

Longitudinal retinal phenotype and NEI VFQ-25-assessed vision-related quality of life in four Palestinian siblings with CFAP418 c.155+1G>A-related ciliopathy: a familial case series

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Abstract

Background

Biallelic CFAP418 variants cause a clinically broad autosomal-recessive ciliopathy that can include cone–rod or rod–cone retinal degeneration and variable Bardet–Biedl syndrome features. Longitudinal within-family descriptions paired with patient-reported visual function remain limited, and the recurrent splice-donor variant c.155 + 1G > A has only recently been phenotyped systematically.

Case presentation

Four adult siblings from a consanguineous Palestinian family had homozygous CFAP418 c.155+1G>A documented in retained clinical genetics reports. Two 28-year-old men, reported to be monozygotic twins, had congenital postaxial polydactyly; their 30-year-old brother and 26-year-old sister did not. Across the sibship, childhood myopia or daylight difficulty and photophobia preceded progressive dyschromatopsia, central visual loss, later nyctalopia, and peripheral field loss. The twins had counting-fingers vision. Peripheral bone-spicule pigmentation, posterior subcapsular cataract, and absent rod and cone electroretinographic responses. Their older brother had a visual field index of 0%, severely depressed electroretinography, outer nuclear layer thinning, and cane dependence. For the sister who is a mother, her poor vision on the path to blindness has a major impact on every aspect of her life. Body mass index ranged from 24.7 to 32.0 kg/m²; the sister's obesity followed pregnancy. A one-time administration of the validated English-language National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) yielded composite scores of 22.7–44.1 on a 0–100 scale, indicating substantial vision-related functional burden.

Conclusions

A shared CFAP418 genotype was associated with a similar broad retinal trajectory but variable extraocular expression within one sibship. The history supports progression from early cone-predominant symptoms to mixed rod–cone dysfunction; it does not establish a categorical conversion between diagnoses. Molecular diagnosis should be paired with standardized serial retinal assessment, multidisciplinary ciliopathy surveillance, low-vision care, and transparent measurement of vision-related quality of life.

Background

CFAP418 (formerly C8orf37) encodes a cilia-associated protein involved in photoreceptor outer-segment organization and membrane homeostasis. Biallelic variants have been reported with cone–rod dystrophy, rod–cone dystrophy, retinitis pigmentosa, macular involvement, and a variable multisystem phenotype historically labeled Bardet–Biedl syndrome 21 [1–10]. In 2024, the ClinGen Retina Gene Curation Expert Panel classified the association between CFAP418 and autosomal-recessive CFAP418-

related ciliopathy as definitive, supporting a spectrum-based disease concept rather than treating the ocular and syndromic labels as unrelated entities [2].

The splice-donor variant c.155 + 1G > A is not novel. It was reported in two Jordanian families in 2021 and, in 2026, in three Jordanian families with retinal phenotypes ranging from rod–cone to cone–rod dystrophy and with variable obesity, postaxial polydactyly, and renal abnormalities [11, 12]. The clinical value of the present report is therefore not variant discovery. It is the comparison of four adult siblings—including reported monozygotic twins—with reconstructed symptom trajectories, available objective testing, systemic context, and a vision-related quality-of-life assessment. We aimed to describe the shared and discordant features without over-interpreting non-standardized historical data.

Case presentation

Ascertainment and data sources

This descriptive familial case series included all four affected siblings identified in a consanguineous Palestinian nuclear family. Data were collated from available ophthalmic records, genetic letters, electrophysiology and low-vision reports, participant recall, and the validated English-language NEI VFQ-25 administered in 2025. All four participants were educated and completed the instrument in English. All ophthalmic, electrophysiological, genetic, laboratory, and low-vision findings included in this report were cross-checked against retained source reports before manuscript finalization; patient-reported and psychosocial information was confirmed directly with the participants. No missing clinical or laboratory value was imputed. Objective findings are reported only when they appear in the available source record. Because examinations and tests were not performed at uniform intervals or with a common protocol, this report reconstructs clinical trajectories but does not estimate rates of progression. The authors confirmed that none of the four participants were included in the Jordanian cohorts reported in 2021 or 2026 [11, 12].

Genetic and family findings

Retained clinical genetics reports confirmed homozygosity for CFAP418 c.155 + 1G > A in all four siblings and heterozygosity in both parents. The reported variant and zygosity were checked directly against those reports; raw sequencing data were not reanalyzed for this case series. Figure 1 presents the two generations for which verified family information was supplied; it does not infer unavailable common ancestors or assign status to untested relatives.

Vision-related quality-of-life assessment

The validated English-language NEI VFQ-25 was administered once to each participant. The instrument measures self-reported vision-targeted health status in chronic eye disease [13]. Responses and

subscales are transformed to a 0–100 scale, where 0 represents the worst and 100 the best vision-targeted function; the standard composite excludes general health [13, 14]. Because none of the participants had ever driven, the driving items were not applicable, and the driving subscale was not included. The four values are cross-sectional composite scores, not change-from-baseline scores, and the instrument has no diagnostic normal range.

Reporting and manuscript preparation

The report was organized using the CARE guidance for case reports [15]. OpenAI Codex (OpenAI) supported structural and language editing. It was not listed as an author and did not determine authorship, infer participant findings, or make the final scientific decisions. All authors verified the source-record-derived clinical content, citations, wording, tables, and figures and accept responsibility for the submitted work.

Individual clinical courses

Case 1 was a 28-year-old man and one of the reported monozygotic twins. He had congenital postaxial polydactyly. Myopia was recognized at approximately 6 years and worsened by 13. At 17–18 years, he recalled mild color disturbance and photophobia with severe acuity impairment; central loss and moderate photophobia were evident by approximately 22 years. At 25, he experienced transient diplopia and nystagmus and first noticed nyctalopia. At 26, visual acuity was recorded as counting fingers at 1 m in the right eye and 15 cm in the left. At 28 years, photophobia, nyctalopia, and central and peripheral loss prevented reading. Available examinations documented posterior subcapsular cataract, peripheral bone-spicule pigment, outer-segment loss on optical coherence tomography, severely depressed fields, and absent rod and cone electroretinographic responses.

Case 2, the other 28-year-old male twin, also had congenital postaxial polydactyly. Photophobia and daylight difficulty were recalled from approximately 6 years, followed by worsening myopia, color disturbance, central loss, and the first recognition of nyctalopia at about 25 years. Diplopia resolved, whereas nystagmus persisted. At 28 years, his course closely paralleled Case 1. Examination documented minimal posterior subcapsular cataract, bone-spicule pigment, severely depressed fields, and absent rod and cone responses.

Case 3 was a 30-year-old man without polydactyly. Myopia and spectacle use began at about 5 years old. Vision worsened in early adolescence; by 17–18 years, he reported moderate photophobia, severe acuity impairment, and mild-to-moderate color disturbance. He first recognized nyctalopia at 28, when photophobia, acuity loss, and dyschromatopsia were severe. At 29, the visual field index was 0%, and electroretinographic responses were severely depressed. Fundus and optical coherence tomography records described an advanced retinitis-pigmentosa-like appearance with bone-spicule pigment and

outer nuclear layer thinning, together with a mild retinal detachment and posterior subcapsular cataract. He used a cane and assistive technology for mobility and daily tasks.

Case 4 was a 26-year-old woman without polydactyly. Mild daylight difficulty and photophobia began at approximately 9 years. By her mid-twenties, she reported severe central and color vision loss, followed by severe nyctalopia and peripheral loss. A posterior subcapsular cataract and a historical diagnosis of cone–rod dystrophy were recorded. Her body mass index was 32.0 kg/m² after pregnancy; no childhood-onset obesity was reported.

Figure 2 replaces the former ophthalmic table and separates recalled symptoms from documented examinations. The timeline makes visible the shared sequence—early daylight or cone-predominant complaints followed by nyctalopia and field loss—while preserving the substantial differences in data completeness.

Systemic and functional context

Current anthropometric and reported extraocular findings are summarized in Table 1. The twins' combination of a report-confirmed biallelic genotype, retinal dystrophy, and postaxial polydactyly would support the 2024 European Reference Network genotype-first framework for Bardet–Biedl syndrome [1]. The available records do not document enough features to satisfy the older classical clinical threshold, although incomplete reverse phenotyping limits that assessment [17]. The available information is insufficient to apply that framework confidently to Cases 3 and 4.

Table 1
Current systemic phenotype and diagnostic context

Case	Age/sex	Postaxial polydactyly	BMI, kg/m ² (WHO category)	Other documented context	BBS interpretation from available data
1	28/M	Present	24.7 (normal weight)	No childhood obesity reported	Retinal dystrophy, PAP, and biallelic genotype support the adult genotype-first framework
2	28/M	Present	26.4 (overweight)	No childhood obesity reported	Retinal dystrophy, PAP, and biallelic genotype support the adult genotype-first framework
3	30/M	Absent	29.0 (overweight)	Reduced mobility	Insufficient documented extraocular features for confident syndromic classification
4	26/F	Absent	32.0 (obesity class I)	Weight gain reported after pregnancy	Timing of obesity and incomplete reverse phenotyping make classification uncertain
BMI categories follow WHO adult cut-offs: normal weight 18.5–24.9 kg/m ² , overweight 25.0–29.9 kg/m ² , and obesity ≥ 30.0 kg/m ² [16]. BMI is a screening classification, not a stand-alone diagnosis. BBS interpretation uses the 2024 European consensus [1] and does not replace a clinical genetics assessment. BBS, Bardet–Biedl syndrome; BMI, body mass index; PAP, postaxial polydactyly; M, male; F, female.					

NEI VFQ-25 composite scores ranged from 22.7 to 44.1 (Table 2). Case 3 had the lowest score and the greatest mobility dependence. The twins reported similar scores despite excellent self-rated general health, illustrating the distinction between generic health and vision-targeted functioning. These values describe the four participants only; they should not be interpreted as a diagnostic measure or as evidence of longitudinal change.

Table 2
NEI VFQ-25 vision-related quality-of-life findings

Case	General health	Self-rated vision	NEI VFQ-25 composite (0–100)	Prominent activity limitations	Reported coping or role impact
1	Excellent	Very poor	43.0	Near print, street signs, social visits, and events	Marked role limitation; strong use of adaptations
2	Excellent	Very poor	44.1	Near print, street signs, events, and peripheral awareness	Marked burden with fewer reported social restrictions than Case 1
3	Very good	No useful vision	22.7	Near tasks, street signs, night mobility, and help needs	Greatest dependency: cane and assistive technology
4	Very good	Very poor	29.3	Near tasks, street signs, night mobility, and independence	Home and maternal-role restriction
The published NEI VFQ-25 scale runs from 0 (worst) to 100 (best), and the standard composite excludes general health [13, 14]. All four participants completed the validated English-language instrument. Because none had ever driven, the driving questions were not applicable, and the driving subscale was not included. These one-time values have no pre-disease or longitudinal baseline and no diagnostic reference interval.					

Patient perspective

Across the family, progressive visual loss affected independence, education or work, mobility, social participation, and family roles. The twins relied on tinted lenses, controlled lighting, dark-mode interfaces, and smartphone magnification. Case 3 described the adjustment to cane use and increasing reliance on assistive technology. Case 4 described difficulty with domestic and maternal tasks. Family members reported relief when molecular testing unified years of changing diagnostic labels while emphasizing the need for earlier genetic counseling, practical rehabilitation, and recognition of the psychosocial burden of an often-invisible disability.

Discussion and conclusions

This sibship illustrates variable expression of CFAP418-related ciliopathy around a shared molecular diagnosis. The most conspicuous intrafamilial difference was postaxial polydactyly in the twins but not in their brother or sister. The retinal histories were more concordant: daylight difficulty, photophobia, and color disturbance preceded nyctalopia and peripheral field loss. The sequence is clinically compatible with early cone-predominant dysfunction followed by severe mixed rod–cone disease. However, because serial full-field electroretinography, fields, imaging, and acuity were not obtained using a common

prospective protocol, it should not be described as proof that cone–rod dystrophy converted to retinitis pigmentosa. The latter labels and fundus appearance may instead reflect stage-dependent expression of one progressive retinal ciliopathy.

The literature comparison in Table 3 places the family in an already heterogeneous phenotypic spectrum [3–12, 18]. The c.155 + 1G > A variant was identified in three Jordanian families in the 2026 reverse-phenotyping study; affected people differed in retinal pattern, polydactyly, weight trajectory, and renal findings [12]. That report makes renal imaging an especially important gap in the present series. The authors confirmed that the present siblings were not participants in either Jordanian cohort. The present series therefore does not claim variant novelty; its contribution is a separate within-family comparison with longitudinal history and patient-reported visual function.

Table 3
Published CFAP418 phenotypes in a clinical context

Report	Participants	Variant context	Retinal phenotype	Extraocular context
Estrada-Cuzcano 2012 [3]	Four families	Multiple biallelic variants	CRD or RP with early macular involvement	Unilateral PAP in two siblings; otherwise, limited systemic findings
van Huet 2013 [4]	Multiple families	Missense and splice variants	Rod- or cone-predominant dystrophy; early macular disease	No consistent syndromic pattern reported
Ravesh 2015 [5]	Two families	Novel biallelic variants	RP with progressive nyctalopia and field loss	No PAP or consistent extraocular features
Khan 2016 [6]	BBS family	Biallelic C8orf37	Retinal dystrophy	PAP and other BBS features
Heon 2016 [7]	BBS families	Biallelic C8ORF37	Retinal dystrophy	Variable obesity, PAP, renal, or learning features
Rahner 2016 [18]	Two patients, one family	Homozygous c.155 + 2 T > C splice variant	Cone-rod dystrophy	Postaxial polydactyly in both affected relatives
Goyal 2023 [9]	One arRP family	Homozygous nonsense variant	RP, early macular degeneration, cataract, and myopia	No defining multisystem phenotype highlighted
Azab 2021 [11]	Jordanian IRD cohort	c.155 + 1G > A in two families	Inherited retinal dystrophy	Extraocular reverse phenotyping was not then reported
Azab 2026 [12]	Three Jordanian families	Homozygous c.155 + 1G > A	RCD to CRD spectrum; marked variability	Variable PAP, obesity, and renal abnormalities
Present family	Four siblings	Reported homozygous c.155 + 1G > A	Early cone-predominant symptoms; later mixed rod-cone dysfunction	PAP in twins only; postpartum obesity in one; renal imaging unavailable
The table is a focused clinical comparison rather than a systematic review. The present series does not claim variant novelty. arRP, autosomal-recessive retinitis pigmentosa; BBS, Bardet-Biedl syndrome; CRD, cone-rod dystrophy; IRD, inherited retinal disease; PAP, postaxial polydactyly; RCD, rod-cone dystrophy; RP, retinitis pigmentosa.				

Current nosology also argues against describing CFAP418 as an unconfirmed Bardet-Biedl gene. ClinGen regards CFAP418-related ciliopathy as a definitive autosomal recessive gene-disease relationship, and the 2024 European consensus includes CFAP418 in a genotype-informed Bardet-Biedl

framework [1, 2]. A spectrum label is still useful because it does not assume that every molecularly affected person has the same extraocular burden. In the twins, polydactyly plus retinal dystrophy supports a syndromic interpretation; in their siblings, the available data support CFAP418-related retinal ciliopathy but remain too incomplete for definitive syndromic classification.

The low NEI VFQ-25 composite scores add a patient-centered dimension to the severe ocular phenotype. The validated English-language instrument was feasible for these four educated participants, and the title and keywords make this outcome discoverable. The driving domain was not applicable because none had ever driven; the published scoring framework permits subscales with no applicable responses to remain unscored [13, 14]. Item-level responses and the scoring worksheet should be retained with the study records so the reported composites can be audited if requested.

This report has the strengths of complete affected-sibship ascertainment, molecular stratification, family-level comparison, an explicit symptom timeline, and inclusion of the participants' functional experience. Its limitations are substantial: retrospective recall; heterogeneous timing and protocols across the historical ophthalmic reports; no standardized contemporary evaluation for Case 4; no renal imaging; no independent reanalysis of raw sequencing data; and a single cross-sectional NEI VFQ-25 assessment without a longitudinal baseline. The four related observations are descriptive and do not support statistical or genotype–phenotype inference.

In conclusion, four siblings with report-confirmed homozygosity for CFAP418 c.155 + 1G > A showed a broadly shared retinal course and variable extraocular expression. The findings support stage-aware phenotyping, early molecular testing, low-vision and psychosocial support, and lifelong multidisciplinary surveillance—including renal assessment—even when routine blood tests or early systemic history appears reassuring. Prospective follow-up using standardized retinal tests and a verified patient-reported outcome instrument is needed.

Abbreviations

BBS
Bardet–Biedl syndrome
BMI
body mass index
CF
counting fingers
CRD
cone–rod dystrophy
ERG
electroretinography
MZ
monozygotic

NEI
National Eye Institute
OCT
optical coherence tomography
ONL
outer nuclear layer
PAP
postaxial polydactyly
PSC
posterior subcapsular cataract
RD
retinal detachment
VFQ-25
25-Item Visual Function Questionnaire
VFI
visual field index.

Declarations

Ethics approval and consent to participate

Under Al-Quds University's institutional requirements, formal ethics committee approval was not required for this descriptive familial case series. Written informed consent to participate was obtained from all four adult participants.

Consent for publication

Written informed consent for publication of the clinical information and pedigree was obtained from all four adult participants. The signed forms are retained securely by the authors.

Competing interests

The authors declare that they have no competing interests.

Authors' information

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Author Contribution

AA conceptualized the study; led the investigation, methodology, source-record collation and verification, and resources; and drafted the original manuscript. BG made substantial contributions to the investigation, participant communication, acquisition and interpretation of psychosocial information, writing of the psychosocial and patient-perspective components, and critical review and editing of the manuscript. AH and HH collected clinical and interview data, communicated with and interviewed participants, refined the clinical narratives, and critically reviewed and edited the manuscript. MA supervised the study, provided specialist clinical and ophthalmic interpretation, contributed to validation of the clinical account, and critically reviewed and edited the manuscript. All authors reviewed the source-record-derived content relevant to their contributions, approved the final manuscript and author order, and accepted accountability for their own contributions and for appropriately investigating and resolving questions about the work's accuracy or integrity.

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Availability of data and materials

The de-identified data supporting this report are included in the article. Additional source records are not publicly available because their release could compromise participant and family privacy but may be available from the corresponding author on reasonable request and subject to participant consent.

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Figures

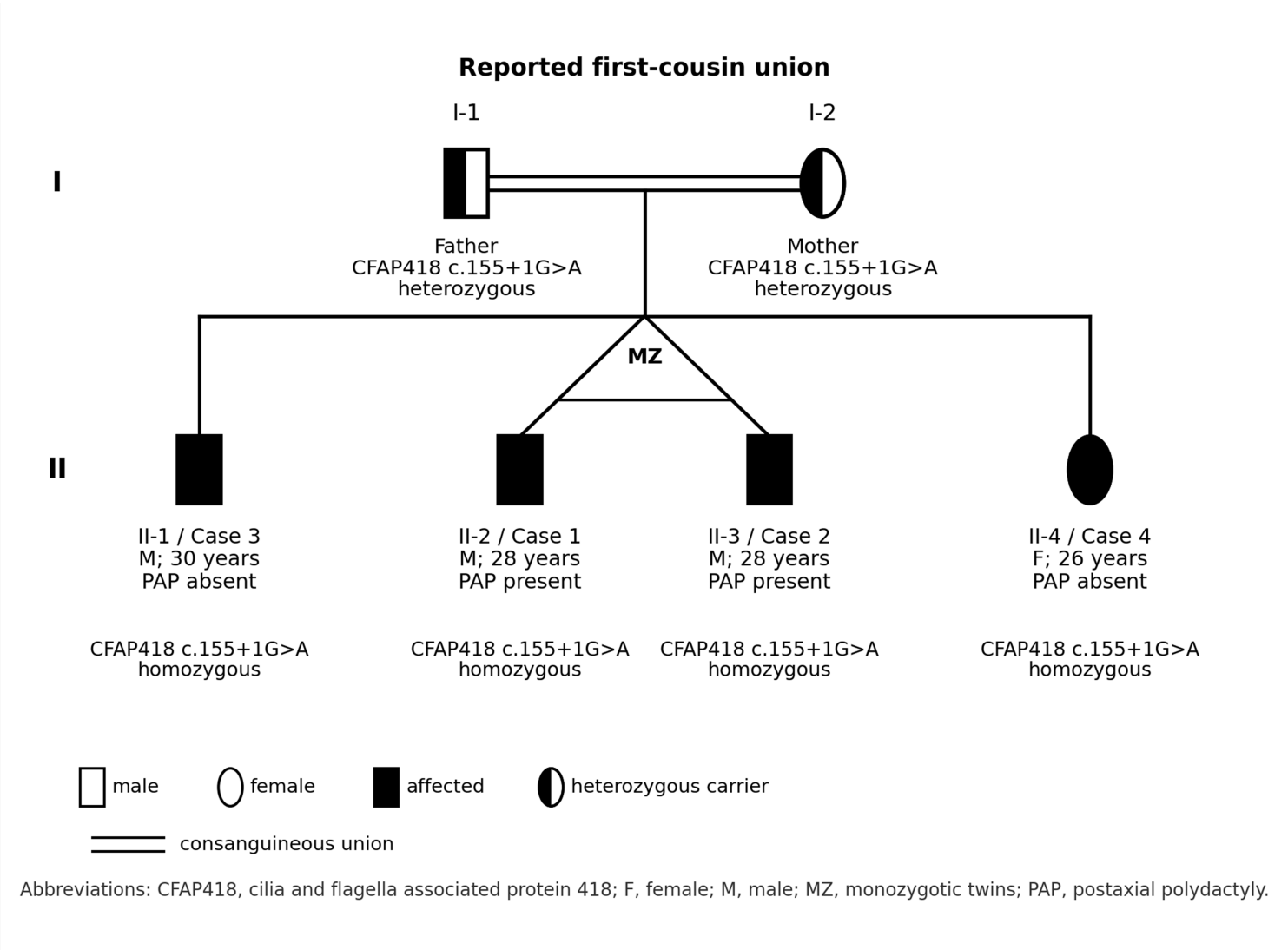


Figure 1

Two-generation pedigree. Filled symbols denote affected siblings reported as homozygous for c.155+1G>A; half-filled symbols denote parents reported as heterozygous carriers. The double partner

line denotes a first-cousin union; the shared twin junction and horizontal bar denote reported monozygosity. Birth order is left to right. Unavailable common ancestors are not inferred. MZ, monozygotic; PAP, postaxial polydactyly.

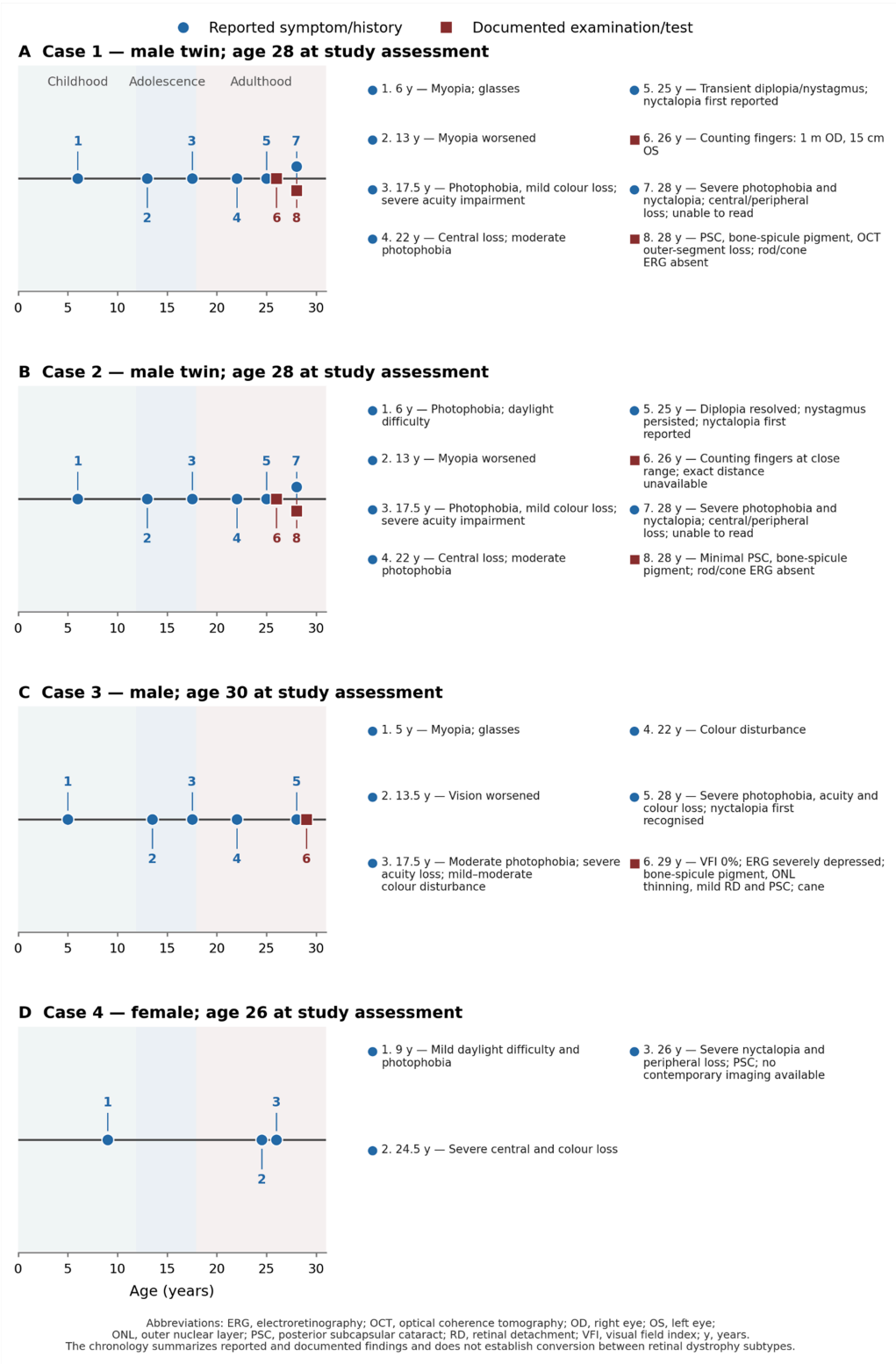


Figure 2

Reconstructed ophthalmic timelines. Circles show reported history; squares show documented findings. Ages are approximate when reconstructed. Both twins were 28 at assessment. Case 2: The counting-fingers distance conflicted, so only close-range vision is shown. The sequence suggests early cone-predominant, then mixed rod-cone dysfunction, not proven conversion. ERG, electroretinography; OCT, optical coherence tomography; OD, right eye; ONL, outer nuclear layer; PSC, posterior subcapsular cataract; RD, retinal detachment; VFI, visual field index.