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CASE REPORT

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Ocular findings in Baraitser–Winter syndrome with a de novo mutation in the *ACTG1* gene: a case report

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Abstract

Background Baraitser–Winter syndrome (BWS) is rare, and no previous reports have described the visual course of patients with this condition. Herein, we report the long-term visual outcomes and ocular features of a 6-year-old patient diagnosed with BWS.

Case presentation A 6-year-old female patient visited our clinic complaining of low vision. External examination revealed mild ptosis and hypertelorism, and the patient had mild intellectual disability. Her visual acuity during the first visit was 20/100 in the right eye and 20/50 in the left eye. Cycloplegic refraction revealed compound hyperopic astigmatism that was more severe in the right eye than in the left eye. Anterior segment examination revealed an iris coloboma at the inferior margin in both eyes. Fundus examination revealed huge, inferior retinal colobomata in both eyes. The macular contours were normal on optical coherence tomography. Considering the ophthalmic features and systemic signs, the patient was recommended to undergo genetic evaluation. Whole-exome sequencing revealed a heterozygous, de novo, and likely pathogenic variant (c.502G > T; p.Gly168Cys) in *actin gamma 1* (*ACTG1*), and the patient was finally diagnosed with BWS. To further evaluate her systemic abnormalities, examinations including brain imaging and laboratory tests, were performed. Brain magnetic resonance imaging revealed a congenital cortical malformation with pachygyria, and pure-tone audiometry demonstrated bilateral sensorineural hearing loss. Echocardiographic and kidney ultrasonographic features were normal. The patient's amblyopia was treated with eye glasses for full correction and occlusion of her left eye. After 3 years of regular follow-up after the initial diagnosis, the patient's visual acuity improved to 25/25 in both eyes. With the collaboration of pediatricians, the patient and her guardians were fully counseled on the expected symptoms and complications associated with BWS, and her long-term growth trends were being observed at the time of reporting.

Conclusions BWS, a rare genetic disease, was diagnosed in a pediatric patient who presented with various ophthalmic signs, including ptosis, retinal colobomata, and iris colobomata. If the optic disc and macula are spared from the retinal coloboma, a favorable visual outcome may be achieved via consistent treatment for amblyopia and regular follow-up.

Keywords Baraitser–Winter syndrome, *ACTG1*, *ACTB*, Visual acuity, Ocular outcomes

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Background

Baraitser–Winter syndrome (BWS) is a rare condition, with <100 cases reported worldwide [1, 2]. Since the first case was described in 1988 by Michael Baraitser and Robert Winter [3], various clinical features have been reported. The representative clinical signs include dysmorphic facial features with hypertelorism, congenital non-myopathic ptosis, and arched eyebrows. The intraocular findings often include iris or retinal coloboma [4]. Systemic symptoms include intellectual disability, brain pachygyria, sensorineural deafness, and congenital heart or renal anomalies. These clinical features are thought to result from genetic abnormalities affecting actin formation [5].

Although many of the clinical features are ophthalmological, no reports on the visual course in patients with BWS have been published. Herein, we describe the case of a 6-year-old female patient diagnosed with BWS with a confirmed *actin gamma 1* (*ACTG1*) mutation and long-term follow-up. We report on the patient's clinical manifestations, including the course of her visual acuity and ocular lesions, over a 3-year period.

Case presentation

A 6-year-old girl with developmental delay visited our clinic owing to low vision in both eyes detected upon vision screening. She had a medical history of mild intellectual disability. The patient's parents had no symptomatic disease, she had been delivered via normal, spontaneous vaginal delivery at 39 weeks. Her birth weight was 3 kg (30th percentile). Upon presentation to our clinic, the patient presented with mild intellectual disability. Her body weight and height were 21 kg and 114 cm, respectively, corresponding to the 42nd and 27th percentiles.

Physical examination revealed minor facial dysmorphism, including hypertelorism, congenital non-myopathic ptosis, and arched eyebrows. Ophthalmological examination revealed a best-corrected visual acuity of 20/100 in the right eye and 20/50 in the left eye, with normal intraocular pressure. The patient's eye position was orthophoria, and full extraocular muscle movements were observed. Slit-lamp examination revealed an inferior iris coloboma and unusual stroma along the iris margin in both eyes (Fig. 1C and D). Funduscopic examinations revealed huge colobomas in the inferior retina of both eyes (Fig. 1A and B). B-scan ultrasonography features suggested microphthalmia with a short axial length in the areas without a coloboma in both eyes (Fig. 1E and F). Optical coherence tomography revealed that the patient's average peripapillary retinal nerve-fiber-layer thicknesses and macular contours were normal. Cycloplegic refraction was performed to evaluate the cause of her low vision, revealing significant astigmatism in both eyes, with stronger astigmatism in the right eye. Values of with-the-rule astigmatisms were 3.0 and 2.0 diopter in the right and left eyes, respectively.

Considering the patient's external morphology, intellectual delay, and distinctive ophthalmological features, we recommended that she undergo genetic evaluation. Whole-exome sequencing revealed a heterozygous, de novo, and likely pathogenic variant (c.502G > T; p.Gly168Cys) in *ACTG1* (NM_001614.5; OMIM 614583). The genetic test results were consistent with a diagnosis of BWS. Neither parent shared the patient's external morphology or gene mutation. Thus, this mutation was considered sporadic. After the genetic mutation was identified, further systemic examinations, including brain imaging, were performed. Brain magnetic resonance imaging revealed abnormal thickening of the patient's bifrontal cortex, suggesting a congenital cortical malformation such as frontal pachygyria (Fig. 2A). Pure-tone audiometry revealed bilateral sensorineural hearing loss (Fig. 2B). Echocardiographic features were normal, and results of laboratory tests, including the complete blood count, comprehensive metabolic panel, urinalysis, kidney ultrasonography, and chest radiography, were negative or unremarkable.

For amblyopia treatment, glasses were prescribed for full correction, and occlusion therapy was started for the left eye. After 3 years of regular follow-up after the initial diagnosis, the patient's visual acuity had improved to 25/25 in both eyes. At the last visit, her body weight and height were in the 43rd and 6th percentiles, respectively, for her age. With the collaboration of pediatricians, the patient and her guardians were counseled about the expected systemic symptoms and complications associated with BWS, including cardiac malformation, abnormalities of the genitourinary system, gastrointestinal manifestations, and long-term growth trends, for which she was being observed by the time of reporting.

Discussion and conclusions

BWS was first recognized by Baraitser and Winter, who reported on three patients with similar clinical features, including an unusual appearance and colobomata of the iris [3]. As genetic testing has advanced, BWS is now diagnosed based on confirmed mutations in *β-actin* (*ACTB*) and *ACTG1* via DNA sequencing [5, 6]. This disorder is caused by autosomal dominant mutations in these two genes. Although these mutations are normally inherited, but there have also been patients with sporadic pattern.

The characteristic clinical manifestations of BWS include dysmorphic facial features, with hypertelorism, ptosis, iris and retinal colobomata, congenital heart defects, and urinary-tract anomalies. These are thought to occur owing to mutations in *ACTB* and *ACTG1*,

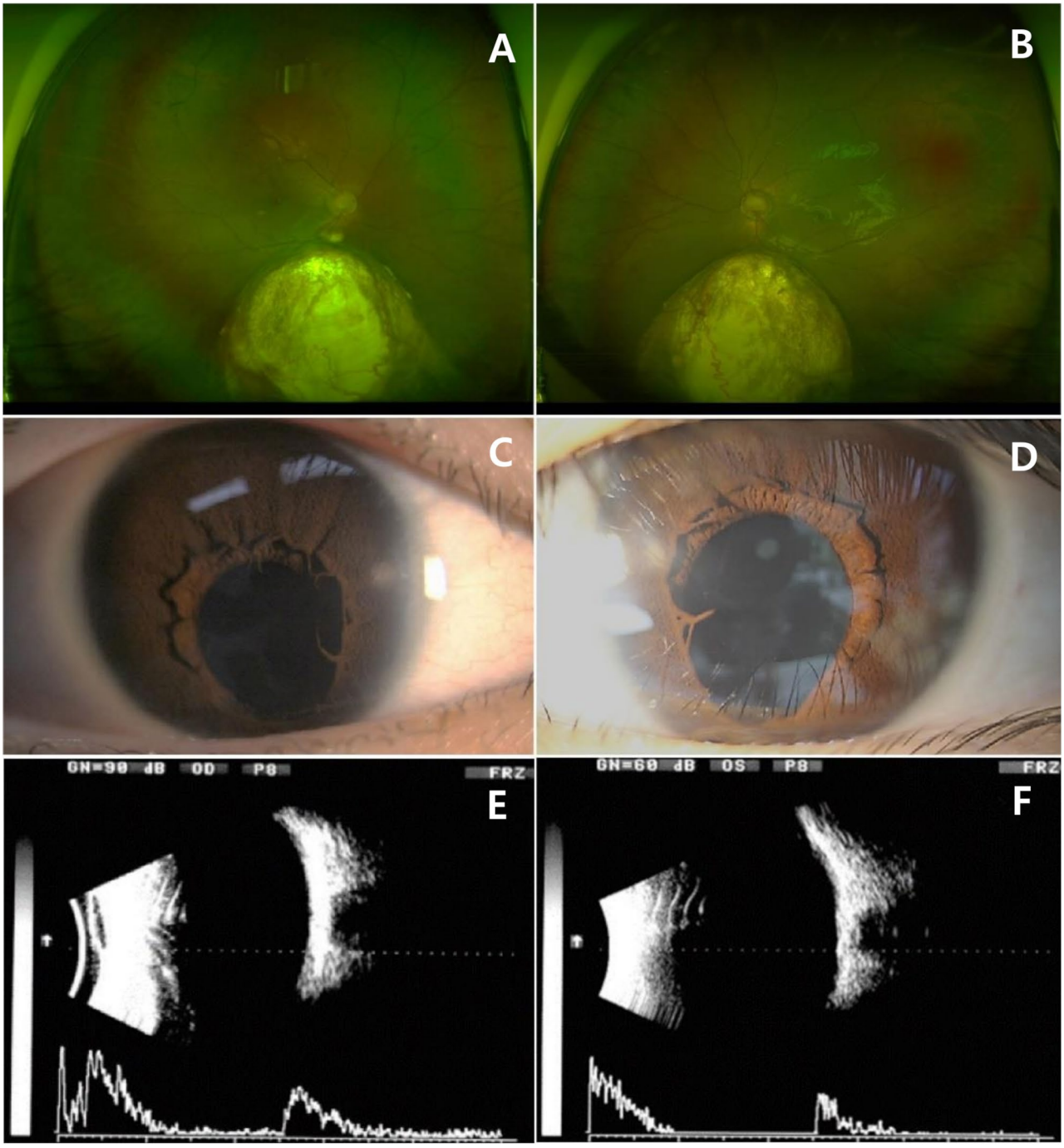

Fig. 1 Ocular findings of A 6-year-old female patient with Baraitser-Winter Syndrome. Funduscopy showed huge colobomas at the inferior retina in both eyes. (**A**; RE, **B**; LE). Anterior segment photography shows revealed inferior iris coloboma and unusual stroma along the iris margin in both eyes (**C**; RE, **D**; LE). The B-scan findings suggested microphthalmia with short axial length in the areas without coloboma in both eyes (**E**; RE, **F**; LE)

which encode β- and γ-actin and can negatively affect actin formation. Actins are proteins that are involved in cell motility, cytoskeleton maintenance and integrity, and intercellular signaling. Thus, mutations in these genes may cause intellectual disability, a distinctive facial appearance, and variable muscular involvement [6].

A recent, large-scale clinical case series of 42 patients with *ACTB* and *ACTG1* mutations reported that compared with *ACTG1* mutations, *ACTB* mutations are more common, occurring in 78% of cases, and cause a more severe facial dysmorphism and intellectual disability [1]. Di Donato et al. also suggested that *ACTB* mutations may be associated with a more severe phenotype [7] and that

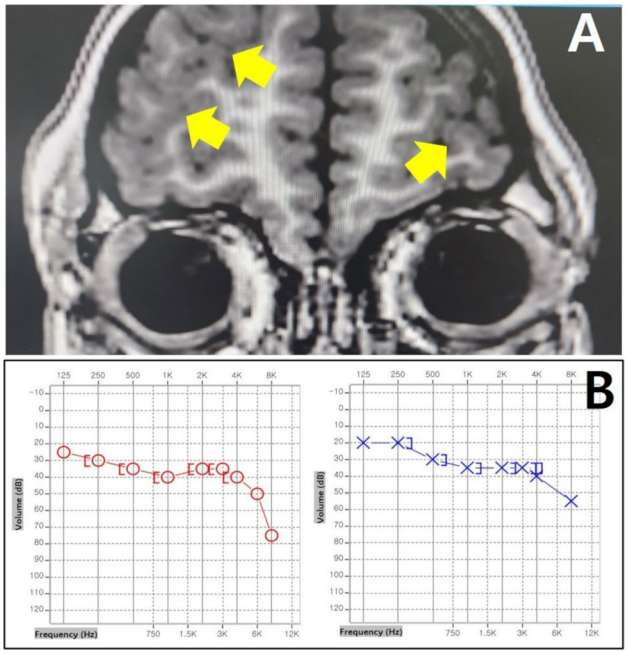

Fig. 2 Brain MRI and pure-tone audiometry of a patient. (**A**) T1 coronal view shows abnormal thickening of bifrontal cortex (yellow arrow). (**B**) Pure-tone audiometry revealed bilateral sensorineural hearing loss

the effects of *ACTG1* mutations were milder and easily missed during routine examinations. The authors proposed that these differences may be attributed to different subcellular localizations of these proteins despite the similarities in the mutations, their overlapping expression, and effects on the same positions in β- and γ-actin. In addition, homozygous deletion of these genes in mice results in different phenotypes; the *ACTB* mutation results in embryonic lethality, and the *ACTG1* mutation results in reduced viability [8, 9]. Indeed, the patient in the present case had an *ACTG1* mutation, she had mild intellectual disability, and she exhibited no other systemic malformations except pachygyria, similar to patient 61,458 in Di Donato et al., which was the only patient with an *ACTG1* mutation in that study [10]. The mild musculoskeletal manifestations other than the patient's short stature might have contributed to the late diagnosis in the present case.

The typical ocular characteristics of BSW include iris colobomata, ptosis, and hypertelorism. Uni- or bilateral colobomata are present in approximately one-third of patients and affect the iris or retina [11]. New ocular features include corectopia, microcornea, congenital esotropia, and an anomalous appearance of the optic disc [4, 12, 13], possibly due to a spectrum of cytoplasmic actin-associated phenotypes. However, few reports have described the visual acuity of patients with BSW. Kemerley et al. reported varying visual acuities among three generations of individuals with BSW, from 20/40 to 20/20 [12]. The male patient with low vision in their report was diagnosed at 35 years of age and had large chorioretinal colobomata. Owing to the late age at diagnosis, the authors believed that appropriate treatment for amblyopia was not possible. The present case also had huge colobomata in both eyes, but favorable visual outcomes were achieved with eye glasses for full correction, consistent occlusion treatment, and regular follow-up.

As the clinical features of BWS resemble those of other complex syndromes, such as Noonan syndrome, Kabuki syndrome, and frontonasal dysplasia, genetic confirmation is needed to confirm the diagnosis, and pre-test genetic counselling to the patient and their families is important [11]. Furthermore, post-test genetic counseling should include the cause, clinical manifestations, and long-term prognosis of the disease. Because BWS is usually diagnosed at an early age owing to the patients' striking facial features or developmental delay, patients and their families may be dismayed after the diagnosis and struggle to understand the different aspects of the disease. Detailed counselling about expected systemic symptoms and complications should be provided as the patients grow to prevent future complications and achieve optimal growth. As psoriatic arthropathy, epilepsy, acute myeloid leukemia, and cutaneous lymphoma are reportedly associated with BWS [7, 14, 15], regular follow-up with systemic examinations, including cerebral neuroimaging, blood sampling, and audiometry, is mandatory.

In conclusion, we reported our experiences with a 6-year-old patient who was diagnosed with BWS via DNA sequencing. Her ocular abnormalities included mild ptosis, retinal and iris colobomata, refractive errors, and subsequent amblyopia. For cases in which the retinal coloboma spares the optic disc and macula, favorable visual outcomes may be achieved via consistent amblyopia treatment and regular follow-up.

Abbreviations

ACTB	Actin beta
ACTG1	Actin gamma 1
BWS	Baraitser–Winter syndrome
RE	Right eye
LE	Left eye

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Not applicable.

Author contributions

Data curation: JWK, DL. Resources: DL. Writing – original draft: JWK, DL. Investigation: SYK, DL. Conceptualization: SYK, DL. Writing – review & editing: DL.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Daegu Catholic University Hospital Institutional Review Board (number: 2024-11-011).

Consent for publication
Written informed consent for publication has been obtained from the patient's guardians.

Competing interests
The authors declare no competing interests.

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