

A review of Alström syndrome: a rare monogenic ciliopathy

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SUMMARY Alström syndrome is a rare monogenic ciliopathy caused by a mutation to the *Alström syndrome 1 (ALMS1)* gene. Alström syndrome has an autosomal recessive nature of inheritance. Approximately 1,200 cases of Alström syndrome have been identified worldwide. Complications of the disease are likely caused by dysfunctional cilia with complications arising early in life. The known complications of Alström syndrome have been reported to impact multiple major organ systems, including the endocrine system, cardiac system, renal system, sensory system, and hepatic system. The symptoms of Alström syndrome have great variability in presentation and intensity but often lead to organ damage. This has resulted in a shortened lifespan for individuals affected by Alström syndrome. Individuals with the disease rarely exceed the age of 50. Currently, there are no specific treatments for Alström syndrome that can cure the disease, prevent the complications, or reverse the complications. Current management involves management of symptoms with the goal of improving quality of life and lifespan. This review aims to summarize the current knowledge on the epidemiology, diagnosis, pathophysiology, complications, management, and prognosis of Alström syndrome. In addition to that, this review also aims to raise awareness and encourage research on Alström syndrome as the condition has a huge impact on affected individuals.

Keywords genetic disorder, rare disease, cilia, reduced lifespan

1. Introduction

Alström syndrome is a rare condition that was first revealed in the literature in 1959 by Carl-Henry Alström from Sweden (1). The syndrome is an autosomal recessive genetic disorder. The disorder is caused by a mutation to the *Alström syndrome 1 (ALMS1)* gene and affects many systems in the body (2,3). The symptoms of Alström syndrome usually first arise in infancy and further develop during childhood and later in life. Common complications of Alström syndrome include endocrine complications, cardiac complications, renal complications, hepatic complications, complications with vision and complications with hearing (4). The symptoms and complications of Alström syndrome vary greatly in severity. Currently there are no specific treatments for Alström syndrome with the management currently involving management of symptoms with the goal of improving quality of life and lifespan (2).

This review aims to summarize the current knowledge of Alström syndrome. Furthermore, this paper also aims to promote further research and develop awareness of Alström syndrome.

2. Epidemiology

Alström syndrome is a rare condition, and while current incidence is unknown, estimates have created a range from 1 in 500,000 to 1 in 1,000,000 (5). The rare nature of the disease has potentially resulted in many cases of Alström syndrome being undiagnosed. Worldwide, approximately 1200 cases of Alström syndrome have been identified (6). The condition affects both sexes equally (7).

3. Pathophysiology

Alström syndrome is caused by a mutation in the *ALMS1* gene. It is an autosomal recessive condition meaning that both copies of the *ALMS1* gene need to be mutated for the syndrome to occur (2). The *ALMS1* gene is located on the short arm of chromosome 2 (8,9).

The pathophysiology of the symptoms of Alström syndrome has potential links to the ALMS1 protein. The ALMS1 protein is a protein that is found in primary cilia within the centrosomes and the basal bodies. The protein is comprised of 4,169 amino acids (10). ALMS1

protein has a significant impact on the function of cilia, with a paper published in 2007 suggesting that the absence of the protein results in an impairment in the formation of cilia (11). In addition to that, the ALMS1 protein has also been shown to be related to energy metabolism homeostasis, cell differentiation, ciliary signalling pathways, cell cycle control and intracellular trafficking (9). These facts aid in the classification of Alström syndrome as a ciliopathy, a disorder that results in abnormal cilia function or formation (12,13). While more research needs to be conducted on the pathophysiology of Alström syndrome, there appears to be a significant relationship between the *ALMS1* gene, ALMS1 protein, cilia function and the disorder.

4. Diagnosis

Due to the wide range of symptoms and great variability in presentations, the diagnosis of Alström syndrome is often challenging. Furthermore, certain symptoms have a delayed presentation until later in life, meaning that the diagnosis during early life is often missed (14). The characteristic features of Alström syndrome often become more evident as a child grows, meaning that the diagnosis and clinical suspicion of Alström syndrome become more evident in late childhood. A study published in 2007 established a set of criteria that aid in the diagnosis of Alström syndrome (2). The molecular diagnosis of Alström syndrome is established when a patient is found to have two *ALMS1* mutations, with one mutation coming from each parent. This screening is done by molecular genetic testing (14).

5. Complications

The main complications of Alström syndrome are summarized in Table 1.

5.1. Endocrine complications

Alström syndrome has an impact on endocrine and metabolic function resulting in endocrine complications. The main endocrine complications are related to growth, pubertal development, obesity, and diabetes mellitus (15).

A common complication of Alström syndrome is obesity and early onset diabetes mellitus. *ALMS1* mutations allow glucose transport through the actin cytoskeleton, which helps in insulin-mediated Glucose transporter type 4 (GLUT4) transport. Among the various metabolic derangements in cases with Alström syndrome, a study shows that 76% had obesity and 37% had type 2 diabetes mellitus. These patients had very high fasting and mixed-meal test (MMT) insulin resistance indices, higher MMT glucose, insulin, and C-peptide values, higher haemoglobin A1c (HbA1c), and higher prevalence of type 2 diabetes mellitus (16).

Table 1. Summary of the major complications of Alström syndrome

Items	Complications
Endocrine	Obesity and early onset diabetes mellitus Short Stature Hypogonadism and testicular fibrosis (in males) Gynecomastia (in males) Issues with menstruation (in females) Poor breast development (in females)
Cardiovascular	Dilated cardiomyopathy Early onset coronary artery disease Early onset Hypertension
Sensory	Progressive vision loss Progressive sensorineural hearing loss
Renal/Urinary	End-stage renal disease Renal cysts Recurrent urinary tract infections
Hepatic	Non-alcoholic fatty liver disease Cirrhosis
Respiratory	Recurrent respiratory tract infections

It has been found that extreme insulin receptor and β -cell failure are the two main factors responsible for the glucose metabolism alterations in Alström syndrome (17). A cross-sectional cohort study showed that patients may develop early child obesity, but the body mass index, waist circumference, and body fat decreased with age as insulin resistance increased. This insulin resistance is also associated with increased levels of triglycerides in patients with Alström syndrome (15).

Growth complications are also a major endocrine issue of Alström syndrome. Almost 98% of adults with Alström syndrome are in the 5th percentile or less for height. The growth complications are likely to arise during puberty as studies conducted have shown that pre-pubertal heights of children with Alström syndrome are not dissimilar to their peers (18). No study has specifically investigated growth hormone (GH) deficiency in a large population. Small sample studies have shown that Alström syndrome patients may be functionally GH deficient. Tested Alström syndrome patients had an inadequate GH reserve to growth hormone release hormone-arginine (GHRH-arg) leading to a low growth velocity despite advanced bone ages and normal insulin like growth factor 1 concentration. Growth hormone deficiency accounts for the short stature in some patients with Alström syndrome, while the advanced bone age and normal early growth may be due to hyperinsulinism (19,20). A specific defect in the signal transduction of insulin action accounts for the existence of insulin resistance in the presence of growth hormone deficiency (21).

Pubertal development is another endocrine complication of Alström syndrome. In males, hypogonadotropic hypogonadism and testicular fibrosis

have been reported to halt or delay puberty. This has resulted in patients with Alström syndrome developing gynecomastia (18). In females, insulin resistance has resulted in patients with low concentrations of plasma gonadotropin, which have resulted in symptoms such as hirsutism, irregular menses, amenorrhea, or precocious puberty. Breast development is often poor in patients with Alström syndrome (22). Limited studies have been done on male or female fertility in patients with Alström disease, although there have been reports of females with the condition that have given uncomplicated birth to healthy infants (23).

5.2. Cardiac complications

Cardiac complications are common in Alström syndrome. The severity and symptoms of cardiac complications have great variability in patients with Alström syndrome (24). In Alström syndrome, heart failure due to a form of dilated cardiomyopathy is a frequent finding, occurring in approximately 60% of cases and representing the most common cause of death (25,26). The mechanism of cardiomyopathy is not currently known (27).

Dilated cardiomyopathy presents in infancy in 50% of cases and, if treated successfully, apparent atypical recovery of cardiac function within 3 years can occur with restitution of near normal cardiac function into adult life (26). Importantly, infantile congestive heart failure can recur in adolescence or adulthood with a poor prognosis for affected patients (26,28).

There are suggestions that hemodynamic changes associated with large artery stiffening have been shown to lead to maladaptive changes of myocardial hypertrophy and can contribute to development of left ventricular failure in patients with Alström syndrome. However, in a study published in 2007, it did not find clear associations between left ventricular structure and function and parameters of large artery function, suggesting that primary cardiac pathology is likely to play an important role in the pathogenesis of cardiomyopathy in Alström syndrome (26). The primary cardiac pathology concept is supported by another paper published in 2017, which states that although some patients had a history of significant cardiac risk factors for many years, they were unable to find a relationship between metabolic derangements and cardiac abnormalities (27). Furthermore, another study, which was published in 1996 found that clinically and histologically, the cardiomyopathy associated with Alström syndrome in their five patients was indistinguishable from other sporadic and familial forms of isolated cardiomyopathy (25).

Histopathology of the heart in such cases has not revealed any specific findings other than a variable degree of cardiac dilatation and fibrosis (26,29). Most cases of myocardial fibrosis are gradual and

non-reversible; so, the infantile onset of dilated cardiomyopathy and the high rate of resolution are difficult to explain. As an example a paper published in 2012 speculates that the myocardial fibrosis and the infantile dilated cardiac myopathy may follow different pathogenic processes (28).

Comorbidities associated with Alström syndrome could also lead to early onset coronary artery disease. A 2012 study suggests that patients with Alström syndrome should be assessed for classical coronary risk factors and investigated specifically to exclude coronary artery disease (30).

Echocardiography is critical in establishing the diagnosis, guiding therapy, and determining an overall prognosis (31). Cardiac magnetic resonance imaging not only provides pathological insights, but gives a chance to detect early functional changes, track the natural history and progression of the disease, and assess the impact of therapeutic interventions, as well as guide referral for transplantation in patients with Alström syndrome (32). Early diagnosis allows greater opportunities to introduce therapies for cardiac complications of Alström syndrome. This is particularly true of cardiomyopathy, which presents acutely in childhood in 45% of cases and is potentially fatal if unrecognized and recurs (33).

5.3. Sensory complications

Progressive loss of vision is a common finding in cases of Alström syndrome. Like many other features of Alström syndrome, disease severity and age of onset can differ considerably. The process of visual impairment begins within the first decade of life, usually between birth and 15 months of age (22). The impairment begins with the loss of visual acuity, photophobia, and horizontal nystagmus (2,22,34). This is followed by loss of residual light perception, which eventually progresses to complete loss of light awareness within the second decade of life (22). Photopic electroretinogram findings in the beginning of the disease show evidence of cone dystrophy. Follow-up photopic electroretinogram testing reveals how rapidly the visual impairment progresses to typical cone-rod dystrophy (35).

Auditory impairment is also a classic complication of Alström syndrome. The onset and severity of hearing loss can vary significantly between individuals. The hearing loss is progressive, and up to 70% of patients develop some degree of high frequency sensorineural hearing loss within the first decade of life (36). Many patients with Alström syndrome suffer from chronic otitis media, which contributes to progressive hearing loss (4,36). Histopathology findings of a 2015 study have shown atrophy of the stria vascularis and degeneration of the organ of Corti (37). This may play a role in the pathophysiology of auditory impairment.

5.4. Renal complications

Renal complications are common in patients with Alström syndrome. The renal complications have high variability and often slowly progress. Onset of symptoms and complication are usually late in childhood or during adulthood. Significant renal complications include end-stage renal disease, which can occur during late childhood in some patients (38). Renal cysts are another renal feature of Alström syndrome (39). Interstitial fibrosis and hyalinization of tubules are visible on histopathological investigation (40).

5.5. Hepatic complications

Complications related to the liver are common in most patients with Alström syndrome although there is great variability in symptoms and severity. Elevated liver enzymes are often present since childhood and patients with Alström syndrome often have a high liver fat concentration (15). Portal hypertension and associated symptoms are also a common hepatic complication of Alström syndrome. Non-alcoholic fatty liver disease and cirrhosis are also more likely in patients with Alström syndrome when compared to the general population (41). Chronic active hepatitis, steatohepatitis, hepatic fibrosis, and cirrhosis are common findings on liver biopsy in patients with Alström syndrome (42).

5.6. Other complications

Upper and lower respiratory tract infections are often a complication of Alström syndrome. The symptoms vary in severity and can result in pulmonary fibrosis, pulmonary hypertension, and impaired pulmonary function (2,14).

Urinary symptoms are also a complication of Alström syndrome with patients presenting with lower urinary tract symptoms and abdominal pain prior to urination. Recurrent urinary tract infections and urinary strictures can also arise as a complication (2,43).

Hypertension is also a common and significant complication of Alström syndrome. Studies have shown that approximately 40% of patients with Alström syndrome have hypertension. Furthermore, there have been cases of patients with hypertension at an age of 2 (2,14).

6. Management

Currently there are no specific treatments for Alström syndrome that can cure the disease, prevent the complications, or reverse the complications. A multidisciplinary approach is currently preferred to detect, predict, and treat the complications of Alström syndrome. Regular monitoring *via* blood tests of levels of various markers including: liver enzymes, blood

Table 2. Common assessments/investigations in patients with Alström syndrome

Items	Nvestigations/Assessments
Endocrine	Fasting blood glucose, HbA1c Height, weight, body mass index Gonadal function test (in males)
Cardiovascular	Electrocardiography Echocardiography Blood pressure
Sensory	Visual acuity Electroretinogram Audiometric assessment
Renal/Urinary	Urinalysis Renal function test
Hepatic	Liver function test/liver enzymes

glucose and gonadotropins are suggested. Cardiac monitoring with the use of echocardiography is also suggested. Management of sensory deficits is essential, and this is especially significant in young children. A study published in 2007 has outlined the assessments and interventions that should be considered in patients with Alström syndrome (2) (Table 2).

7. Prognosis

Due to the wide range of symptoms, complications and severities of complications, the prognosis for patients with Alström syndrome can greatly vary. That being said, the disease often results in severe complications such as organ failure. As a result, patients with Alström syndrome generally have a reduced lifespan. Patients rarely exceed the age of 50 (4).

8. Conclusion

Alström syndrome is a rare genetic disorder caused by mutations to the *ALMS1* gene. Complications of the disease are likely caused by dysfunctional cilia with complications arising early in life. The symptoms of Alström syndrome have great variability in presentation and intensity and can affect a great range of organ systems. Complications include: endocrine complications, sensory complications, renal complications, hepatic complications, and cardiac complications. Due to the wide range of complications and the high rates of organ damage and failure, lifespan is greatly reduced in individuals with Alström syndrome. There are no specific treatments for Alström syndrome with the current treatment only aiming to manage the complications of the condition. Alström syndrome has a huge impact on affected individuals, and more research should be conducted on this subject.

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References

- Alstrom CH, Hallgren B, Nilsson LB, Asander H. Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from the Laurence-Moon-Bardet-Biedl syndrome: a clinical, endocrinological and genetic examination based on a large pedigree. *Acta Psychiatr Neurol Scand Suppl.* 1959; 129:1-35.
- Marshall JD, Beck S, Maffei P, Naggert JK. Alstrom syndrome. *Eur J Hum Genet.* 2007; 15:1193-1202.
- Ding Y, Zhang Q, He Y, Zhang L, Li N, Chang G, Chen Y, Wang J, Wu J, Fu L, Wang X. Analysis of ALMS1 gene variants in seven patients with Alstrom syndrome. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi.* 2021; 38:112-116. (in Chinese)
- Marshall JD, Maffei P, Collin GB, Naggert JK. Alstrom syndrome: genetics and clinical overview. *Curr Genomics.* 2011; 12:225-235.
- Marshall JD, Maffei P, Beck S, Barrett TG, Paisey R, Naggert JK. Clinical utility gene card for: Alstrom Syndrome - update 2013. *Eur J Hum Genet.* 2013; 21(11).
- Bdier AY, Al-Qahtani FA, Kumar Verma P, Alshoabi NA, Mohammed Alrayes N, Shaik NA, Foo RSY, Bhuiyan ZA, Al-Aama JY. A novel homozygous ALMS1 protein truncation mutation (c.2938dupA) revealed variable clinical expression among Saudi Alström syndrome patients. *Arch Med Sci.* 2020; 100635.
- Koray F, Dorter C, Benderli Y, Satman I, Yilmaz T, Dinccag N, Karsidag K. Alstrom syndrome: a case report. *J Oral Sci.* 2001; 43:221-224.
- Khoo EY, Risley J, Zaitoun AM, El-Sheikh M, Paisey RB, Acheson AG, Mansell P. Alström syndrome and cecal volvulus in 2 siblings. *Am J Med Sci.* 2009; 337:383-385.
- Álvarez-Satta M, Castro-Sánchez S, Valverde D. Alström syndrome: current perspectives. *Appl Clin Genet.* 2015; 8:171-179.
- Knorz VJ, Spalluto C, Lessard M, Purvis TL, Adigun FF, Collin GB, Hanley NA, Wilson DI, Hearn T. Centriolar association of ALMS1 and likely centrosomal functions of the ALMS motif-containing proteins C10orf90 and KIAA1731. *Mol Biol Cell.* 2010; 21:3617-3629.
- Li G, Vega R, Nelms K, Gekakis N, Goodnow C, McNamara P, Wu H, Hong NA, Glynn R. A role for Alström syndrome protein, *alms1*, in kidney ciliogenesis and cellular quiescence. *PLoS Genet.* 2007; 3:e8.
- Girard D, Petrovsky N. Alström syndrome: insights into the pathogenesis of metabolic disorders. *Nat Rev Endocrinol.* 2011; 7:77-88.
- Waters AM, Beales PL. Ciliopathies: an expanding disease spectrum. *Pediatr Nephrol.* 2011; 26:1039-1056.
- Paisey RB, Steeds R, Barrett T, Williams D, Geberhiwot T, Gunay-Aygun M. Alstrom Syndrome. In: *GeneReviews(R)* (Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, eds.). Seattle (WA), 1993.
- Han JC, Reyes-Capo DP, Liu CY, Reynolds JC, Turkbey E, Turkbey IB, Bryant J, Marshall JD, Naggert JK, Gahl WA, Yanovski JA, Gunay-Aygun M. Comprehensive endocrine-metabolic evaluation of patients with alström syndrome compared with BMI-matched controls. *J Clin Endocrinol Metab.* 2018; 103:2707-2719.
- Minton JA, Owen KR, Ricketts CJ, Crabtree N, Shaikh G, Ehtisham S, Porter JR, Carey C, Hodge D, Paisey R, Walker M, Barrett TG. Syndromic obesity and diabetes: changes in body composition with age and mutation analysis of ALMS1 in 12 United Kingdom kindreds with Alstrom syndrome. *J Clin Endocrinol Metab.* 2006; 91:3110-3116.
- Dassie F, Favaretto F, Bettini S, Parolin M, Valenti M, Reschke F, Danne T, Vettor R, Milan G, Maffei P. Alström syndrome: an ultra-rare monogenic disorder as a model for insulin resistance, type 2 diabetes mellitus and obesity. *Endocrine.* 2021; 71:618-625.
- Marshall JD, Bronson RT, Collin GB, *et al.* New Alström syndrome phenotypes based on the evaluation of 182 cases. *Arch Intern Med.* 2005; 165:675-683.
- Romano S, Maffei P, Bettini V, Milan G, Favaretto F, Gardiman M, Marshall JD, Greggio NA, Pozzan GB, Collin GB, Naggert JK, Bronson R, Vettor R. Alström syndrome is associated with short stature and reduced GH reserve. *Clin Endocrinol (Oxf).* 2013; 79:529-536.
- Alter CA, Moshang T, Jr. Growth hormone deficiency in two siblings with Alström syndrome. *Am J Dis Child.* 1993; 147:97-99.
- Tai TS, Lin SY, Sheu WH. Metabolic effects of growth hormone therapy in an Alström syndrome patient. *Horm Res.* 2003; 60:297-301.
- Russell-Eggitt IM, Clayton PT, Coffey R, Kriss A, Taylor DS, Taylor JF. Alström syndrome. Report of 22 cases and literature review. *Ophthalmology.* 1998; 105:1274-1280.
- Iannello S, Bosco P, Camuto M, Cavaleri A, Milazzo P, Belfiore F. A mild form of Alstrom disease associated with metabolic syndrome and very high fasting serum free fatty acids: two cases diagnosed in adult age. *Am J Med Sci.* 2004; 327:284-288.
- Hollander SA, Alsaleh N, Ruzhnikov M, Jensen K, Rosenthal DN, Stevenson DA, Manning M. Variable clinical course of identical twin neonates with Alström syndrome presenting coincidentally with dilated cardiomyopathy. *Am J Med Genet A.* 2017; 173:1687-1689.
- Michaud JL, Héon E, Guilbert F, Weill J, Puech B, Benson L, Smallhorn JF, Shuman CT, Buncic JR, Levin AV, Weksberg R, Brevière GM. Natural history of Alstrom syndrome in early childhood: onset with dilated cardiomyopathy. *J Pediatr.* 1996; 128:225-229.
- Smith JC, McDonnell B, Retallick C, McEniery C, Carey C, Davies JS, Barrett T, Cockcroft JR, Paisey R. Is arterial stiffening in Alström syndrome linked to the development of cardiomyopathy? *Eur J Clin Invest.* 2007; 37:99-105.
- Brofferio A, Sachdev V, Hannoush H, Marshall JD, Naggert JK, Sidenko S, Noreuil A, Sirajuddin A, Bryant J, Han JC, Arai AE, Gahl WA, Gunay-Aygun M. Characteristics of cardiomyopathy in Alström syndrome: Prospective single-center data on 38 patients. *Mol Genet Metab.* 2017; 121:336-343.
- Mahamid J, Lorber A, Horovitz Y, Shalev SA, Collin GB, Naggert JK, Marshall JD, Spiegel R. Extreme clinical variability of dilated cardiomyopathy in two siblings with Alström syndrome. *Pediatr Cardiol.* 2013; 34:455-458.
- Corbetti F, Razzolini R, Bettini V, Marshall JD, Naggert J, Tona F, Milan G, Maffei P. Alström syndrome: cardiac magnetic resonance findings. *Int J Cardiol.* 2013;

- 167:1257-1263.
30. Jatti K, Paisey R, More R. Coronary artery disease in Alström syndrome. *Eur J Hum Genet.* 2012; 20:117-118.
 31. Makaryus AN, Zubrow ME, Marshall JD, Gillam LD, Mangion JR. Cardiac manifestations of Alström syndrome: echocardiographic findings. *J Am Soc Echocardiogr.* 2007; 20:1359-1363.
 32. Nerakh G, Ranganath P. Alström syndrome presenting as isolated dilated cardiomyopathy. *Indian J Pediatr.* 2019; 86:296-298.
 33. Loudon MA, Bellenger NG, Carey CM, Paisey RB. Cardiac magnetic resonance imaging in Alström syndrome. *Orphanet J Rare Dis.* 2009; 4:14.
 34. Van Groenendael S, Giacobazzi L, Davison F, Holtkemper O, Huang Z, Wang Q, Parkinson K, Barrett T, Geberhiwot T. High quality, patient centred and coordinated care for Alstrom syndrome: a model of care for an ultra-rare disease. *Orphanet J Rare Dis.* 2015; 10:149.
 35. Tremblay F, LaRoche RG, Shea SE, Ludman MD. Longitudinal study of the early electroretinographic changes in Alström's syndrome. *Am J Ophthalmol.* 1993; 115:657-665.
 36. Welsh LW. Alström syndrome: progressive deafness and blindness. *Ann Otol Rhinol Laryngol.* 2007; 116:281-285.
 37. Nadol JB Jr., Marshall JD, Bronson RT. Histopathology of the human inner ear in Alström's syndrome. *Audiol Neurootol.* 2015; 20:267-272.
 38. Waldman M, Han JC, Reyes-Capo DP, Bryant J, Carson KA, Turkbey B, Choyke P, Naggert JK, Gahl WA, Marshall JD, Gunay-Aygun M. Alström syndrome: renal findings in correlation with obesity, insulin resistance, dyslipidemia and cardiomyopathy in 38 patients prospectively evaluated at the NIH clinical center. *Mol Genet Metab.* 2018; 125:181-191.
 39. Baig S, Paisey R, Dawson C, *et al.* Defining renal phenotype in Alström syndrome. *Nephrol Dial Transplant.* 2020; 35:994-1001.
 40. Goldstein JL, Fialkow PJ. The Alström syndrome. Report of three cases with further delineation of the clinical, pathophysiological, and genetic aspects of the disorder. *Medicine (Baltimore).* 1973; 52:53-71.
 41. Gathercole LL, Hazlehurst JM, Armstrong MJ, *et al.* Advanced non-alcoholic fatty liver disease and adipose tissue fibrosis in patients with Alström syndrome. *Liver Int.* 2016; 36:1704-1712.
 42. Quiros-Tejeira RE, Vargas J, Ament ME. Early-onset liver disease complicated with acute liver failure in Alstrom syndrome. *Am J Med Genet.* 2001; 101:9-11.
 43. Charles SJ, Moore AT, Yates JR, Green T, Clark P. Alstrom's syndrome: further evidence of autosomal recessive inheritance and endocrinological dysfunction. *J Med Genet.* 1990; 27:590-592.

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