tvst

Retina

Ocular Characteristics and Genotype-Oriented Disease Spectrum of Alström Syndrome in Taiwan

Chien-Chien Cheng[1], Chien-Yu Lin[2], Ting-Chieh Ko[2], Yu-Shu Huang[2,3], Chu-Hsuan Huang[4,5], Chang-Hao Yang[2], Tzyy-Chang Ho[2], Pei-Lung Chen[3,6,7], and Ta-Ching Chen[2,8–10]

[1] National Taiwan University Hospital, Taipei, Taiwan
[2] Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan
[3] Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan
[4] Department of Ophthalmology, Cathay General Hospital, Taipei, Taiwan
[5] School of Medicine, National Tsing Hua University, Hsinchu, Taiwan
[6] Graduate Institute of Medical Genomics and Proteomics, Medical College, National Tai- wan University, Taipei, Taiwan
[7] Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan
[8] Center of Frontier Medicine, National Taiwan University Hospital, Taipei, Taiwan
[9] Research Center for Developmental Biology and Regenerative Medicine, National Taiwan University, Taipei, Taiwan
[10] Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan

Correspondence: Ta-Ching Chen, Department of Ophthalmology, National Taiwan University College of Medicine and Hospital, No. 7, Chung-Shan S. Rd., Taipei 10051, Taiwan. e-mail: tachingchen1@ntu.edu.tw

Received: December 6, 2024
Accepted: April 29, 2025
Published: June 11, 2025

Keywords: alström syndrome; ALMS1; Inherited retinal disease; cone–rod dystrophy; syndromic ciliopathy; LINE-1 (long interspersed nuclear element-1)

Citation: Cheng CC, Lin CY, Ko TC, Huang YS, Huang CH, Yang CH, Ho TC, Chen PL, Chen TC. Ocular characteristics and genotype-oriented disease spectrum of Alström syndrome in Taiwan. Transl Vis Sci Technol. 2025;14(6):22, https://doi.org/10.1167/tvst.14.6.22

Purpose: This study aimed to describe the ophthalmological features of Alström syndrome, a rare syndromic ciliopathy, and to delineate the genotype-associated disease spectrum.

Methods: Eight Taiwanese patients were recruited for this study. Pathogenic variants were identified using next-generation sequencing, and medical records were reviewed for systemic involvement. Best-corrected visual acuity, cycloplegic refraction, blue light fundus autofluorescence imaging, International Society for Clinical Electrophysiology of Vision-standard full-field flash electroretinography, optical coherence tomography, and visual field testing were obtained and studied retrospectively.

Results: Common ocular manifestations included hyperopia, nystagmus, photophobia, and visual impairment. Most patients also exhibited obesity, sensorineural hearing loss, and developmental delays. Phenotype variability was observed in age of onset (0–8 years), severity of visual impairment, and extent of extraocular involvement. Electroretinography results reflected varying degrees of retinal degeneration. We identified c.11110_11128del as a genotype frequently occurring in Asian populations that demonstrated a more severe phenotype within our cohort. In addition, we discovered three novel variants, including a LINE-1 insertion in exon 8 (c.3565insL1), c.6166_6167insAT, and 8077del.

Conclusions: Alström syndrome may manifest with early-onset ocular and syndromic features, or demonstrate a later onset with limited extraocular involvement. This is the first report of a LINE-1 insertion in ALMS1, with affected patients exhibiting comparatively mild phenotypes.

Translational Relevance: Combined ophthalmological and extraocular phenotypes combined may aid in diagnosing this rare disease and differentiating it from other possible causes.

Introduction

Inherited retinal disorders (IRDs) constitute a genetically and clinically heterogeneous group of conditions that result in progressive and irreversible visual impairment.[1] Although most IRDs manifest exclusively as ophthalmic impairments, a subset—syndromic IRDs—demonstrates extraretinal features and, although rare, can impose significant socioeconomic burdens on patients.[2] Ciliopathies, a subset of syndromic IRDs, result from dysfunction of the primary cilium, leading to multisystem involvement. Representative disorders include Bardet–Biedl syndrome, Usher syndrome, and Alström syndrome (AS; OMIM 203800), which affect both the retina and other organ systems. Although these disorders represent a minority of IRDs, their propensity to induce the metabolic syndrome and multisystem dysfunction necessitates frequent hospital visits. Combined with limitations in occupational capacity owing to visual and auditory impairment, the financial burden of these disorders is likely to surpass previously reported estimates for IRDs as a whole.[3]

AS is a rare autosomal recessive monogenic syndromic IRD, with an estimated prevalence of fewer than 1 in 1,000,000 individuals. It is caused by biallelic pathogenic variants in the ALMS1 gene, most frequently affecting exons 8, 10, and 16.[4] ALMS1 is ubiquitously expressed and localizes to the basal body and centrosome of cilium[5,6] and is involved in the regulation of energy homeostasis, cell-cycle progression, intracellular trafficking, and cell-specific functions of the primary cilia.[7] Clinically, AS is characterized by progressive cone–rod retinal dystrophy, neurosensory hearing loss, childhood obesity, and insulin resistance that may progress to type 2 diabetes mellitus. Additional features include early-onset cardiomyopathy and hepatic and renal involvement.[8,9] Although no definitive treatment is available currently, proactive management of metabolic comorbidities is essential. Patients may also benefit from genetic counseling and molecular testing of at-risk family members.

Given the variable onset and multisystem nature of AS, early diagnosis remains challenging and often requires molecular confirmation—a process historically limited by the prohibitive costs of conventional genetic testing.[10,11] The advent of next-generation sequencing (NGS) techniques has substantially enhanced diagnostic accessibility, with targeted gene panels offering a cost-effective and efficient approach.[12] To explore the genomic epidemiology of IRDs in Taiwan, we established the Taiwan Inherited Retinal Degeneration Project, which provides molecular surveillance for Taiwanese patients with IRDs using a capture-based NGS platform. Between July 2015 and December 2023, 741 families received genetic counseling through the referral network, among whom 8 patients from 6 families were diagnosed with genetically confirmed AS. This study presents their ophthalmological and systemic features.

Material and Methods

Patient Recruitment and Clinical Evaluation

This study included eight patients from six unrelated families recruited from July 2015 to December 2023 through the Taiwan Inherited Retinal Degeneration Project. Patients who met the enrollment criteria were diagnosed clinically with AS, which was confirmed by the identification of biallelic disease-causing variants in the ALMS1 gene. Participants were recruited either from our outpatient clinic or through referrals from medical centers across Taiwan. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (IRB number: 201408082RINC) and conformed with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients or from the legal guardians of minor participants.

All patients were evaluated by retinal specialists at the Department of Ophthalmology at the National Taiwan University Hospital. A comprehensive ophthalmological workup was performed in patients who were able to cooperate with the examination. Best-corrected visual acuity (BCVA), cycloplegic refraction, blue light fundus autofluorescence (FAF) imaging, International Society for Clinical Electrophysiology of Vision standard full-field flash electroretinography (ERG),[13] optical coherence tomography (OCT), and visual field testing were obtained and studied retrospectively. Clinical information, including sex, age, presenting symptoms, family history, past medical history, and relevant laboratory test results, was obtained through self-report forms and a retrospective review of patient charts.

NGS After Capture-Based Target Enrichment

Blood samples were collected in EDTA tubes and genomic DNA was extracted from peripheral blood mononuclear cells using a DNA extraction kit (Gentra Puregene Blood Kit, QIAGEN, Hilden, Mettmann, Germany). Subsequently, genetic testing was conducted using a probe capture-based NGS

technique designed to target 212 IRD-associated genes. Relevant genes were selected from the RetNet database (https://sph.uth.edu/retnet/), OMIM database (https://www.ncbi.nlm.nih.gov/omim), and publications (PubMed search queries: hereditary retinal dystrophy), using a method utilized and validated in previous studies[14,15] (Supplementary Table 1). Pathogenicity prediction algorithms, including SIFT, PolyPhen-2, MutationTaster, and PROVEAN were used to predict the pathogenicity of the retained variants following the American College of Medical Genetics and Genomics guidelines.[16] DNA fragments containing the suspected variants were further confirmed using Sanger sequencing (ABI 3730xl; Applied Biosystems, Waltham, MA).

Mobile Element Insertions Detection

The SCRAMble tool was used to analyze the mobile element insertions. Computational outcomes were assessed by examining clusters of soft-clipped reads within a BAM file using Integrative Genomics Viewer. This method facilitated the visualization and interpretation of insertions in the genomic context (Supplementary Fig. S2).

Long Interspersed Nuclear Element-1 (LINE-1) Insertion Confirmation

A heterozygous LINE-1 insertion in exon 8 of ALMS1 was identified in cases 5 and 6 through long-range PCR with the following primers: forward, 5′-TTCTATCAACAGGAGTGGCC-3′; reverse, 5′-CAGTTGGATGACTATGTGGC-3′, generating three PCR products (Supplementary Fig. S2). Long-range PCR was performed with Platinum SuperFi II DNA polymerase (Thermo Fisher Scientific, Waltham, MA) under the following conditions: 98°C for 30 seconds, followed by 35 cycles of 98°C for 10 seconds, 60°C for 10 seconds, and 72°C for 5 minutes, with a final extension 72°C for 5 minutes.

Results

Patient Demographics

Eight patients, including one female and seven males from six unrelated families, were recruited for this study (Table 1). The age of participants ranged from 2 to 31 years, with a mean age of 4.13 ± 3.18 years at ocular symptom onset and 10.75 ± 9.63 years at initial clinical evaluation. All individuals self-identified as Taiwanese and were born to nonconsanguineous, unaffected parents. A positive ophthalmological family history was noted only in cases 1 and 2, who were siblings. They reported retinitis pigmentosa manifesting as night blindness in their great grandfather and retinal pigmentary deposits in their first cousin once removed on the maternal side. No relevant family history of retinal disease was reported in any of the remaining patients. The pedigrees of these six families are illustrated in Figure 1.

Biallelic pathogenic variants of *ALMS1* were identified in all cases. These include single-nucleotide variants, small insertions or deletions, and LINE-1 insertions, all of which resulted in frameshift alterations or premature termination codons (Table 1). The most frequent variants were c.11110_11128del, found in four patients (50%), and c.10825_10826del, found in two patients (25%). Additionally, three novel pathogenic variants were identified: c. 8077del, c.6166_6167insAT, and LINE-1 insertion in exon 8 (c.3565insL1), all of which were predicted to produce frameshift effects or truncated protein products.

Ophthalmological Involvement

All patients presented with decreased visual acuity. BCVA could not be obtained in two younger patients owing to poor cooperation. One patient (case 4) had vision limited to hand motion from the age 10 years, and the remaining individuals demonstrated vision ranging from 20/50 to 20/600. The primary symptoms among the cohort included moderate-to-high hyperopia (5/8) and photophobia (4/8). Horizontal nystagmus was noted at the initial presentation in the two patients with the earliest symptom onset (cases 3 and 7).

Fundus photography and FAF were obtained from six patients, excluding cases 2 and 7 owing to their young age and limited cooperation (Fig. 2). The anterior segment examination was largely unremarkable, except for bilateral posterior subcapsular cataracts in case 4. Fundoscopic examination revealed blunted foveal reflex and hypopigmented mottling in all patients, and vessel attenuation and optic disc pallor were observed in case 3. FAF imaging revealed a parafoveal ring of increased autofluorescence in four patients and a tendency of a hyperautofluorescent ring towards the rim of the vascular arcades in one patient. ERG was performed in four patients. Cone and rod responses were markedly reduced in cases 1 and 3 (Fig. 3), whereas cases 5 and 6 exhibited a more significant decrease in photopic responses with relatively preserved, yet subnormal, scotopic responses (Fig. 4). OCT findings in the five cases revealed varying degrees of outer retinal degeneration. Case 4 showed

Table 1. Clinical Features of Eight Patients Recruited in the Cohort

ID	S	Age (Current/ Examination/Onset of Ocular Symptoms)	Genotype	Protein	Ocular Findings	Extraocular Findings
Case 1	F	11 years /5 years/ 2 years	c.7528C>T(;) 11110_11128del[26]	p. (Arg2510Ter) p. (Arg3704LeufsTer11)	Amblyopia, astigmatism, photophobia	Sensorineural hearing loss, hyperinsulinemia with prediabetes, obesity with acanthosis nigricans, mild fatty liver, hyperlipidemia, advanced bone age, premature puberty, developmental delay
Case 2	M	4 years /5 years / 4 years	c.7528C>T(;) 11110_11128del[26]	p. (Arg2510Ter) p. (Arg3704LeufsTer11)		Obesity, advanced bone age
Case 3	M	9 years /4 years/1y	c.[5022C>G]; [10825_10826del][26,31]	p. (Tyr1674Ter) p. (Arg3609AlafsTer6)	Horizontal nystagmus, torticollis, photophobia	Obesity, epilepsy
Case 4	M	17 years /13 years /8 years	c.[11110_11128del]; [11110_11128del][26]	p. (Arg3704LeufsTer11)	Neonatal dilated cardiomyopathy Increased intraocular pressure (17.5/27.7)	Sensorineural hearing loss, recurrent otitis media and upper respiratory tract infection, type 2 diabetes mellitus, obesity, hypertension, advanced bone age, hypogonadism, hypothyroidism, fatty liver, hepatitis, hyperuricemia; psychomotor retardation, developmental delay
Case 5	M	30 years /26 years / 8 years	c.11704C>T(;) c.3565insL1[26,*]	p. (Arg3902Ter) –	Visual impairment	Sensorineural hearing loss
Case 6	M	31 years /27 years / 8 years	c.11704C>T(;) c.3565insL1[26,*]	p. (Arg3902Ter) –	Visual impairment Reduced color vision	Sensorineural hearing loss
Case 7	M	2 years/1 year/0 year	c.[10825_10826del]; [11110_11128del][26,31]	p. (Arg3609AlafsTer6) p. (Arg3704LeufsTer11)	Horizontal nystagmus, photophobia	Obesity, developmental delay
Case 8	M	6 years /5 years / 2 years	c.[6166_6167insAT]; [8077del][*]	p. (Ile2056AsnfsTer18) p. (Glu2693LysfsTer16)	Astigmatism, hyperopia, photophobia	Obesity

[*]Novel mutation.

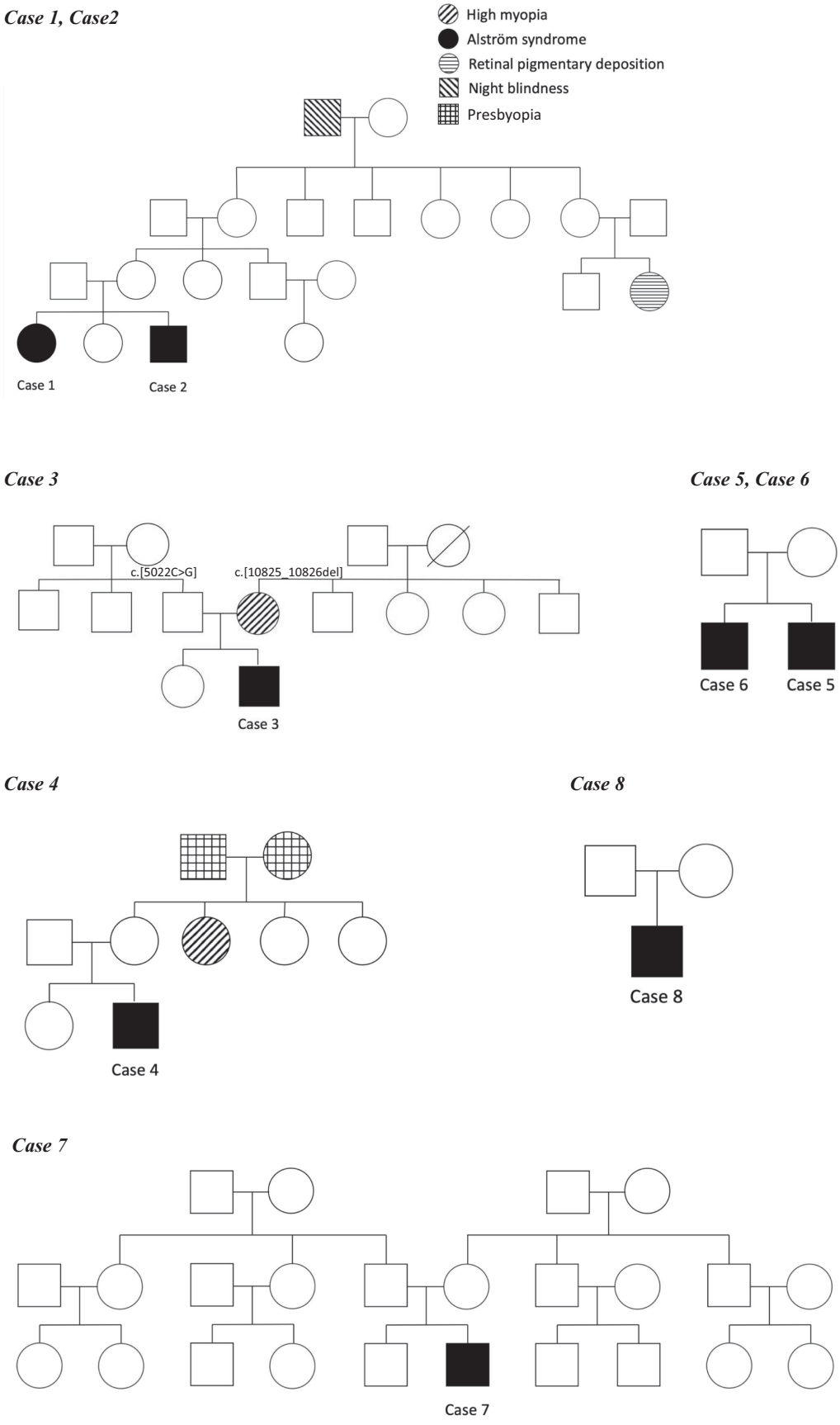

Figure 1. Pedigrees of six families.

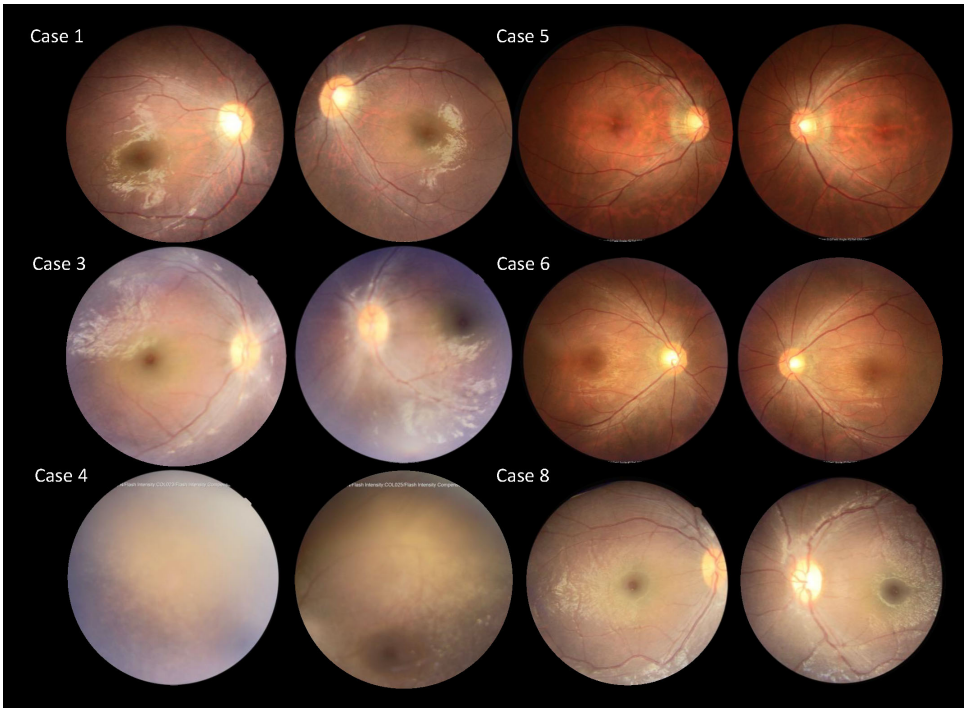

Figure 2. Color fundus of AS patients showing varying degrees of retinal hypopigmentation, optic disc pallor, and pale optic discs. Posterior subcapsular cataracts obscured the view of case 4.

the most severe findings, including loss of the ellipsoid zone (EZ), interdigitation zone, obscuration of the external limiting membrane in the macular region, and widespread peripheral photoreceptor loss with residual photoreceptor segments in the central macula. Case 1 had milder structural disruption with a preserved photoreceptor layer and slight external limiting membrane blurring, disruption in the EZ, and absence of the interdigitation zone at the central macula (Figs. 3A and 3B). In contrast with the two prior cases, case 5 exhibited a milder phenotype with midperipheral photoreceptor thinning and central blurring of the EZ junction. Similarly, cases 6 and 8 mainly exhibited peripheral photoreceptor loss, with case 8 also displaying external limiting membrane and EZ blurring in the macular area (Fig. 4 and Supplementary Fig. S1). A summary of the ophthalmological findings is presented in Table 2.

Extraocular Involvement

Extraocular findings included obesity (6/8), sensorineural hearing loss (4/8), type 2 diabetes mellitus (1/8), and developmental delay (3/8). One patient (case 4) was diagnosed with neonatal dilated cardiomyopathy, which later resolved with medical treatment (Table 1). Case 3 initially presented with nystagmus and torticollis and was diagnosed with spasmus nutans. However, he later developed generalized tonic–clonic seizures and was diagnosed with Lennox–Gastaut syndrome after inconclusive neuroimaging and genetic workup.

Representative Cases With Single Nucleotide, Insertional, and/or Deletional Variants

Pathogenic point, insertional, and/or deletional variants in ALMS1 were identified in six patients, all of whom exhibited early-onset retinopathy and multisystemic features of variable severity.

Case 1 presented at age 5 with a 3-year history of photophobia and poor vision. On initial examination, truncal obesity and acanthosis nigricans were noted (Fig. 3). Her BCVA had deteriorated from 20/125 to 20/400 over time. She was diagnosed with sensorineural hearing loss within 1 year. The metabolic involvement in this patient included hyperlipidemia, advanced bone age, premature puberty, hyperinsulinemia, and elevated hemoglobin A1c levels, which reached the threshold for prediabetes by the age of 9 years. Her visual acuity stabilized after 6 years of follow-up. During follow-up, we further identified her younger brother (case 2), who displayed similar ocular features and exhibited obesity since infancy.

Case 4 presented at 5 months with obesity and neonatal dilated cardiomyopathy, the latter resolv-

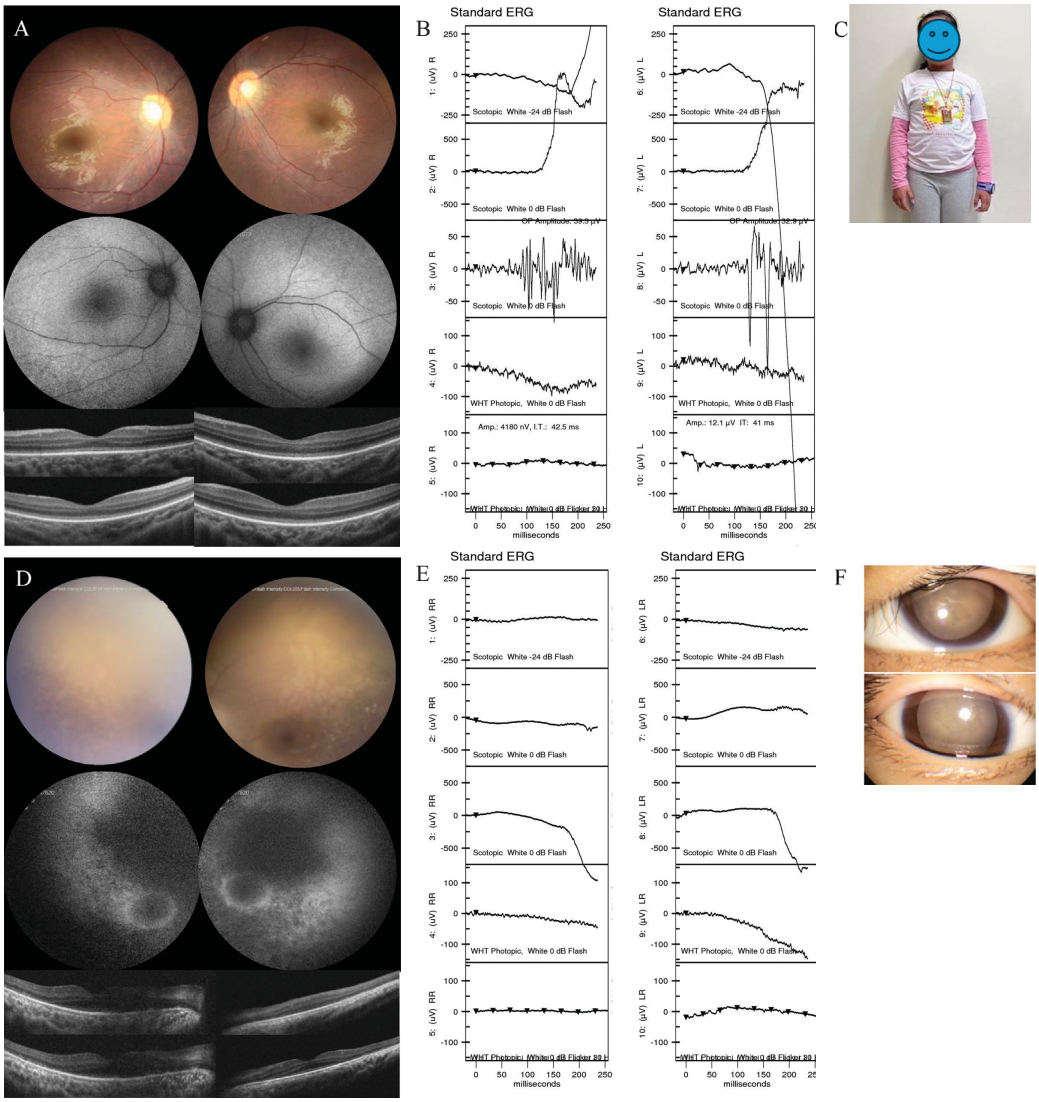

Figure 3. (**A**) Fundoscopy, FAF imaging, OCT of case 1 showing diffuse hypopigmented retinal changes and a ring of increased autofluorescence around the macular region. OCT revealed preserved photoreceptor layer with mild blurring of external limiting membrane at central macula (**B**) ERG of case 1 showing diminished cone rod response. (**C**) Image of characteristic truncal obesity in case 1. (**D**) Fundoscopy, FAF, and OCT of case 4. Fundoscopy is obscured by cataracts while FAF showed a ring of increased autofluorescence and round hypoautofluorescent spots at parafoveal region. (**E**) ERG of case 4 showing diminished cone rod response. (F) Photo of posterior subcapsular cataracts in case 4.

ing after medical treatment. The patient later developed recurrent respiratory tract infections, chronic otitis media, and sensorineural hearing impairment. At the age of 9 years, he was diagnosed with type 2 diabetes and treated with oral hypoglycemic agents. His vision was severely affected early in the disease course and bilateral posterior subcapsular cataracts developed during follow-up. Fundus examination revealed loss of foveal reflex and diffuse pigmentary changes.

ERG revealed severely diminished cone and rod responses upon initial evaluation in both cases 1 and 4 (Fig. 3). Both patients had elevated liver enzymes and triglyceride levels, along with mild-to-moderate fatty liver on abdominal ultrasonography. They shared the pathogenic variant c.11110_11128del, with case 4 being homozygous for this variant.

Cases 2, 3, 7, and 8 also presented with childhood-onset visual impairment and obesity. Although extraocular involvement was limited at the time of assessment, the younger age compared with cases 1 and 4 suggests that additional features of AS may emerge over time.

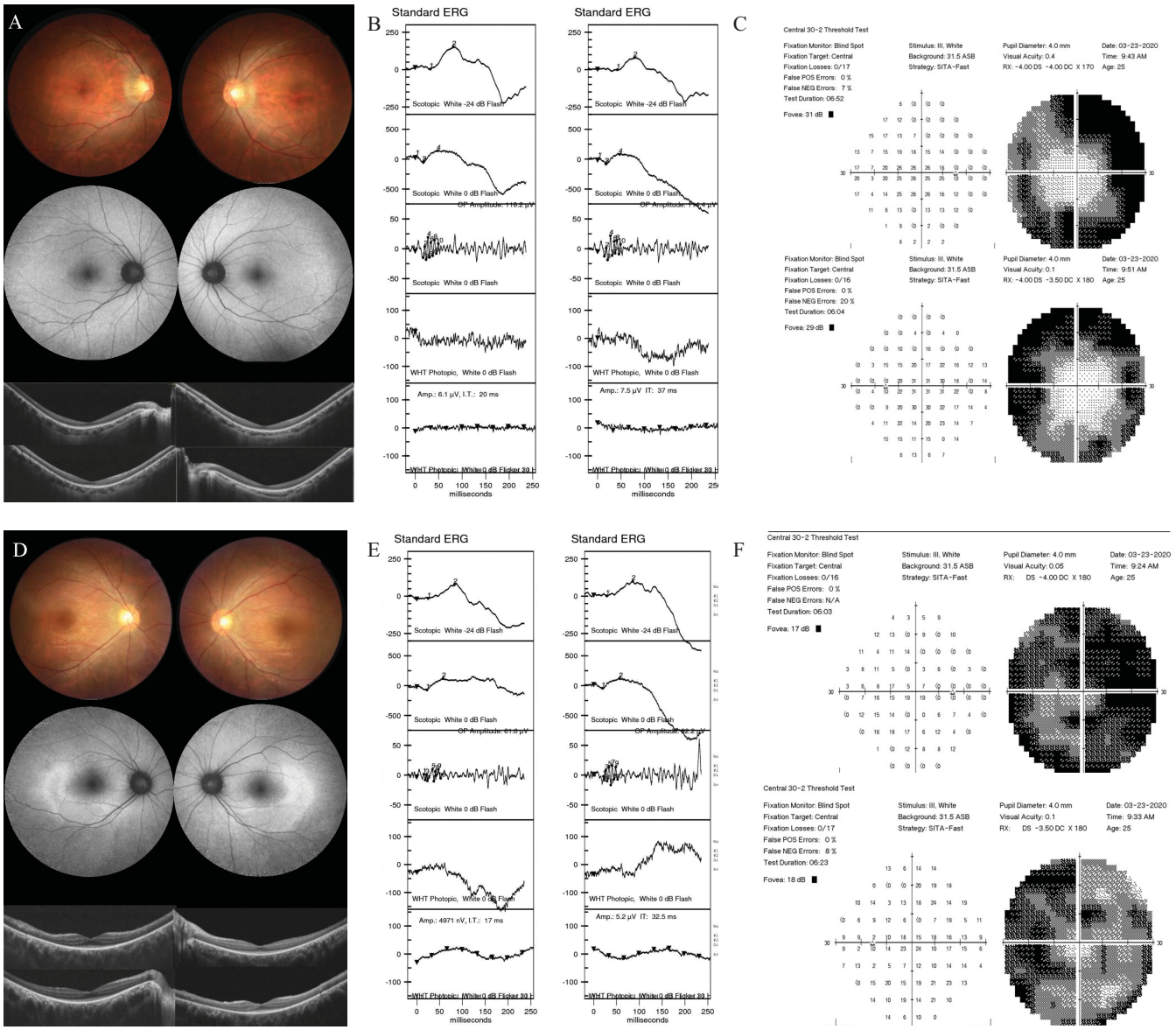

Figure 4. (**A**) Fundoscopy, FAF imaging, and OCT of case 5 showing a near normal fundus with peripheral photoreceptor thinning and central blurring of EZ junction. (**B**) ERG of case 5 showing diminished photopic response and relatively preserved but subnormal scotopic responses. (**C**) Visual field of case 5. (**D**) Fundoscopy, FAF, and OCT of case 6 showing mild hypopigmentary changes and a prominent parafoveal hyperfluorescent ring. Loss of photoreceptor layer in the peripheral retina is observed. (**E**) ERG of case 6 showing diminished photopic response and relatively preserved but subnormal scotopic responses. (**F**) Visual field of case 6.

Representative Cases With LINE-1 Insertion

Cases 5 and 6 were biological brothers carrying identical biallelic variants of ALMS1 (c.11704C>T(;)c.3565insL1). BCVA was 20/60 in the right eye (OD) and 20/50 in the left eye (OS) in case 5, and 20/400 OD and 20/600 OS in case 6. Both patients had myopia and similar ages of onset. Case 6 exhibited reduced color vision and variable visual fields. FAF in case 5 was unremarkable except for a subtle hyperautofluorescent ring along the vascular arcades, consistent with his relatively preserved visual acuity. In contrast, case 6 displayed a parafoveal hyperautofluorescent ring (Fig. 4). Similarly, OCT revealed peripheral photoreceptor loss in case 6 and mild mid-peripheral thinning in case 5. Notably, despite preservation of the EZ on OCT, the BCVA was reduced in case 6, indicating a structural functional dissociation. ERG from both patients showed diminished photopic responses with relatively preserved, yet subnormal, scotopic responses. Neither patient exhibited obesity or other extraocular involvement beyond the self-reported hearing loss. These findings suggest that LINE-1 insertions in the

Table 2. Summary of Ophthalmological Findings

	Refraction		BCVA				
ID	OD	OS	OD	OS	Color Fundus/FAF	OCT	ERG
Case 1	+2.25	+1.75	20/400	20/400	Blunted foveal reflex, and diffuse hypopigmented mottling/ Ring of increased autofluorescence	Preserved photoreceptor layer with mild blurring of ELM at central macula	Severely diminished cone rod response
Case 2	−3.5	−2.75	20/200	20/400	Early pigmentary change	NA	NA
Case 3	+10.00 (PG)	+9.50 (PG)	NA	NA	Blunted foveal reflex, mild vessel attenuation and blunted foveal reflex Diffuse hypopigmented mottling and pinkish disc Pale optic disc (OS)/NA	NA	NA
Case 4	+12.75 (2022) +7.75 (2017)	− +7.75 (2017)	LS/HM (poor coopera-tion)	LS/HM	Blunted foveal reflex, macular region RPE change; periphery diffuse pigmentary change/Ring of increased autofluorescence Round hypoautofluorescent spots at parafoveal region	Loss of interdigitation zone, EZ and obscured ELM in macular area Loss of photoreceptor layer in the peripheral retina	Severely diminished cone rod response
Case 5	−4.75	−4.25	20/60	20/50	Mild hypopigmented retina, normal disc (near normal fundus)/ hyperautofluorescent ring towards the rim of vascular arcades	Midperipheral photoreceptor thinning and central blurring of EZ junction	Severely reduced photopic response
Case 6	−0.50	−0.75	20/400	20/600	Prominent nerve fiber layer/parafoveal hyperfluorescent ring	Loss of photoreceptor layer in the peripheral retina	Severely reduced photopic response
Case 7	+3.0 (skia)	+4.0 (skia)	NA	NA	NA	NA	NA
Case 8	+6.75	+10.00	20/125	20/200	Blunted foveal reflex Diffuse hypopigmented mottling/parafoveal hyperfluorescent ring	Thinning of photoreceptor layer in peripheral retina Blurred ELM and EZ in the macular area	NA

ELM, external limiting membrane; NA, did not perform; ND, number of digits.

The age of participants ranged from 2 to 31 years, with a mean age of 4.13 ± 3.18 years at ocular symptom onset and 10.75 ± 9.63 years at initial clinical evaluation.

ALMS1 gene may be associated with the later onset and milder phenotypes of AS.

Discussion

Our study reviewed the clinical manifestations of eight Taiwanese patients with AS, with an emphasis on ophthalmological findings. Early ocular features included moderate-to-severe hyperopia, photophobia, and nystagmus, consistent with previous reports.[17,18] Horizontal nystagmus was most prominent in patients with an earlier onset. Notably, nearly all patients initially presented with visual symptoms, with the exception of one patient who presented with neonatal dilated cardiomyopathy, highlighting the diagnostic

value of early ophthalmic signs. Our findings may serve as valuable clues to facilitate early diagnosis of this rare disorder. Three novel disease-causing variants were identified in our cohort, all of which were predicted to result in frameshift alterations or premature terminations. To the best of our knowledge, this Taiwanese AS cohort is the largest to date, and the first study to incorporate a detailed ophthalmological evaluation.

Our findings highlight the clinical heterogeneity of AS. Of the four patients who underwent ERG, two (cases 1 and 4) showed diminished responses in both photoreceptor types, consistent with advanced photoreceptor degeneration and a more severe phenotype. These findings are consistent with previous reports linking extinguished full-field ERG with widespread peripheral photoreceptor loss.[19] Other ocular features included posterior subcapsular cataracts (case 4) and peripheral visual field defects, although these findings were not consistently observed across patients. The absence of cataracts in most cases may reflect the younger age of our cohort, as lens opacities typically develop later in childhood.[20,21] Extensive extraocular involvement was notable in both patients, including hearing impairment, childhood-onset obesity, advanced bone age, and various endocrinopathies, which is consistent with the previously described multisystem involvement.[22] Interestingly, both patients carried the c.11110_11128del variant in exon 16, a recurrent deletion in our cohort predominantly reported in East Asian populations and previously linked to myogenic cardiomyopathy.[8,23–25] Notably, case 4, who was homozygous for this variant, was the only patient in our cohort who presented with neonatal dilated cardiomyopathy and demonstrated the most severe visual impairment. Pathogenic variants in exon 16 have been associated previously with more severe disease phenotypes. Although limited to a single case, our findings may contribute to the growing evidence supporting this genotype–phenotype correlation.[8,26]

In contrast, cases 5 and 6 demonstrated a milder ocular phenotype characterized by later-onset visual impairment, relatively preserved yet subnormal scotopic responses on ERG, and minimal fundus abnormalities limited to subtle retinal hypopigmentation. OCT revealed peripheral photoreceptor thinning with relative macular sparing. Unlike the remainder of the cohort, both patients had myopia and no reported extraocular manifestations, aside from hearing loss. Their presentation was consistent with previous reports of mild AS phenotypes featuring an initially normal fundus appearance and isolated ERG abnormalities.[27,28] Interestingly, despite being in their early 30s, neither patient developed obesity or other metabolic complications. A previous study similarly described milder phenotypes in two adults over the age of 20 years, although these patients exhibited hyperopia and cataracts.[20] Both cases 5 and 6 harbored identical *ALMS1* genotypes, including a novel LINE-1 insertion in exon 8. Although their shared genotype supported a mild disease course, case 6 showed more severe visual impairment, suggesting a role for environmental or additional genetic modifiers.

To date, more than 200 *ALMS1* pathogenic variants have been reported, clustered in exons 8, 10, and 16.[8] This was in line with our findings, with 7 of 16 variants (43.8%) involving exon 16 and 6 of 16 (37.5%) involving exon 8. We identified three novel variants, including a small deletion, a small insertion, and a LINE-1 insertion, all of which likely resulted in protein truncation (Table 1). LINE-1 elements are active human retrotransposons constituting approximately one-sixth of the human genome.[29] Their mobilization to disease-associated genes may disrupt coding sequences, cause frameshifts or premature stop codons, and induce RNA decay or epigenetic dysregulation.[30,31] In this study, LINE-1 insertion occurred within exon 8, which likely disrupted the reading frame. However, because these insertions introduce large repetitive sequences of variable lengths, their precise impact on protein translation remains difficult to predict. Although cases 5 and 6, who harbored this variant, presented with a milder phenotype, it should be emphasized that given the autosomal recessive nature of AS, the clinical presentation is more likely influenced by the combined effect of both variants rather than by a single variant alone. Additionally, because this novel variant has not been reported in another family with AS, the shared genetic background between first-degree relatives should also be considered when interpreting phenotype-genotype relationship. There is currently insufficient evidence to establish the prognostic value of this novel variant. Nonetheless, our findings expand on the known genetic spectrum of AS and highlight the usefulness of systematic screening for transposable element insertions in suspected cases.

This study has several limitations. Comprehensive systemic evaluation was not performed in all patients, and some manifestations may have developed later or remained subclinical. Furthermore, ophthalmological assessments often require patient cooperation, which may have been more challenging in this patient population because of young patient age and developmental disabilities commonly associated with AS. Last, the rarity of AS limited our sample size, constraining the statistical power to assess phenotype-genotype associations.

In summary, we reported eight patients with AS with variable ocular and extraocular involvement and identified three novel disease-causing variants. Our findings reinforce the high prevalence of specific genotypes in individuals of East Asian descent. Despite the considerable heterogeneity in the onset and severity of visual manifestations among individuals with AS, visual impairment is nearly universal. Therefore, ophthalmologists play a pivotal role in the early recognition and diagnostic evaluation of this rare syndromic disorder.

Acknowledgments

Disclosure: **C.-C. Cheng**, None; **C.-Y. Lin**, None; **T.-C. Ko**, None; **Y.-S. Huang**, None; **C.-H. Huang**, None; **C.-H. Yang**, None; **T.-C. Ho**, None; **P.-L. Chen**, None; **T.-C. Chen**, None

References

1. Berger W, Kloeckener-Gruissem B, Neidhardt J. The molecular basis of human retinal and vitreoretinal diseases. *Prog Retina Eye Res*. 2010;29:335–375.
2. Tatour Y, Ben-Yosef T. Syndromic inherited retinal diseases: genetic, clinical and diagnostic aspects. *Diagnostics (Basel)*. 2020;10:779.
3. Chiou GJ, Huang DS, Hu FR, et al. Metabolic syndromes as important comorbidities in patients of inherited retinal degenerations: experiences from the nationwide health database and a large hospital-based cohort. *Int J Environ Res Public Health*. 2021;18:2065.
4. Marshall JD, Maffei P, Collin GB, Naggert JK. Alström syndrome: genetics and clinical overview. *Curr Genomics*. 2011;12:225–235.
5. Hearn T, Spalluto C, Phillips VJ, et al. Subcellular localization of ALMS1 supports involvement of centrosome and basal body dysfunction in the pathogenesis of obesity, insulin resistance, and type 2 diabetes. *Diabetes*. 2005;54:1581–1587.
6. Dassie F, Favaretto F, Bettini S, et al. Alström syndrome: an ultra-rare monogenic disorder as a model for insulin resistance, type 2 diabetes mellitus and obesity. *Endocrine*. 2021;71:618–625.
7. Álvarez-Satta M, Castro-Sánchez S, Valverde D. Alström syndrome: current perspectives. *Appl Clin Genet*. 2015;8:171–179.
8. Marshall JD, Müller J, Collin GB, et al. Alström syndrome: mutation spectrum of ALMS1. *Hum Mutat*. 2015;36:660–668.
9. Choudhury AR, Munonye I, Sanu KP, Islam N, Gadaga C. A review of Alström syndrome: a rare monogenic ciliopathy. *Intractable Rare Dis Res*. 2021;10:257–262.
10. Alexopoulos P, Symeonidis C, Rotsos T. Alström's syndrome, Leber's hereditary optic neuropathy, or retinitis pigmentosa? A case of misdiagnosis. *Case Rep Ophthalmol Med*. 2023;2023:9409036.
11. Gullapalli RR, Desai KV, Santana-Santos L, Kant JA, Becich MJ. Next generation sequencing in clinical medicine: Challenges and lessons for pathology and biomedical informatics. *J Pathol Inform*. 2012;3:40.
12. Dockery A, Whelan L, Humphries P, Farrar GJ. Next-generation sequencing applications for inherited retinal diseases. *Int J Mol Sci*. 2021;22:5684.
13. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV standard for full-field clinical electroretinography (2015 update). *Doc Ophthalmol*. 2015;130:1–12.
14. Sung Y-C, Yang C-H, Yang C-M, et al. Genotypes predispose phenotypes—clinical features and genetic spectrum of ABCA4-associated retinal dystrophies. *Genes*. 2020;11:1421.
15. Chen T-C, Huang D-S, Lin C-W, et al. Genetic characteristics and epidemiology of inherited retinal degeneration in Taiwan. *NPJ Genom Med*. 2021;6:16.
16. Richards S, Aziz N, Bale S, et al. 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;17:405–424.
17. 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.
18. Wang Y, Huang L, Sun L, et al. Ocular findings and genetic test in Alström syndrome in childhood. *Exp Eye Res*. 2022;225:109277.
19. Almoallem BM. Unique phenotypic-genotypic correlation in Saudi patients with ALMS1 mutations. *Saudi J Ophthalmol*. 2023;37:307–309.
20. Nasser F, Weisschuh N, Maffei P, et al. Ophthalmic features of cone-rod dystrophy caused by pathogenic variants in the ALMS1 gene. *Acta Ophthalmol*. 2018;96:e445–e454.
21. Malm E, Ponjavic V, Nishina PM, et al. Full-field electroretinography and marked variability in clinical phenotype of Alström syndrome. *Arch Ophthalmol*. 2008;126:51–57.
22. Marshall JD, Beck S, Maffei P, Naggert JK. Alström syndrome. *Eur J Hum Genet*. 2007;15:1193–1202.

23. Rethanavelu K, Fung JLF, Chau JFT, et al. Phenotypic and mutational spectrum of 21 Chinese patients with Alström syndrome. *Am J Med Genet A*. 2020;182:279–288.
24. Shenje LT, Andersen P, Halushka MK, et al. Mutations in Alström protein impair terminal differentiation of cardiomyocytes. *Nat Commun*. 2014;5:3416.
25. Wang H, Wang X, Zou X, et al. Comprehensive molecular diagnosis of a large Chinese Leber congenital amaurosis cohort. *Invest Ophthalmol Vis Sci*. 2015;56:3642–3655.
26. Marshall JD, Hinman EG, Collin GB, et al. Spectrum of ALMS1 variants and evaluation of genotype-phenotype correlations in Alström syndrome. *Hum Mutat*. 2007;28:1114–1123.
27. Cheng WY, Ma MJ, Yuan SQ, Qi XL, Rong WN, Sheng XL. New pathogenic variants of ALMS1 gene in two Chinese families with Alström Syndrome. *BMC Ophthalmol*. 2022;22:386.
28. Russell-Eggitt IM, Clayton PT, Coffey R, Kriss A, Taylor DSI, Taylor JFN. Alström syndrome: report of 22 cases and literature review. *Ophthalmology*. 1998;105:1274–1280.
29. Beck CR, Garcia-Perez JL, Badge RM, Moran JV. LINE-1 elements in structural variation and disease. *Annu Rev Genomics Hum Genet*. 2011;12:187–215.
30. Hancks DC, Kazazian HH, Jr. Roles for retrotransposon insertions in human disease. *Mob DNA*. 2016;7:9.
31. Xu Y, Guan L, Xiao X, et al. ALMS1 null mutations: a common cause of Leber congenital amaurosis and early-onset severe cone-rod dystrophy. *Clin Genet*. 2016;89:442–447.