal sites. Consistent with the complexity of the clinical features of Alström syndrome, ALMS1 appears to have multiple functions. Although the precise functions of ALMS1 are not fully understood, evidence suggests that it is implicated in formation and maintenance of primary cilia but also has non-ciliary functions including actin organization and endosomal trafficking. The mitotic nature of the infantile-onset cardiomyopathy in Alström syndrome demonstrates the importance of ALMS1 in cell cycle regulation in perinatal cardiomyocytes. Similarly, consistent with the severe insulin resistance / T2DM, a hallmark of Alström syndrome, ALMS1 is shown to be required for trafficking of the insulin receptor GLUT4 to the plasma membrane, adipogenesis, and regulation of pancreatic beta cell mass [Hearn 2019]. ALMS1 is widely expressed in a context-dependent manner: its expression level increases during terminal differentiation of neonatal mouse cardiomyocytes, and during primary cilium formation, but decreases as preadipocytes differentiate to mature adipocytes [Hearn 2019].

Mechanism of disease causation. Alström syndrome is caused by loss of function of ALMS1 protein. More than 200 *ALMS1* pathogenic variants have been identified to date; almost all are nonsense or frameshift variants associated with complete lack of protein expression [Marshall et al 2015, Chen et al 2017].

***ALMS1*-specific laboratory technical considerations.** The majority of *ALMS1* variants are clustered in three large exons: exon 8 (which harbors almost half of the variants, consistent with its large size encompassing 49% of the coding sequence of the gene), exon 10, and exon 16 [Marshall et al 2015].

Given the clinical overlap between Alström syndrome and other ciliopathies, extreme caution should be exercised in classifying *ALMS1* missense variants as pathogenic. A ciliopathy gene panel should be performed especially in individuals with mild/atypical Alström syndrome who have *ALMS1* missense variants.

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Chapter Notes

Author History

Tim Barrett, MD (2019-present)
Catherine Carey, MD, FRCP; Torbay Hospital, Devon (2003-2019)
Tarekegn Geberhiwot, MD (2019-present)
Meral Gunay-Aygun, MD (2019-present)
Ian Hopkinson, BSc (Hons), MBChB, PhD, MRCGP; University College London (2003-2010)
Seamus Macdermott, MD, FRCS; Torbay Hospital, Devon (2003-2019)
Jan D Marshall, MS; The Jackson Library, Bar Harbor (2003-2016*)
Richard B Paisey, MD, FRCP (2005-present)
Rick Steeds, MD (2019-present)
Denise Williams, MD (2019-present)

*Author Jan Marshall died September 6, 2016.

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