American Journal of Ophthalmology Case Reports 29 (2023) 101745

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Alström syndrome caused by maternal uniparental disomy

Madeline Q.R. Lopour [a], Lisa A. Schimmenti [b], Nicole J. Boczek [c], Hutton M. Kearney [c], Arlene V. Drack [d], Michael C. Brodsky [e,*]

[a] Department of Clinical Genomics, Mayo Clinic, Rochester, MN, USA
[b] Department of Clinical Genomics and Department of Otolaryngology, Biochemistry and Molecular Biology, and Ophthalmology, Mayo Clinic, Rochester, MN, USA
[c] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
[d] Department of Ophthalmology, University of Iowa and the University of Iowa Institute for Vision Research, Iowa City, IA, USA
[e] Department of Ophthalmology and Department of Neurology, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Keywords:
Alstrom syndrome
Nystagmus
Uniparental disomy

ABSTRACT

Purpose: To describe a case of Alström syndrome arising from maternal uniparental disomy.
Observations: A 13-month-old boy with poor vision and nystagmus was diagnosed with Alström syndrome based on genetic testing that identified a homozygous pathogenic variant, *ALMS1* c.2141_2141del (p.Ser714Tyrfs*6), that was only found in his mother and not his father. In contrast to the usual autosomal recessive inheritance pattern in which a child inherits a variant from each parent, multi-step genetic testing of the child and both parents confirmed uniparental disomy as the mechanism of inheritance.
Conclusions and Importance: Confirmation of uniparental disomy in autosomal recessive disorders allows for parental assurance that future offspring will be unaffected.

1. Case report

A 13-month-old boy was referred for evaluation of poor vision and nystagmus. His parents noted that he could see things up close but struggled to see things far away. He was noted to have vertical nystagmus and head shaking at 5 months of age which improved. He was intolerant of outside light and squinted and turned his head to the side to avoid it, but seemed to see well in dim illumination. He had developmental delay and was not meeting his speech milestones. Family history identified no other similarly affected family members. Parents were non-consanguineous and were of Asian-European and African American heritage.

On examination, the baby was photophobic but was able to follow optokinetic stimuli using either eye. Both pupils reacted briskly to light with no afferent pupillary defect, but he showed paradoxical pupillary constriction to darkness. He had frequent eye rubbing with a moderate amplitude, moderate frequency upbeating conjugate nystagmus with occasional horizontal intrusions. There was no head shaking or torticollis. Results of anterior segment examination were normal. Retinoscopy disclosed a refractive error of $+4.50 + 1.00 \times 90^{\circ}$ in both eyes. Retinal examination showed normal optic discs, maculas, and peripheral retinas, with retinal arteriolar constriction in both eyes. Electroretinography performed with skin electrodes showed absent cone function but robust, nearly normal rod function. The child's weight was above the 90th centile for his age. Hemoglobin A1C testing was normal, and his hearing was within normal limits.

Genetic testing involved four separate steps to establish a diagnosis of this Alström syndrome in this child. First, targeted next generation sequencing and copy number analysis was initiated using Molecular Vision Panel version 12 (Molecular Vision Laboratory, Portland, Oregon). Panel testing was chosen as the first line of testing given the significant genetic heterogeneity of inherited retinal dystrophies and the significant phenotypic overlap between different genetic conditions leading to retinal dystrophy.[1] This panel identified a homozygous pathogenic variant in *ALMS1*, c.2135_2136delCT (p.Ser712TyrfsTer6). The variant meets ACMG criteria for pathogenicity.[2,3] Specifically, this variant has previously been reported in compound heterozygous state with another pathogenic variant in a patient affected with Alström syndrome, thereby meeting PM3 criteria.[2,4] It has not been reported in gnomAD (gnomAD.broadinstitute.org), meeting PM2 criteria.[2] Finally, this is a frameshift variant causing premature truncation, in a gene where loss-of-function variants are a known mechanism of disease.[2]

Parental testing was conducted next; the *ALMS1* pathogenic variant was detected in the patient's mother but not in his father. The next step

* Corresponding author. Department of Ophthalmology and Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN, 55905, USA.
E-mail address: brodsky.michael@mayo.edu (M.C. Brodsky).

https://doi.org/10.1016/j.ajoc.2022.101745
Received 21 July 2022; Received in revised form 13 October 2022; Accepted 1 November 2022
Available online 31 December 2022

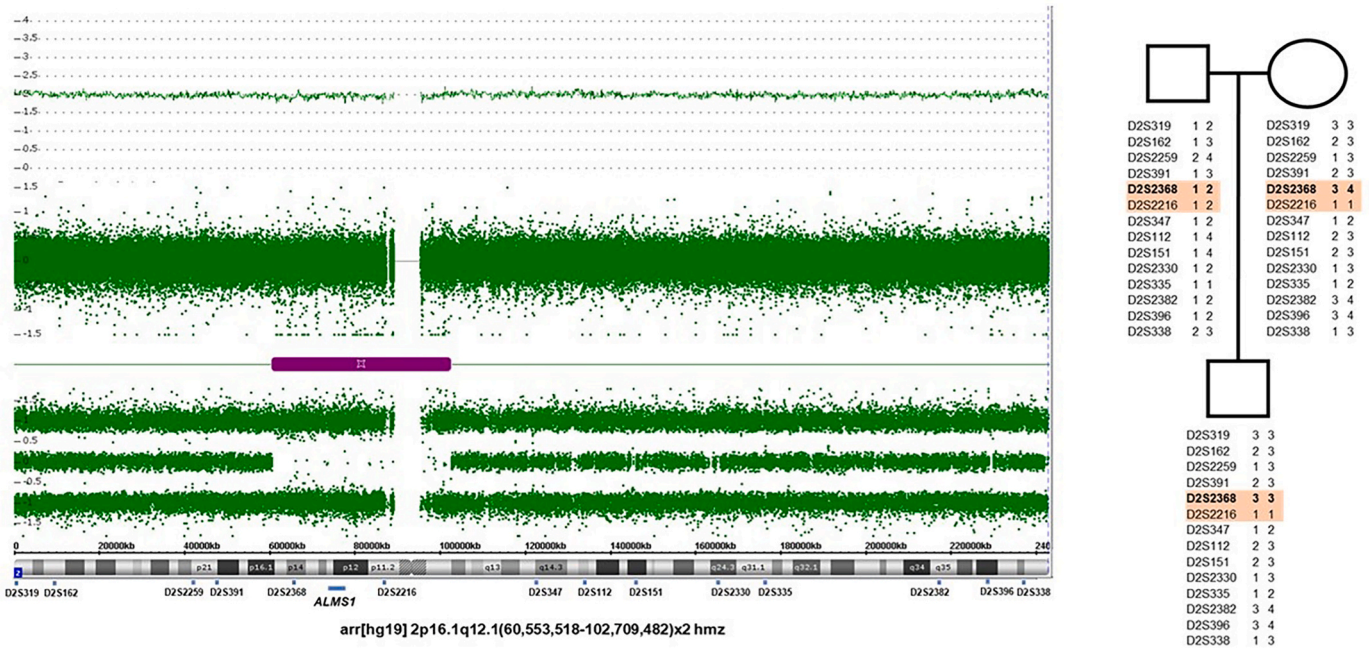

Fig. 1. Chromosomal microarray for chromosome 2 (left) showed a 42.2 megabase segment from 2p16.1 to 2q12.1 with absence of heterozygosity (AOH), represented by the purple bar. This region includes the *ALMS1* gene. Uniparental disomy results (right) shows allele sizes for each microsatellite marker on chromosome 2. The chromosomal location of the microsatellite markers are displayed along chromosome 2 on the left image. The two microsatellite markers highlighted in orange are within the region of AOH on the chromosomal microarray, with the bolded marker, D2S2368, showing maternal isodisomy. Due to allele sizes, the other marker within the AOH region, D2S2216, is uninformative. Other informative markers showing maternal heterodisomy include D2S319, D2S2259, D2S112, D2S151, D2S2382, D2S396, which aligns with the heterozygosity observed on the chromosomal microarray. The remaining markers were uninformative. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

in testing was a chromosomal microarray using both copy number and single nucleotide polymorphism probes (SNPs) on a whole-genome array (Applied Biosystems (Affymetrix) CytoScan HD platform that included 1.9 million copy number probes and 750,000 SNPS) using in silico controls. The microarray revealed a 42.2 Mb stretch of homozygosity (isodisomy) on chromosome 2p16.1q12.1. This was followed by PCR analysis of the patient and his parents using the microsatellite markers D2S319, D2S162, D2S2259, D2S391, D2S2368, D2S2216, D2S347, D2S112, D2S151, D2S2330, D2S335, D2S2382, D2S396, and D2S338, which confirmed that the patient inherited only maternal alleles on chromosome 2 (Fig. 1). Thus, the mechanism of Alström syndrome in this patient is a homozygous pathogenic variant in *ALMS1* due to maternal isodisomy from 2p16.1 to p21.1 of which the *ALMS1* gene is within the region of isodisomy. The remainder of chromosome 2 consisted of all maternal heterodisomic alleles.

2. Discussion

Mutations in the *ALMS1* gene are associated with Alström syndrome, a multisystem disorder defined by a variable constellation of features that can include congenital nystagmus, cone-rod dystrophy, bilateral sensorineural hearing loss, cardiomyopathy, insulin resistance and type 2 diabetes, chronic kidney disease, non-alcoholic fatty liver disease, short stature, hypogonadism in males, bladder dysfunction, and obesity. The *ALMS1* gene encodes a protein that localizes to the centrosomes and the base of the cilium[5,6] Pathogenic variants are associated with age-dependent loss of primary cilia, suggesting that the Alström syndrome phenotype results in impaired ciliary function rather than abnormal ciliary development.[5] Accordingly, Alström syndrome is now classified among the *ciliopathies*, which are characterized by abnormal ciliary function affecting multiple organs, including the retina, central nervous system, renal epithelium, body axis, and other sensory organs.[7,8]

Children with Alström syndrome may phenocopy Leber congenital amaurosis by presenting with early visual impairment, nystagmus, and photophobia before going on to develop truncal obesity within the first year, sensorineural hearing loss in the first decade, and insulin-resistant diabetes in the second decade.[6,8] However, most patients maintain a recordable ERG, showing a cone-rod dysfunction with a nearly electronegative waveform.[9] OCT shows extensive outer retinal layer atrophy.[9] Another ciliopathy, Bardet-Biedl syndrome, can present with cone-rod dystrophy, obesity, hypogonadism, and renal disease similar to Alström syndrome.[10]

However, nearly 80% of patients with Bardet-Biedl syndrome have post-axial polydactyly and 66% have cognitive impairment, while these features are not characteristic of Alström syndrome. Additionally, cardiomyopathy, progressive sensorineural hearing loss, pulmonary fibrosis, and pulmonary hypertension may be observed in Alström syndrome, but are not characteristic of Bardet-Biedl syndrome.[11]

Infants with Alström syndrome can manifest respiratory distress with tachypnea and tachycardia secondary to cardiomyopathy with left ventricular dilatation and decreased myocardial function. Infants that survive the initial episode often show progressive improvement, with little evidence of long-term deleterious effect in cardiac function.[12–14] A transient cardiomyopathy and progressive renal function are also common. Due to their ciliopathy, some patients with Alström syndrome have difficulty clearing the airway of debris, and as a result may have pulmonary symptoms including recurrent respiratory infections and ear infections.[15]

Alström syndrome is typically inherited in an autosomal recessive pattern, in which a child inherits one pathogenic variant in the *ALMS1* gene from each parent. In this case, however, the patient inherited both copies of chromosome 2 from his mother, reflecting a mechanism known as uniparental disomy (UPD), in which both copies of a chromosome are inherited from a single parent. UPD is attributed to errors in meiosis that result in a zygote with three copies of one chromosome (aneuploidy), followed by mitotic error that results in an embryo with the typical number of chromosomes (trisomy rescue).[16] In this case, the patient had

mixed heterodisomy and isodisomy, in which a portion of chromosome 2 was identical on both copies as the origin of the 42.2 Mb region of chromosome 2 was from one maternal grandparent while the remaining portions of chromosome 2 were from both maternal grandparents as a result of crossing over during meiosis 1. While the mother was a carrier of a single pathogenic variant in the *ALMS1* gene on chromosome 2, the patient inherited two copies of the *ALMS1* pathogenic variant within the region of homozygosity. While this appears to be the first reported case of Alstrom syndrome caused by uniparental disomy, uniparental disomy is a known, but uncommon, cause of autosomal recessive disease.[16]

In genetic investigation, it is common practice to assume parental carrier status when an affected child is identified to have a homozygous pathogenic variant. In this case, parental testing was performed because the variant in *ALMS1* was extremely rare, and because the patient's parents were non-consanguineous and came from different ethnic backgrounds, making it unlikely for both parents to be carriers for the same rare variant. When the *ALMS1* variant was detected in the patient's mother but not his father, chromosomal microarray testing was performed and revealed a large region of homozygosity, confirmed to be of maternal origin only. UPD was confirmed by PCR and supported that the maternal chromosome 2 in the patient was of mixed heterodisomy and isodisomy. This case illustrates the importance of parental testing when autosomal recessive variants are identified. Indeed, a recent study of genotype data from over four million research participants in the 23andMe and UK Biobank databases estimated that UPD occurs in approximately 1 in 2000 relatively healthy individuals.[17] UPD appears to be further enriched in some clinical populations, with a study of over 30,000 clinical exome trios from a cohort of patients with neurodevelopmental disorders resulting in a UPD rate as high as 3 per 1000.[18]

This case illustrates the importance of genetic testing for a child with vision impairment and nystagmus as a syndromic condition such as Alstrom syndrome can be uncovered. This diagnosis requires close follow up and care coordination. This case also supports the importance of parental testing. Identification of uniparental disomy provides a framework for genetic counseling and significantly reduces the recurrence risk for this recessive condition.

Funding

Supported in part by a grant from the Knights Templar Eye Foundation, Flower Mound, TX (Dr Brodsky).

Authorship

All authors attest that they meet the current ICMJR criteria for authorship.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Declaration of competing interest

None.

Acknowledgments

None.

References

1. Lam BL, Leroy BP, Black G, Ong T, Yoon D, Trzupek K. Genetic testing and diagnosis of inherited retinal diseases. *Orphanet J Rare Dis*. 2021 Dec 14;16(1):514. https://doi.org/10.1186/s13023-021-02145-0. PMID: 34906171; PMCID: PMC8670140.
2. Richards S, Aziz N, Bale S, et al, ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and Genomics and the association for molecular Pathology. *Genet Med*. 2015;17(5):405–424.
3. Del Gaudio D, Shinawi M, Astbury C, Tayeh MK, Deak KL, Raca G, ACMG Laboratory Quality Assurance Committee. Diagnostic testing for uniparental disomy: a points to consider statement from the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22(7):1133–1141.
4. Hearn T, Renforth GL, Spalluto C, et al. Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alström syndrome. *Nat Genet*. 2002 May;31(1):79–83. https://doi.org/10.1038/ng874. Epub 2002 Apr 8. PMID: 11941370.
5. Collin GB, Marshall JD, Ikeda A, et al. Mutations in ALMS1 cause obesity, type 2 diabetes, and neurosensory degeneration in Alström syndrome. *Nat Genet*. 2002;31:74–78.
6. Girard D, Petrovsky N. Alström syndrome: insights into the pathogenesis of metabolic disorders. *Nat Rev Endocrinol*. 2011;7(2):77–88.
7. Baker K, Beales PL. Making sense of cilia in disease: the human ciliopathies. *Am J Med Genet C Semin Med Genet*. 2009;151C(4):281–295.
8. Dollfus H. Pediatric retinal degeneration in systemic and inherited retinal diseases. In: Taylor D, Hoyt CS, eds. *Pediatric Ophthalmology and Strabismus*. fourth ed. Edinburgh: Elsevier Saunders; 2013:474–487, 201.
9. Khan AO, Bifari IN, Bolz HJ. Ophthalmic features of children not yet diagnosed with Alström syndrome. *Ophthalmol*. 2015;122(8):1726–1727.
10. Mockel A, Perdomo Y, Stutzmann F, Letsch J, Marion V, Dollfus H. Retinal dystrophy in Bardet-Biedl syndrome and related syndromic ciliopathies. *Prog Retin Eye Res*. 2011;30(4):258–274.
11. Forsyth RL, Gunay-Aygun M. Bardet-biedl syndrome overview [Updated 2020 Jul 23]. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 2003 Jul 14:1993–2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1363/.
12. DeBecker I, Tremblay F, LaRoche RG, et al. Acute cardiac failure and rod-cone degeneration in infancy: alström syndrome. In: *Poster Presentation*. ISGED; 1995.
13. Michaud JL, Héon E, Guilbert F, et al. Natural history of Alström syndrome in early childhood: onset with dilated cardiomyopathy. *J Pediatr*. 1996;128(2):225–229.
14. Russell-Eggitt IM, Clayton PT, Coffey R, Kriss A, Taylor DS, Taylor JF. Alström syndrome. Report of 22 cases and literature review. *Ophthalmol*. 1998;105(7):1274–1280.
15. Paisey RB, Steeds R, Barrett T, Williams D, Geberhiwot T, Gunay-Aygun M. Alström syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 2003 Feb 7:1993–2022 [updated 2019 Jun 13].
16. Benn P. Uniparental disomy: origin, frequency, and clinical significance. *Prenat Diagn*. 2021;41(5):564–572.
17. Nakka P, Pattillo Smith S, O'Donnell-Luria AH, McManus KF, , 23andMe Research Team, Mountain JL, Ramachandran S, Sathirapongsasuti JF. Characterization of prevalence and health consequences of uniparental disomy in four million individuals from the general population. *Am J Hum Genet*. 2019;105(5):921–932.
18. Scuffins J, Keller-Ramey J, Dyer L, et al. Uniparental disomy in a population of 32,067 clinical exome trios. *Genet Med*. 2021;23(6):1101–1107.