



Research paper

Alström syndrome: A rare cause of dilated cardiomyopathy in five Chinese children

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ABSTRACT

Background: The ALMS1 gene is predominantly localized to cilia, particularly in the photoreceptor cells of the retina, auditory neurons, kidneys, and other ciliated structures. Pathogenic mutations in this gene cause Alstrom syndrome (AS), which is characterized by dilated cardiomyopathy, retinal degeneration, neurodeafness, and centripetal obesity. However, the genetic mechanism of the ALMS1 gene remains unclear. This study reports five cases of Chinese children with heterozygous variants in the ALMS1 gene, aiming to expand the genetic map of AS and provide insights into its pathogenesis.

Methods: Whole exome sequencing (WES) was performed on 128 children diagnosed with DCM. ALMS1 variants were identified, and their pathogenicity and conservation were analyzed using bioinformatics tools. A retrospective analysis of genotype/phenotype associations was also conducted in conjunction with previously reported cases.

Results: A total of eleven variants were identified in the five patients, including seven nonsense variants c.2035C > T(p.R679*), c.10825C > T(p.R3609*), c.5230C > T(p.Q1744*), c.3008C > A(p.S1003*), c.11686delG(p.V3896*), c.2090C > A(p.S697*), c.12373C > T(p.Q4125*), two frameshift variants c.10383delT(p.I3461fs*48), c.1685_c.1686insCAG(p.D563fs*4), and two missense variants c.12163C > G(p.R4055G) and c.7867G > A(p.A2623T). Cardiac ultrasound revealed improvements in left ventricular ejection fraction (LVEF) following treatment, although no significant change in nystagmus was observed.

Conclusions: This study expands the genetic spectrum of ALMS1 gene variants and reinforces their pathogenicity through bioinformatics analysis. Additionally, we emphasize the importance of comprehensive cardiac evaluation and genetic testing in patients with DCM presenting with nystagmus.

1. Introduction

Alström syndrome (AS) (OMIM: #203800) is an autosomal recessive disorder resulting from homozygous or compound heterozygous mutation in the *ALMS1* gene (OMIM: *606844) on chromosome 2p13. The phenotypic manifestations of AS can exhibit considerable variability in both severity and presentation among affected individuals. Typical

clinical features include photoreceptor dystrophy, dilated cardiomyopathy, nystagmus and sensorineural hearing loss (Tahani et al., 2020). Additional common characteristics encompass centripetal obesity, diabetes mellitus (DM), acanthosis nigricans, hypertriglyceridemia and various endocrine abnormalities. Among these, dilated cardiomyopathy (DCM) is a recognized and potentially fatal complication (Bond et al., 2005) that leads to progressive heart failure in childhood or

Abbreviations: AS, Alstrom syndrome; ALMS1, Centrosome-associated protein ALMS1/Alstrom syndrome protein 1; WES, whole-exome sequencing; gnomAD, Genome Aggregation Database; MAF, Minor allele frequency; ACMG, American College of Medical Genetics and Genomics; ExAC, Exome Aggregation Consortium; PCR, polymerase chain reaction; VUS, variant uncertain significance; LP, Likely pathogenic; LVEF, Left Ventricular Ejection Fractions; DCM, Dilated Cardiomyopathy; CHF, Congestive heart failure.

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Table 1Variations of *ALMS1* gene identified in this study.

Patient	Nucleotide Change	Amino acid Change	Location	Source	Variant Frequency	ClinVar ID	ACMG	Reported
P1	0c.10825C > T	p.R3609*	E16	mother	<0.005	ID:1700586	P(PVS1 + PM3 + PM2) (PVS1 + PS1 + PM2 + PP3)	No
P1	0c.5230C > T	p.Q174*	E8	father	0.000008	ID:972512	P(PVS1 + PS1 + PM2 + PP3)	No
P2	0c.2035C > T	p.R679*	E7	mother	0.00002499	ID:937720	P(PVS1 + PM2 + PM3 + PP5)	(Xu et al., 2016)
P2	0c.3008C > A	p.S1003*	E7	father	—	—	P(PVS1 + PM2 + PM3)	No
P2	0c.7867G > A	p.A2623T	E8	father	0.0004095	—	VUS(PM2)	No
P3	0c.10383delT	p.I3461fs*48	E15	father	—	—	P(PVS1 + PM2 + PM3)	No
P3	0c.1685_c.1686insCAGCTATT CCTGAACCAGC	p.D563fs*4	E8	mother	—	—	LP(PVS1 + PM2)	No
P4	0c.11686delG	p.V3896*	E18	father	0.000004006	ID:2634032	P (PVS1 + PM2 + PM3)	No
P4	0c.2090C > A	p.S697*	E8	mother	0.000007138	ID:863290	LP (PVS1 + PM2)	No
P5	0c.12163C > G	p.R4055G	E20	mother	0.00002789	ID:1751605	LP(PM1 + PM2_Supporting + PM3 + PP3) (PM1 + PM2_Supporting + PM3 + PP3)	No
P5	0c.12373C > T	p.Q4125*	E22	father	0.000004009	ID:849501	LP (PVS1 + PM2_Supporting)	No

P: Pathogenic; LP:Likely pathogenic; ACMG: American College of Medical Genetics and Genomics ; “reported” means reported in previous publications/case; Variant Frequency: the minor allele frequency detected with the East Asian population (data from gnomAD).

adolescence, occurring in about 70 % of patients during this stage of life (Álvarez-Satta et al., 2015).

The *ALMS1* gene encodes Alström syndrome protein 1 (ALMS1), which is known to play a crucial role in the structure and function of cilia, the tiny, finger-like projections found on the surface of many cells in the body. Cilia are involved in various cellular processes, including signaling, sensory perception, and cellular movement (Álvarez-Satta et al., 2015). ALMS1 is predominantly localized in cilia, particularly in the photoreceptor cells of the retina, ear neuronal slices, and tissues such as the kidney, skin, testis, and adipose tissue, where cilia are present. Mutations in the *ALMS1* gene can disrupt the normal function of ALMS1 protein, leading to impaired cilia structure and functionality. This disruption is believed to contribute to the development of Alström syndrome and its associated clinical manifestations.

In this study, we reported ten novel variants of the *ALMS1* gene in five Alström syndrome patients that expand the spectrum of *ALMS1* and provide new insight into the disease mechanism underlying Alström syndrome.

2. Materials and methods

2.1. Subjects

Molecular diagnostic testing at our center identified 128 children with DCM. Prior to genetic testing, all study participants or their legal guardians provided written informed consent. The study was approved by the Ethics Committee of the Children’s Hospital of Nanjing Medical University.

2.2. Peripheral blood collection and DNA library preparation

Two milliliters of peripheral venous blood samples were collected from the patients and their parents and siblings. Genomic DNA was isolated using the Qiagen DNA Mini Kit. Subsequently, 1 ~ 3 µg of genomic DNA was fragmented to an average size of 150 bp using an S220 Focused-ultrasonicator instrument (Covaris, USA).

2.3. Clinical and laboratory data

The Clinical data included age at diagnosis, symptomatology, family medical history, and cardiac ultrasound findings. Cardiac ultrasound was used to assess the therapeutic response of the child’s DCM.

2.4. Whole exome sequencing

Genomic DNA was extracted from peripheral blood using the DNA isolation kit (Tiangen, Beijing, China). The extracted DNA was analyzed using whole-exome sequencing (WES). This study lists 24 genes associated with childhood-onset DCM in [Supplementary Table 2](#), and their strong/definitive DCM association as determined by ClinGen curation. The average sequencing depth of the target regions in whole exome sequencing (WES) was $\geq 90\times$, with 95 % of the target sequences achieving a sequencing depth of $\geq 20\times$. However, the coverage of deep intronic regions was insufficient. WES was conducted using GenCap whole exons capture kit (MyGenostics GenCap Enrichment technologies), and subsequently the enriched libraries were sequenced on Illumina NovaSeq 6000 sequencer for paired read 150 bp with 100X average coverage. All targeted regions including exons and exon–intron boundaries (plus 50 base pairs at each end) of 286 genes were captured using a GenCap kit (MyGenostics GenCap Enrichment technologies). The enrichment libraries were then sequenced on Illumina HiSeq 2500 sequencer for paired read 150 bp. FastQC was used for sequencing quality control. The obtained sequences were aligned to the reference human genome (hg19 build) using BWA software. Single nucleotide variation (SNV), inserts and deletions (INDEL) were filtered using GATK software (<https://software.broadinstitute.org/gatk/>). Then all variants were further annotated by ANNOVAR software. The variant sites with a frequency less than 1 % in the public databases (Genome Aggregation Database (gnomAD), dbSNP, 1000 Genomes MAF (Chinese), ExAC and an in-house MAF database.) were removed. After above steps, missense variants were predicted tolerated by SIFT, PolyPhen –2, MutationTaster, and GERP++, with pathogenic forecasts and conservative projections. Splice sites were predicted by three web-based programs: Alternative Splice Site Predictor, Human Splicing Finder Version 3.0, Splice Site Prediction by Neural Network. Primer sequences are available upon request. All candidate variants were clarified based on the American College of Medical Genetics and Genomics (ACMG) criteria 22 and further validated through Sanger sequencing.

2.5. Sanger sequencing

Genomic DNA was extracted using a DNA isolation kit (Tiangen, China) following the manufacturer’s instructions. Exonic sequences and intron–exon boundaries of *ALMS1* (Ensembl Accession ENSG00000116127) were amplified by polymerase chain reaction

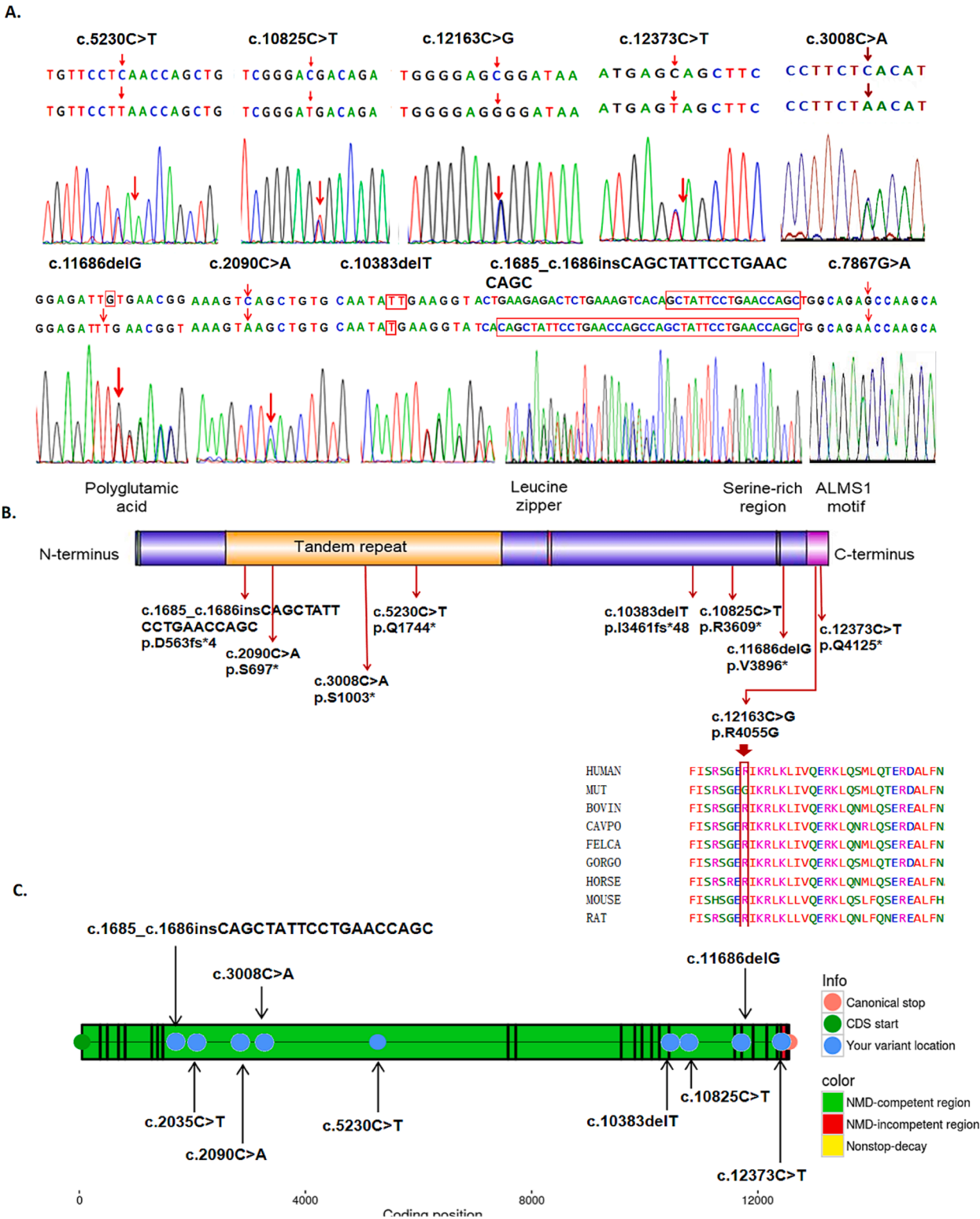


Fig. 1. Novel variants in the *ALMS1* Gene and Nonsense-Mediated mRNA Decay (NMD) Analysis. (A): Direct Sequencing reveals ten novel variants in the *ALMS1* gene including six nonsense variants c.10825C > T, c.5230C > T, c.3008C > A, c.11686delG, c.2090C > A, c.12373C > T, two frameshift variants c.10383delT, c.1685_c.1686insCAGCTATTCTGAACCAAGC, and two missense variant c.12163C > G and c.7867G > A. (B): Schematic representation of *ALMS1* variants. (C): All the nonsense and frameshift variants except the p.Q4125* variant were fully degraded by the NMD pathway. The p.Q4125* variant is partially decay by NMD prediction.

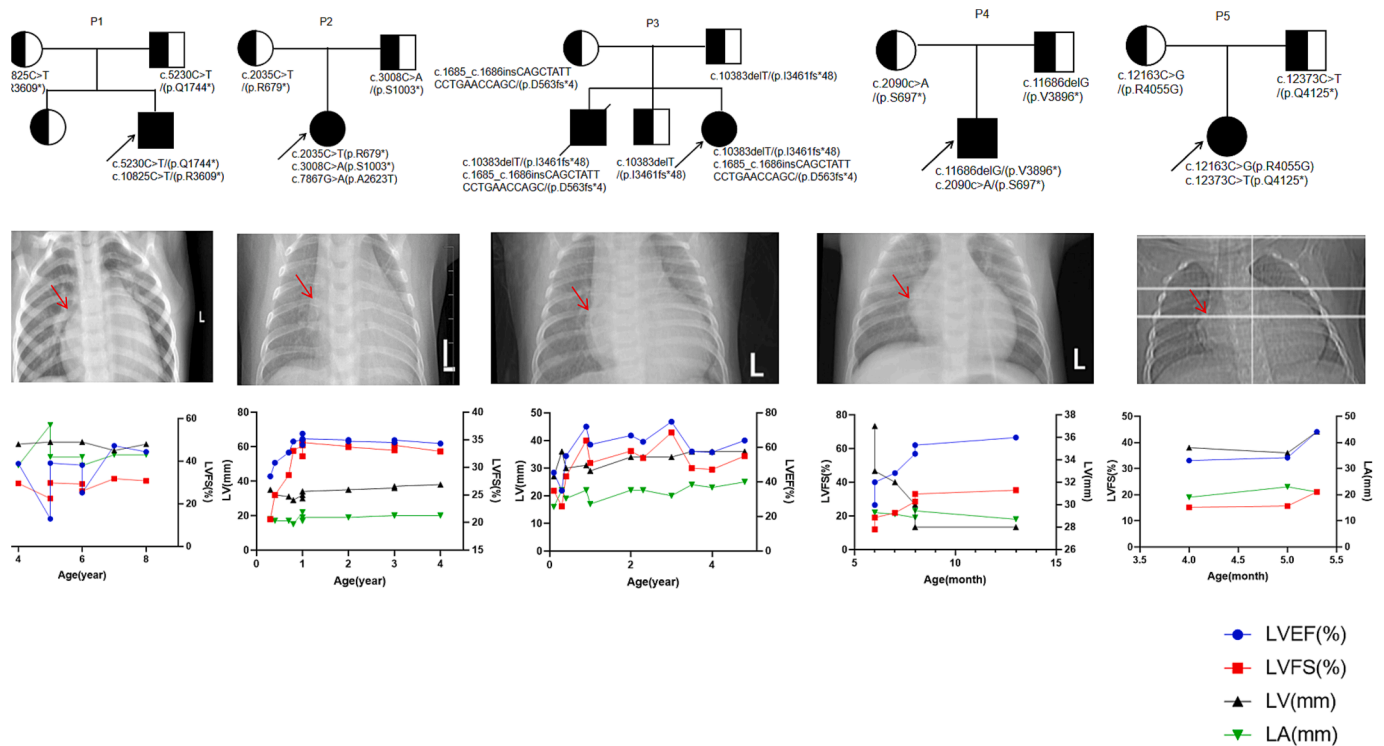


Fig. 2. Genetic and Clinical Characterization of *ALMS1* Variants in Five Pediatric Patients with DCM. (A): Genetic family lineage analysis of *ALMS1* variants in five children, probands shown by arrows, circles corresponding to females, and squares representing males; (B): Chest X-rays of all five children showed dilated cardiomyopathy, red arrows indicate enlarged hearts; (C): Improvement in left ventricular ejection fraction and cardiac function as indicated by cardiac ultrasound after drug treatment in five children; LVEF(%): Left Ventricular Ejection Fractions; LVFS(%): Left ventricular fractional shortening; LV(mm): left ventricle; LA(mm): left atrium.

(PCR) and using primers designed in Primer (S Table 1). The PCR products were column-purified and directly sequenced. The purified PCR fragments were sequenced using Big Dye Terminator (Applied Biosystems, Foster City, CA, USA) on an ABI 3130 genetic analyzer (Applied Biosystems). All variants were denoted based on the NCBI reference sequence for *ALMS1* (NM_015120).

3. Results

3.1. Variants detected in *ALMS1*

All of our patients presented with DCM, and four of them had nystagmus (except for P5) in the absence of a family history that could suggest a specific diagnosis. WES was chosen to explore potential genetic causes. Prior to WES, a diagnosis of AS was not specifically suspected in these patients. Although some extra-cardiac features were observed, they were not sufficient to conclusively suggest AS without genetic confirmation. A total of eleven variants were identified in the five patients (Table 1), including seven nonsense variants c.2035C > T (p.R679*), c.10825C > T (p.R3609*), c.5230C > T (p.Q1744*), c.3008C > A (p.S1003*), c.11686delG (p.V3896*), c.2090C > A (p.S697*), c.12373C > T (p.Q4125*), two frameshift variants c.10383delT (p.I3461fs*48), c.1685_c.1686insCAG (p.D563fs*4), and two missense variants c.12163C > G (p.R4055G) and c.7867G > A (p.A2623T). According to Nonsense-mediated mRNA decay (NMD) prediction tool (<https://nmdpredictions.shinyapps.io/shiny/>), all the nonsense and frameshift variants except the p.Q4125* variant were fully degraded by the NMD pathway. The p.Q4125* variant is predicted to undergo partial degradation by NMD. Consequently, it is plausible that a minor quantity of truncated protein may be produced.

The novel missense variant c.12163C > G was located in exon 20 from P5. This variant leads to the alteration of amino acid 4055 in the

encoded protein from arginine to glycine (p.R4055G). The variant is predicted to affect protein function by SIFT (sift.bii.a-star.edu.sg) with a score of 0.00 (median sequence conservation = 4.32, sequences represented = 4), and MutationTaster (mutationtaster.org) predicts it is disease causing (accuracy = 0.9999, converted rank score = 0.5881). This R4055 is highly conserved across species, from *H. sapiens* to *Dm* (Fig. 1B).

3.2. Clinical characteristics

We identified five children (three girls and two boys) with DCM who carried compound heterozygous variants in the *ALMS1* gene. The median age at their initial clinical evaluation was three months. The youngest child was one month old while the others were between eight months to three years old. In terms of clinical presentation, all patients presented with DCM, which was the reason for most initial consultations. Nystagmus was observed in four of five patients (except P5). Additional clinical manifestations included liver damage (P1, P2 and P3), acanthosis nigricans (P1 and P2), hearing loss (P1 and P4), neurologic damage and growth retardation (P3 and P4), generalized obesity (P2), and renal system abnormalities (enuresis, urinary frequency in P3). Notably, no metabolic abnormalities, such as blood glucose dysregulation, were identified. P3 had an older brother who died 4–5 months after birth due to a “cardiac malformation combined with pneumonia”. Only P3 has renal system manifestations such as enuresis and urinary frequency. Notably, our patients had no metabolic abnormalities such as blood glucose.

Following the characterization of cardiac lesions, we evaluated cardiac function and pharmacologic support in five patients, includes conventional anti-heart failure therapy: digoxin, betalactam, captopril, diuretics. Concurrently, we administered energy supplements such as high-dose coenzyme Q10, levocarnitine, and vitamin B complex. After

Table 2
Clinical features of 5 children with ALMS1 Variants.

Patient	Age at diagnosis	Sex	Nation	Family history	Hearing loss	Nystagmus/ photophobia	Dilated cardiomyopathy	liver damage	Generalized obesity	Acanthosis nigricans	Renal involvement	growth retardation	Neurological damage
P1	3y8m	Male	Han	-	+	+	+	+	-	+	-	-	-
P2	3 m	Female	Han	-	-	+	+	+	+	-	-	-	-
P3	1 m	Female	Han	+	-	+	+	+	-	-	+	+	+
P4	6 m	Male	Han	-	+	+	+	-	-	-	-	+	+
P5	4 m	Female	Han	-	-	+	+	-	-	-	-	-	-

approximately one year of treatment, there was a notable improvement in cardiac function among the children (Fig. 2C).

Currently, these patients are continuing to receive follow-up care in the ophthalmology and cardiology clinics. With consistent medication, all of them showed improvement in left ventricular ejection fraction (LVEF) on cardiac ultrasound (Table 2). While there is no specific treatment for AS, a combination of anti-heart failure therapy and energy support can lead to partial improvement, particularly in cardiac function.

4. Discussion

Based on previously reported cases of AS, DCM is often the initial diagnosis and the most critical finding in AS. Specifically, DCM manifests in approximately two-thirds of patients, with a significant proportion of children (46 %) developing sudden heart failure within the first few months of life, even before the appearance of nystagmus (Michaud et al., 1996; Warren et al., 1987). In many infants, cardiac function improves in the first three years of life and remains stable at “low-normal” level for an extended period. This observation is consistent with our findings that four out five children diagnosed at our center exhibited enlarged hearts during infancy (80 %), prior to the onset of nystagmus. Bond et al. reported that cardiomyopathy associated with AS, when presenting in the first year of life, could completely subside. They observed seven families with children who presented with DCM leading to heart failure within the first three months of life. In that study, all patients responded positively to pharmacologic supportive therapy, with cardiomyopathy improving within six months (Loudon et al., 2009). Unfortunately, although patients with AS may fully recover from cardiomyopathy in infancy, DCM/CHF may recur suddenly during adolescence or adulthood (Collin et al., 2002). Therefore, all patients with AS are at risk of developing DCM at any time (Marshall et al., 2007). The majority of childhood fatalities associated with this syndrome are attributable to heart failure, accounting for approximately 90.5 % of death (Zulato et al., 2011).

We report five Chinese children harboring compound heterozygous variants in the ALMS1 gene, who presented with DCM as the initial symptom. Among these patients, four exhibited retinal damage characterized by nystagmus and photophobia, while some also demonstrated renal damage, acanthosis nigricans, hearing loss, and neurologic delays. Continuous echocardiographic monitoring revealed decreased left ventricular systolic and diastolic function at disease onset. Following consistent medication, significant improvement in cardiac function was observed (Fig. 2C). Interesting, Nicola et al. suggested that the presence of impaired left ventricular systolic function in Alström syndrome may be associated with diffuse interstitial myocardial fibrosis (Edwards et al., 2015). This alerts clinicians to refine cardiac MRI to further define the extent of cardiomyopathy when necessary.

Currently, 278 variants in the ALMS1 gene have been identified according to the human mutation database, with 96 % being nonsense and frameshift variants (insertions or deletions) that produce truncated, non-functional proteins (Tahani et al., 2020; Zhang et al., 2022). Most of the pathogenic variants in ALMS1 are located downstream of exon 7, with “hot spots” in exons 8, 10 and 16 (Marshall et al., 2007; Marshall et al., 2011). Exon 16 harbors 36 % of variants, while exon 8 accounts for over 50 % of the mutation rate, likely due to its larger coding sequence (Marshall et al., 2015; Marshall et al., 2011). We screened five patients carrying ALMS1 variants from 128 Chinese children with DCM, identifying eleven variants: seven nonsense, two missense, and two frameshift variants, which were mainly concentrated in exon regions 7, 8, and 16. However, due to the design of WES focuses primarily on exons and regions adjacent to splice sites, whereas deep intronic regions such as regulatory sequences or non-coding regions located far from exons are typically excluded from the target capture, resulting in insufficient sequencing coverage. We emphasize that these limitations underscore the need for complementary methods, such as targeted sequencing,

RNA-based studies, or long-read sequencing, to improve the detection of variants in low-coverage regions.

Our findings expand the genetic spectrum of the *ALMS1* gene. Despite patients experiencing stable cardiac function and well-being following prolonged symptomatic supportive therapy with furosemide, spironolactone, captopril, metoprolol, and digoxin, no treatment currently exists to prevent organ involvement in AS. The management of AS remains primarily symptomatic and supportive, with no curative options available and a generally poor prognosis. However, with the increasing abundance of genetic information, clinicians can potentially slow disease progression and improve quality of life. Understanding the functional role of *ALMS1* and its interactions with other genes is crucial for developing targeted therapies to prevent and treat the diverse clinical manifestations of AS. Existing studies have identified a role for PBI-4050 (Baig et al., 2018), the sodium salt of 3-pentylphenylacetic acid, which has been found to modulate a wide range of cells including macrophages, fibroblasts, and epithelial cells, with anti-inflammatory, prophylactic, or reversal of fibrosis effects in an in vitro model tested in animals. Currently undergoing clinical trials for safety and efficacy, PBI-4050 represents a potential therapeutic avenue for AS. As research advances, we anticipate the development of additional treatments and therapeutic agents.

5. Conclusion

We identified compound heterozygous variants in the *ALMS1* gene in five out of 128 Chinese pediatric patients with DCM, expanding the genetic spectrum of AS. Our findings highlight the critical role of comprehensive cardiac evaluations and targeted genetic testing in patients with DCM and nystagmus. Early genetic testing and timely administration of anti-heart failure therapy and energy supplementation can help improve cardiac function in patients with AS. Clinicians should integrate these diagnostic tools to enhance early detection and personalized management strategies for affected individuals. Furthermore, we assert that performing ciliary functional testing would provide valuable support for establishing the pathogenicity of the reported variants.

Ethics Approval and Consent to Participate.

The studies involving human participants were reviewed and approved by the institutional ethical committee of the Children's Hospital of Nanjing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Consent for Publication

Not applicable.

CRedit authorship contribution statement

Yuying Qi: Writing – review & editing. **Jie Lu:** Writing – original draft. **Ningning Sun:** Writing – original draft. **Ziwei Wang:** Software. **Yuqi Wang:** Writing – review & editing, Conceptualization. **Jueru Zhou:** Resources. **Jie Yin:** Writing – original draft. **Chunli Wang:** Writing – review & editing. **Shiwei Yang:** Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gene.2025.149285>.

Data availability

The data that has been used is confidential.

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