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Five-Year Structural Progression in Monozygotic Twins with MAK Exon 3- Related Retinitis Pigmentosa

Ayham Slimi
St John of Jerusalem Eye Hospital Group
Mariam Alqam
St John of Jerusalem Eye Hospital Group
Alaa AlTalbishi
St John of Jerusalem Eye Hospital Group
Yahya Alswaiti
Yahya.Swaiti@sjeh.org
St John of Jerusalem Eye Hospital Group
Manar Salameh
St John of Jerusalem Eye Hospital Group

Case Report

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Abstract

Background

Retinitis Pigmentosa (RP) associated with variants in the MAK gene is a relatively uncommon form of inherited retinal degeneration, although certain variants are more prevalent in specific populations. The only reported cases are linked to a homozygous Alu insertion in exon 9, whereas the clinical course and structural progression associated with exon 3 variants have not been described. Longitudinal imaging studies in genetically identical individuals are particularly rare. We report a five-year structural retinal progression in monozygotic twins with RP associated with a genetically confirmed exon 3 deletion in the MAK gene.

Case presentation

Two monozygotic twin brothers aged 47 years presented with progressive nyctalopia and peripheral visual field constriction beginning at approximately 38 years of age. Neither patient had systemic disease or extraocular manifestations. At the most recent evaluation, best-corrected visual acuity was 0.3 (6/12) in both eyes of both patients. Anterior segment examination and intraocular pressure were normal. Fundus examination revealed classic signs of RP, including optic disc pallor, attenuation of retinal vessels, and peripheral bone-spicule pigmentation. Genetic testing identified a homozygous exon 3 deletion in the MAK gene, confirmed by segregation analysis. Multimodal retinal imaging, including fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT), demonstrated progressive contraction of the ellipsoid zone (EZ) and thinning of the outer retinal layers over a five-year follow-up period. Structural progression was highly concordant between the twins, while central visual acuity remained relatively preserved with relatively mild deterioration of the visual field.

Conclusions

This report documents longitudinal structural retinal degeneration in monozygotic twins with RP associated with exon 3 deletion in the MAK gene. Imaging biomarkers, particularly EZ integrity on OCT, may detect disease progression earlier than visual acuity changes. These findings contribute to understanding the natural history of this rare genetic variant and highlight the value of multimodal imaging in monitoring inherited retinal diseases.

Background

MAK-associated RP (RP62; OMIM #614181) is an autosomal recessive retinal dystrophy characterized by progressive photoreceptor degeneration and relative preservation of central visual acuity in early stages[1,2]. Most reported cases to date are associated with a recurrent exon 9 Alu insertion, particularly in individuals of Ashkenazi Jewish ancestry, and are typically linked to relatively mild macular involvement until later decades of life [3].

In contrast, reported variants outside exon 9 are rare, and the structural retinal changes associated with these variants remain scarce [4,5]. In particular, longitudinal imaging data describing macular progression

in individuals with non–exon 9 variants are limited.

Here, we report 5-year multimodal imaging findings in monozygotic Palestinian twins with a homozygous exon 3 deletion in the *MAK* gene. This report provides longitudinal structural observations of a rare coding-region variant and describes progression patterns in genetically identical individuals.

Case Presentation

This longitudinal case series describes monozygotic twin brothers with RP associated with a homozygous exon 3 deletion in the *MAK* gene. Both patients were evaluated at the St. John of Jerusalem Eye Hospital and underwent comprehensive ophthalmic examinations at baseline and follow-up visits over approximately 5 years.

Clinical evaluation included best-corrected visual acuity assessment, slit-lamp biomicroscopy, intraocular pressure measurement, and dilated fundus examination. Multimodal retinal imaging was performed at baseline (2019–2020) and follow-up (2024–2025), including SD-OCT, wide-field color fundus photography, and FAF. Structural progression was assessed qualitatively by evaluating EZ integrity, outer retinal thickness, and areas of hypoautofluorescence over time.

Targeted sequencing of inherited retinal disease-associated genes was performed using molecular inversion probe–based capture followed by next-generation sequencing and analysis with an in-house bioinformatics pipeline [6]. Analysis was done in-house. A homozygous exon 3 deletion in the *MAK* gene (NM_001242957.3) was identified in Twin A. The deletion was subsequently validated by polymerase chain reaction (PCR) and gel electrophoresis and confirmed in Twin B.

Fundus examination revealed typical features of RP, including optic disc pallor, attenuated retinal vessels, and peripheral bone-spicule pigmentation (Fig. 1A-B; Fig. 2A-B). Baseline multimodal imaging (2019–2020) demonstrated diffuse outer retinal atrophy with relative subfoveal preservation and a residual central EZ island in both twins (Fig. 1C; Fig. 2C). At approximately 5-year follow-up (2024–2025), SD-OCT showed interval contraction of the EZ island and progressive parafoveal thinning in both patients while central foveal sparing persisted (Fig. 1D; Fig. 2D). FAF imaging demonstrated enlargement of hypoautofluorescent areas, consistent with progressive retinal pigment epithelium and photoreceptor degeneration (Fig. 1E-F; Fig. 2E-F).

A thin nontractional epiretinal membrane (ERM) was present bilaterally in both twins and remained stable throughout follow-up. Full-field electroretinography demonstrated markedly reduced scotopic and photopic responses consistent with advanced rod–cone dystrophy.

Structural progression patterns were highly concordant between the twins (Fig. 1; Fig. 2). Twin A appeared slightly more structurally advanced at follow-up, with greater contraction of the EZ island and parafoveal thinning compared with Twin B; however, both individuals demonstrated similar macular architecture and preservation of central vision.

Discussion and Conclusions

This longitudinal case series describes monozygotic twins with autosomal recessive RP associated with a homozygous deletion of exon 3 in the *MAK* gene and provides 5-year multimodal imaging follow-up. To our knowledge, this early coding-region deletion has not previously been reported in association with *MAK*-related RP.

The exon 3 deletion identified in this family is predicted to disrupt normal *MAK* protein function, which plays an important role in photoreceptor ciliary regulation and protein trafficking between the inner and outer segments [7]. Disruption of these processes leads to progressive photoreceptor degeneration [7]. In this study, serial imaging demonstrated parallel contraction of the EZ island and expansion of hypoautofluorescent areas over 5 years, while best-corrected visual acuity remained stable. This structural-functional dissociation highlights the limitation of visual acuity as a sole marker of disease progression and supports the value of OCT-–based structural biomarkers.

Most previously reported cases of *MAK*-associated RP involve the recurrent exon 9 Alu insertion, particularly in individuals of Ashkenazi Jewish ancestry, and have been associated with relatively mild macular involvement and preservation of central visual acuity into the eighth decade of life [3]. In contrast, the twins (fifth decade of life) described here demonstrated measurable macular microstructural involvement, despite preserved vision acuity with relatively mild deterioration of the visual field within 5 years follow-up period, suggesting potential phenotypic variability among non-exon 9 variants. Further follow-up in later decades is needed to determine the rate of deterioration. Although conclusions regarding genotype-specific severity cannot be drawn from two individuals, these findings contribute to the expanding phenotypic spectrum of *MAK*-associated disease.

The use of a monozygotic twin model provides a unique opportunity to observe disease progression in a controlled genetic context. Despite minor differences in severity, both individuals exhibited highly concordant structural progression changes over time.

This study has limitations. Imaging was performed using different devices across the follow-up period, which may introduce cross-platform variability in image resolution, segmentation, and measurement scaling. Nevertheless, the observed progression was characterized by clear morphologic changes - including contraction of the EZ island and expansion of hypoautofluorescent areas - that were evident across modalities and unlikely to be attributable solely to device-related differences. Quantitative EZ measurements and standardized platform imaging would further strengthen longitudinal assessment in future studies. The second limitation is the small sample size.

In conclusion, this 5-year longitudinal monozygotic twin study demonstrates progressive structural retinal changes in retinitis pigmentosa associated with an exon 3 deletion in the MAK, with preserved central visual acuity despite measurable microstructural decline and relatively mild deterioration of the visual field. These observations support the use of high-resolution structural imaging as a sensitive biomarker for natural history characterization and potential therapeutic monitoring. Furthermore, they

highlight the importance of comprehensive genetic testing in identifying rare variants and improving genotype–phenotype correlation in inherited retinal diseases.

Abbreviations

BCVA
Best-corrected visual acuity
ERM
Epiretinal membrane
EZ
Ellipsoid zone
FAF
Fundus autofluorescence
MAK
Male germ cell–associated kinase
OCT
Optical coherence tomography
OMIM
Online Mendelian Inheritance in Man
RP
Retinitis pigmentosa
RP62
Retinitis pigmentosa 62
SD-OCT
Spectral-domain optical coherence tomography

Declarations

Ethics approval and consent to participate:

The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee of St. John Eye Hospital Group. Written informed consent for participation and publication of clinical data and imaging was obtained from both patients.

Consent for publication

Written informed consent was obtained from all participants for publication of this case report and any accompanying images

Availability of data and materials

The variant identified in this study has been submitted to the ClinVar database (Submission ID: SUB16091357) and is currently under review. The accession number will be provided upon approval. No

large-scale sequencing datasets were generated. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions:

AS (First Author): Coordinated patient care, conducted imaging, collected data, coordinated referrals, follow-up and drafted the manuscript

MA: Collected clinical data, contributed to analysis, manuscript writing, manuscript revision
MS: Performed molecular validation experiment (PCR) of the variant, contributed to data interpretation, and revised the manuscript

AA: Contributed to manuscript revision and served as research lead

YA: Provided expert review, methodological oversight, major editorial revisions, and co-led the research

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Figures

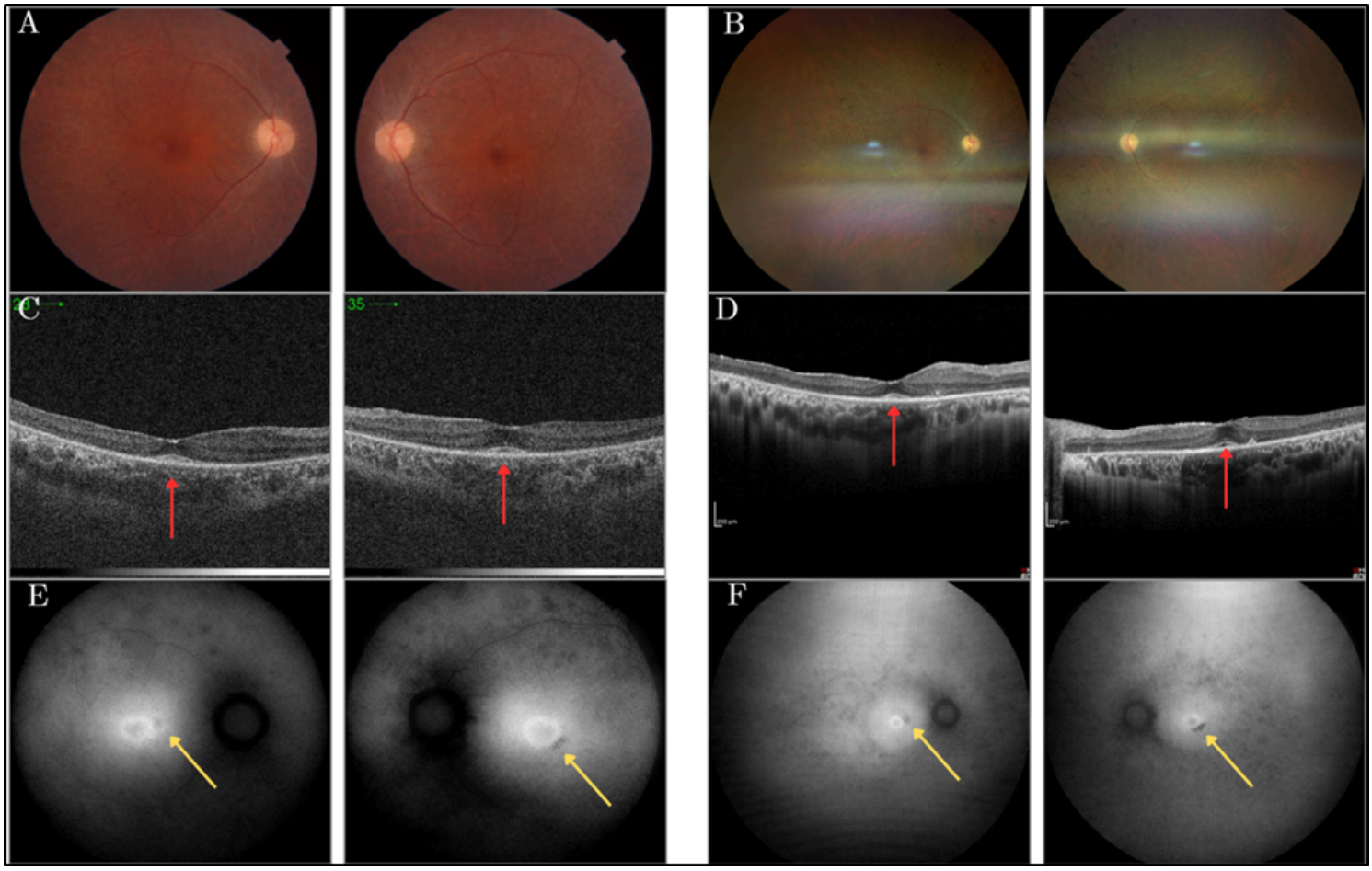


Figure 1

Five-Year Multimodal Imaging in Twin A With *MAK*-Associated Retinitis Pigmentosa. (A–B) Color fundus photographs demonstrating typical retinitis pigmentosa features. (C–D) SD-OCT scans showing contraction of the **EZ** island over 5 years. (E–F) FAF imaging demonstrating enlargement of hypoautofluorescent areas.

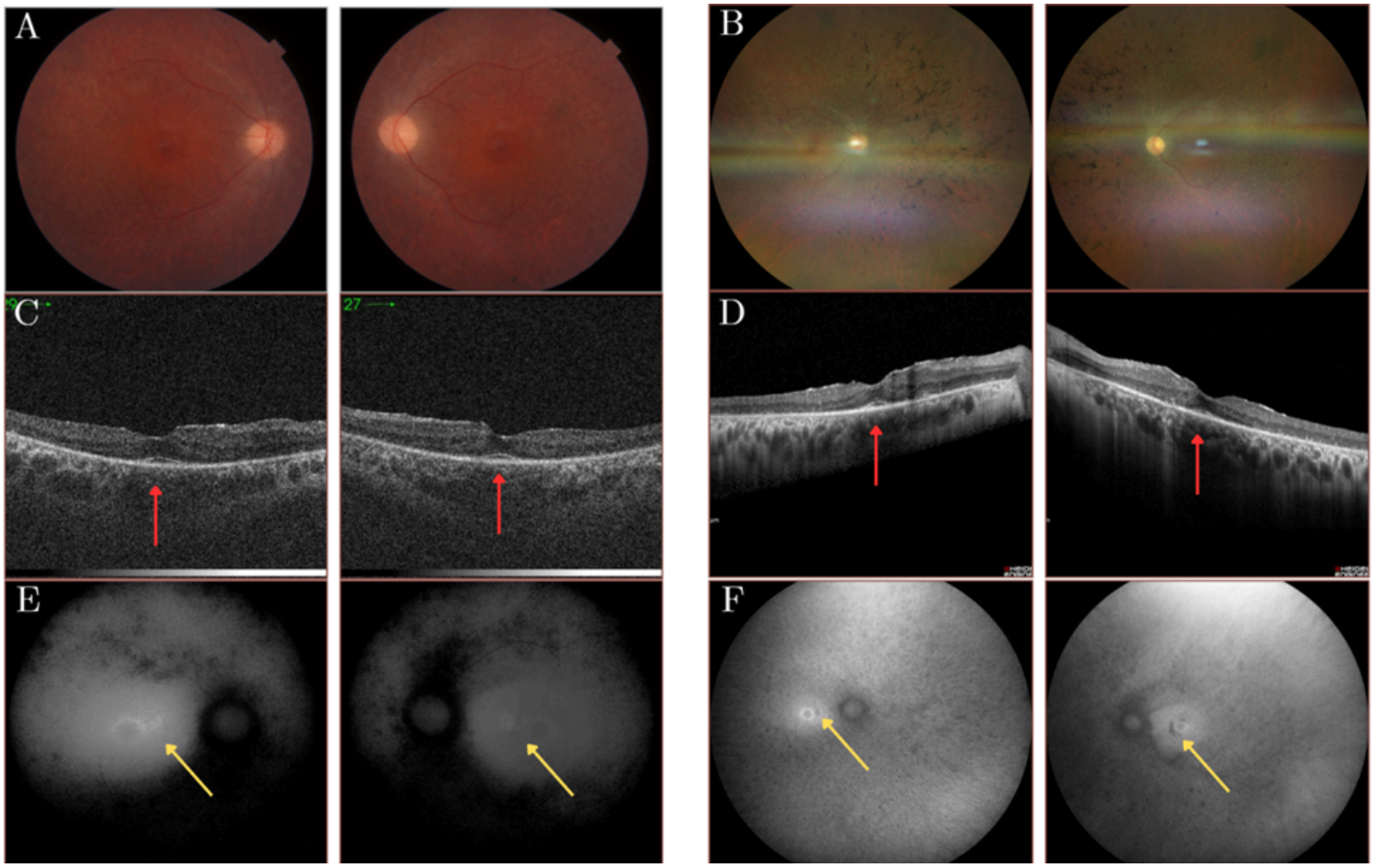


Figure 2

Five-Year Multimodal Imaging in Twin B With *MAK*-Associated Retinitis Pigmentosa. (A–B) Color fundus photographs demonstrating typical retinitis pigmentosa features. (C–D) SD-OCT scans showing contraction of the central EZ island over 5 years. (E–F) FAF imaging demonstrating enlargement of hypoautofluorescent areas.