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A Mild Form of *RPE65*-Associated Retinopathy

Milde Präsentation einer *RPE65*-assoziierten Retinopathie

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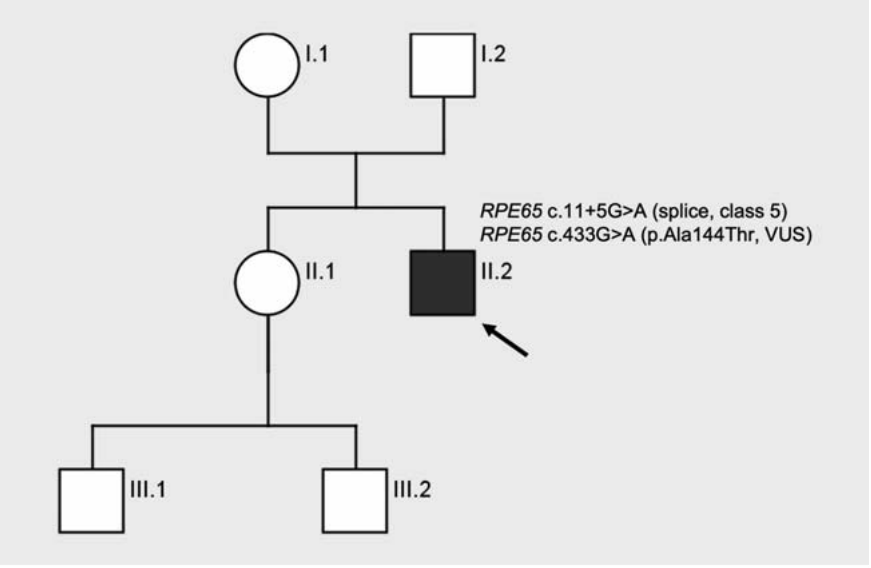
Introduction

Biallelic mutations in *RPE65* give rise to a spectrum of retinal phenotypes ranging from Leber congenital amaurosis (LCA) and early-onset severe retinal dystrophy (EOSRD) to juvenile retinitis pigmentosa (RP) [1, 2].

Since 2017, voretigene neparvovec (VN) has offered the first approved gene therapy in ophthalmology for patients with biallelic mutations in *RPE65*, representing a milestone in ophthalmic therapy for inherited retinal dystrophies (IRDs) [3].

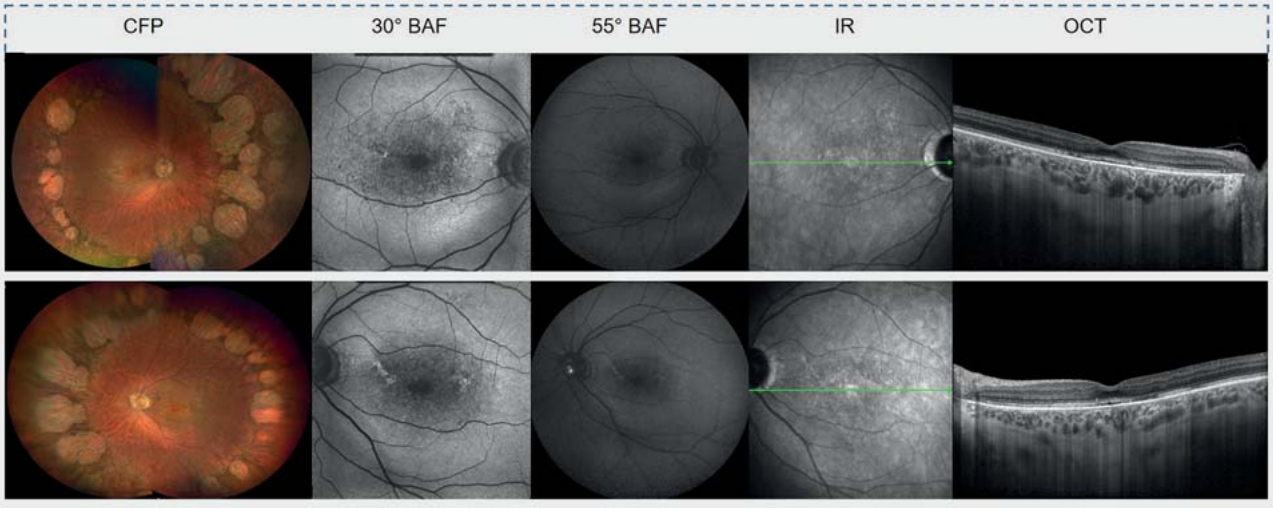
We present a rare case of a 42-year-old male with biallelic *RPE65* mutations, exhibiting an unusually mild phenotype, questioning the decision for or against subretinal gene therapy under these circumstances.



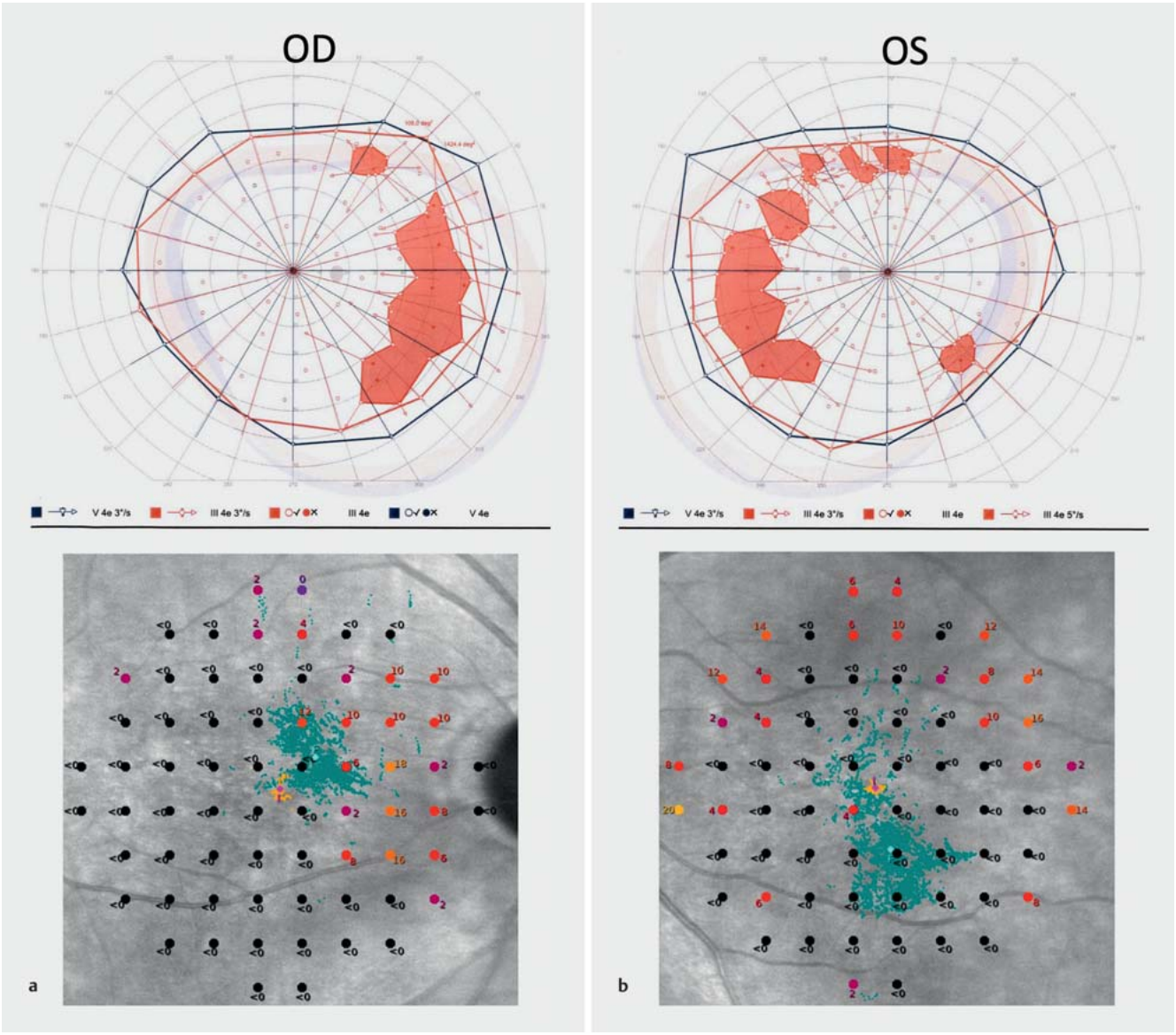
▶ **Fig. 1 The patient's pedigree analysis.** The presence of the biallelic mutations c.11 + 5G>A and c.433 G>A (p.Ala144 Thr) in the *RPE65* gene in the patient are marked.

Case Description

The patient, a 42-year-old male with no family history of genetic retinal diseases, presented with visual difficulties in dim light conditions since his early childhood, but also a recent additional impairment of central visual quality during the last 2–3 years (▶ **Fig. 1**). Remarkably, the patient retained a relatively high level of central vision of 0.5 logMAR (20/63 Snellen) in both eyes, and no subjective peripheral loss of visual field. No previous interven-



▶ **Fig. 2 The phenotype in multimodal imaging.** The clinical phenotype is shown in multimodal imaging. The blue-light fundus autofluorescence (BAF) imaging reveals a generally slight decrease in autofluorescence across the retina, most notably observed in the 55° images. Overall, there is particular emphasis on an irregular, partly granular and spotty pattern of hypoautofluorescence in the macular area. The near-infrared reflectance (IR) images display a dull macular reflection with irregularities. In the optical coherence tomography (OCT), the outer retinal layers, notably the retinal pigment epithelium and photoreceptor layers, are characterized by irregular thinning and a mix of hyporeflective and granular changes. The widefield color fundus photograph depicts circular patchy chorioretinal atrophies in the peripheral retina, marked by hyperpigmentation



▶ **Fig. 3 Spatially resolved visual function.** Goldmann visual field testing illustrates the patient's visual field integrity in response to different stimulus sizes. Red contours represent the boundaries detected using the III 4e stimulus, which typically reveals finer visual field defects. Here, the defects correspond to the patchy chorioretinal atrophy observed in the peripheral retina imaging. Blue contours correspond to the V 4e stimulus, indicative of the broader visual field typically seen in healthy individuals of similar age, showing no central scotomas and peripheral boundaries comparable to healthy controls. The microperimetry shows the severely reduced macular sensitivity.

tions were noted. Low luminance visual acuity was severely reduced to 1.3 logMAR (20/400 Snellen) in both eyes.

Diagnostic Workup

Clinical examination revealed symmetric findings in both eyes. The anterior segment of each eye was normal, with clear optical media. Mydriatic fundus examination showed a normal optic disc and peripapillary atrophy. The macula appeared dull with an irregular aspect. Circular in the peripheral retina, patchy chorioretinal atrophies were noted, characterized by hyperpigmentation and atrophic areas of noticeable retinal thinning (▶ **Fig. 2**). Suspecting an IRD, extensive multimodal imaging was undertaken, including blue-light fundus autofluorescence (BAF) and near-infrared reflectance (IR) imaging of 30° and 55°. The BAF images exhibited a generally slight decrease in autofluorescence. Furthermore, an irregular, partly granular and spotty hypoautofluorescence was observed in the macula. Additionally, optic disc drusen were noted in the left eye (▶ **Fig. 2**). The optical coherence tomography (OCT) volume scan of the macula (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) showed the outer retinal layers, particularly the retinal pigment epithelium (RPE) and photoreceptor layers, as being irregular and partly thinned, with hyporeflective and granular changes (▶ **Fig. 2**).

The absence of complete atrophy of the outer retinal layers on OCT, a reduced but not

extinguished BAF, and peripheral chorioretinal atrophies on widefield color fundus photography aligned with *RPE65* IRDs but deviated from typical progression patterns.

To assess the patient's spatially resolved visual function, Goldmann visual field testing was performed (Octopus 900; Haag-Streit, Koeniz, Switzerland). Utilizing the V4e stimulus, the visual fields obtained were analogous to those of a healthy individual of similar age. When employing the III4e stimulus, the visual field testing revealed sensitivity losses corresponding to the patchy chorioretinal atrophy seen on the widefield color fundus photography (CFP, ▶ **Fig. 2**, **Fig. 3 a**) in the peripheral retina. Notably, the peripheral boundaries were comparable to healthy probands, and no central scotomas were detected. The photopic and scotopic responses in the full-field ERG were flattened. In the mesopic microperimetry (MAIA, iCare, Padova, Italy), the central retinal sensitivity was severely reduced (▶ **Fig. 3 b**). We also performed full-field stimulus threshold testing (FST) with a white stimulus. It showed still preserved, yet reduced, rod function with − 40.7 and − 40.8 dB in the left and right eye respectively.

A comprehensive genetic testing panel revealed two biallelic mutations in the *RPE65* gene: c.11 + 5G>A and c.433G>A (p.Ala144Thr, ▶ **Fig. 1**).

The first (c.11 + 5 G>A) was identified as a splice mutation and classified as class 5, indicative of pathogenicity. The second (c.433G>A (p.Ala144Thr) was classified as a variant of unknown significance. This variant has only been described once in a patient with a fundus albipunctatus phenotype [4].

Clinical Management

In-depth discussions, alongside Intereuropean case presentation with the European Reference Network (ERN Eye, ern-eye.eu), were conducted. The patient did not opt for a treatment with VN. Considering the limited subjective complaints and the unclear possible progression, we supported the decision and agreed to review over time to detect any progression of the disease in order to reevaluate a treatment decision in the future. The decision was further supported by the absence of similar already treated cases in the literature, suggesting that individuals with such mild phenotypes are likely underrepresented.

Discussion

The mild presentation in this case raises intriguing questions regarding the variable expressivity and penetrance of *RPE65* mutations. It is hypothesized that the location of the mutations may result in a hypomorphic effect, allowing for residual RPE65 protein function, which could account for the preservation of visual function [4]. This case underscores the importance of a personalized approach in the management of genetic disorders, where the standard treatment protocol may not be universally applicable. It also highlights the need for further research in the genotype-phenotype correlation in IRDs.

Conclusions

The patient opted to watch and wait, with plans for reevaluation in 1 year. Should progression be noted within this short follow-up period, we shall reevaluate a possible treatment. This case contributes to the understanding of the natural history of *RPE65*-associated retinopathies and emphasizes the necessity of genetic testing in atypical presentations of IRDs. It also illustrates the complexity involved in therapeutic decision-making, and that patient care must be as individual as the genetic variations we encounter [5].

Conflict of Interest

S. H. Künzel: Novartis Pharma, Basel, Switzerland (C), Chiesi GmbH, Hamburg, Germany (C), Apellis, Waltham, US (C). P. Rating: Bayer, Janssen-Cilag. M. Saßmannshausen: Heidelberg Engineering (F); Optos (F), Zeiss (F), CenterVue (F), FemHabil Program, Faculty of Medicine, University of Bonn, Germany. F. G. Holz: Acucela (C, F), Allergan (F), Apellis (C, F), Bayer (C, F), Boehringer-Ingelheim (C), Bioeq/Formycon (F, C), CenterVue (F), Ellex (F), Roche/Genentech (C, F), Geuder (C, F), Graybug (C), Gyroscope (C), Heidelberg Engineering (C, F), IvericBio (C, F), Kanghong (C,F), LinBioscience (C), NightStarX (F), Novartis (C, F), Optos (F), Oxurion (C), Pixium Vision (C, F), Oxurion (C), Stealth BioTherapeutics (C), Zeiss (F, C). P. Herrmann: Novartis (C,F), Janssen-Cilag (C, F). Funding: Novartis Germany (LTW888A_FVHMO001).

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