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Case Report

Cohen Syndrome: Novel VPS13B Genetic Variants in a Male Portuguese Patient with Pigmentary Retinopathy

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Keywords
Cohen syndrome · Pigmentary retinopathy · VSP13B · Rod-cone dystrophy

Abstract
The purpose of this clinical report was to describe a case of Cohen syndrome with its classical ophthalmological manifestations and novel VPS13B genetic variants. A 39-year-old Caucasian male patient with severe rod-cone retinal dystrophy and no history of parental consanguinity was referred to our ophthalmology department. Ophthalmologic history included high bilateral myopia and a 3-year prior bilateral cataract surgery. Systemic history included facial dysmorphism, intellectual disability, transient neutropenia, microcephaly, truncal obesity, and joint hyperextensibility. The patient presented classic fundoscopic features of pigmentary retinopathy in both eyes (OU). Optical coherence tomography (OCT) revealed bilateral central and diffuse retinal pigment epithelium (RPE) and outer retinal atrophy without concomitant macular edema, while fluorescein angiography (FA) demonstrated diffuse RPE atrophy with prominent choroidal vessels. The full-field ERG (ffERG) showed no dark-adapted or light-adapted responses and the P50 wave was not identified in the pattern ERG (pERG). The genetic study revealed two novel heterozygous variants in the *VPS13B* gene: (1) c.5138T>C p.(Leu1713Pro) and (2) c.10179del p.(Asn3393Lysfs*37), thus confirming the diagnosis of Cohen syndrome. This case report introduces these two novel genetic variants to the literature, in a patient with classic phenotypic characteristics of Cohen syndrome, a rare genetic disease which has been increasingly reported since its first description in 1973.

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Introduction

Cohen syndrome was first described by Cohen et al. [1] in 1973. In their inaugural paper, they described 3 children with a characteristic facial appearance, slim, tapering extremities with relative truncal obesity in the mid-childhood years, mental retardation, hypotonia, joint laxity, and ocular anomalies, including high bilateral myopia, microphthalmia (corneal diameter of 8.75 mm in one of the children), uveal coloboma (involving the iris, the retina, and the choroid), mottling of the retinal pigment epithelium (RPE) with prominent choroidal vessels, and sensorial exotropia [1]. Despite lacking genetic diagnosis at the time, the authors suggested that this syndrome may follow an autosomal recessive (AR) mode of inheritance due to the identification of affected siblings from healthy parents [1]. In 1994, a subsequent delineation of a cohort of 29 Finnish patients showed a highly homogeneous clinical phenotype. In the same cohort, molecular genetic analysis identified a single major locus for the vacuolar protein sorting 13 homolog B gene (VPS13B), formerly known as Cohen syndrome gene (COH1), on the long arm of chromosome 8 [2]. Posteriorly, an extended panel of 16 Finnish families with Cohen syndrome underwent linkage disequilibrium and haplotype analysis, allowing for a refined mapping of the *VPS13B* gene [3]. Since then, more than 200 cases have been reported worldwide [4], and whole-exome sequencing has enabled the documentation of multiple *VPS13B* pathogenic variants [5–10]. The *VPS13B/COH1* gene encodes the VPS13B protein, which is part of the cell's Golgi apparatus and is involved in protein glycosylation and sorting and transporting proteins inside the cell. Furthermore, this protein is thought to be involved in the normal growth and development of neurons and adipocytes and may play a role in the storage and distribution of adipose tissue in the body [2, 11]. Missense or nonsense variants in the *VPS13B* gene are the cause of Cohen syndrome, with more than 320 known variants reported in the Human Gene Mutation Database as of 2023 [12, 13].

Children with Cohen syndrome typically present global developmental delay and learning difficulties [4, 10]. There is typically significant weight gain, particularly in the truncal region, in mid-childhood, and virtually all patients >8 years old are truncally obese with comparatively slim limbs [4]. Most children are microcephalic and short stature occurs in around two-thirds of children [4]. The characteristic facial dysmorphism presented by the older child or adolescent with Cohen syndrome includes a thick head of hair, bushy eyebrows, and luxuriant eyelashes, with a short upturned philtrum, a high nasal bridge, and a beak-shaped nose, whose prominence is exaggerated by malar hypoplasia, and a downward slanting palpebral fissures with a characteristic wave-shaped outline [4]. These children also usually present generalized joint hyperextensibility. After puberty, kyphoscoliosis often develops and may be progressive through adult life [4]. Most patients also present neutropenia, with neutrophil count $<1.50 \times 10^{-9}/mm^3$, though associated severe infections are rarely reported [4]. Regarding ophthalmologic abnormalities, which are present in virtually all patients [4], there is usually early onset myopia (<5 years of age) with progression to high myopia by the second decade of life, as well as generalized and symptomatic pigmentary retinopathy with severe rod-cone dysfunction, with or without concomitant bull's eye maculopathy, and attenuated or extinguished responses on electrodiagnostic testing [4]. There are usually also presenile posterior capsular cataracts [4], with recent isolated reports of subluxated microspherophakia lens [14]. Optical coherence tomography (OCT) studies of these children have identified schisis-like changes, with cystoid spaces in the inner retina as well as diffused outer retinal atrophy sparing the subfoveal region [15], with other reports of non-leaking cystoid macular edema (CME) in fluorescein angiography (FA) [16]. Globally, no evidence suggests a shortened lifespan in adult life [4].

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This case report aimed to present a new *VPS13B* heterozygous mutation in a male Portuguese patient with Cohen syndrome and classical systemic and ophthalmological features of this disease. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533974).

Case Report

A 39-year-old Caucasian male patient with severe rod-cone retinal dystrophy was referred to our ophthalmology department to be observed by our retina and genetic consultants. There was no history of parental consanguinity. His ophthalmologic history included high bilateral myopia and complaints of nyctalopia since he was a child. The patient had undergone cataract surgery 3 years before presenting to our department, with implantation of a monofocal intraocular lens (IOL) of 13D in both eyes (OU). His systemic medical history included moderate intellectual disability, transient neutropenia that resolved spontaneously during childhood, microcephaly, truncal obesity, joint hyperextensibility of the hands, feet, ankles, and knees, and adequate social behavior despite the intellectual disability. The patient also presented facial dysmorphism, with thick hair and a short, upturned philtrum, a high nasal bridge and a beak-shaped nose, and an ogival palate (shown in Fig. 1).

In the first consultation, the patient presented a best corrected visual acuity (BCVA) of 2/10 (decimal scale) of his right eye (OD) and 2/10 of his left eye (OS). There were no relevant abnormalities on slit lamp examination, and intraocular pressure (IOP) was normal. He presented classic fundoscopic features of pigmentary retinopathy (disc pallor, generalized arteriolar narrowing, mid-peripheral "bone-spicule" pigmentary changes, and RPE atrophy) in OU (shown in Fig. 2). A multimodal retinal evaluation was conducted, with macular OCT (shown in Fig. 2), peripapillary OCT (shown in Fig. 3), and FA (shown in Fig. 4), as well as kinetic perimetry and electrophysiologic studies (shown in Fig. 5). Macular OCT revealed bilateral diffuse RPE and outer retinal atrophy, which involved the subfoveal area, without concomitant CME. Peripapillary OCT revealed bilateral peripapillary chorioretinal thinning with decreased peripapillary retinal nerve fiber layer (RNFL) thickness (global 3.5 mm peripapillary RNFL thickness of 53 μm in the OD and of 75 μm in the OS, though the RNFL segmentation is questionable due to the generalized chorioretinal thinning), while FA demonstrated diffuse RPE atrophy with prominent choroidal vessels, most evident in the mid and far peripheries, as well as "bone-spicule" pigment mobilization in the mid periphery. There were no identifiable a or b waves in dark-adapted or light-adapted phases of the full-field electroretinogram (ffERG). In addition, the P50 wave was not identified in the pattern ERG (pERG). Unfortunately, the patient did not collaborate for adequate kinetic perimetry. Finally, we performed optical biometry with the ZEISS IOLMaster®500 (Carl Zeiss Meditec AG, Jena, Germany), obtaining an OD axial length (AL) of 26.07 mm and an OS AL of 26.13 mm. Therefore, we were in the presence of a patient with a syndromic pigmentary retinal dystrophy, shown by electrophysiological examination to be a rod-cone dystrophy with associated macular dysfunction, high bilateral myopia, presenile cataracts, facial dysmorphism, transient neutropenia, intellectual disability, truncal obesity, joint hyperlaxity, and microcephaly.

Given the clinical suspicion of Cohen syndrome, the *VPS13B* gene (NM_152564.4) was studied, and two variants were identified: c.5138T>C p.(Leu1713Pro), classified as of uncertain significance and c.10179del p.(Asn3393Lysfs*37), classified as pathogenic [17, 18]. We performed a special gene panel for the VPS13B gene using next-generation sequencing (NGS) technology and confirming detected genetic variants with polymerase chain reaction

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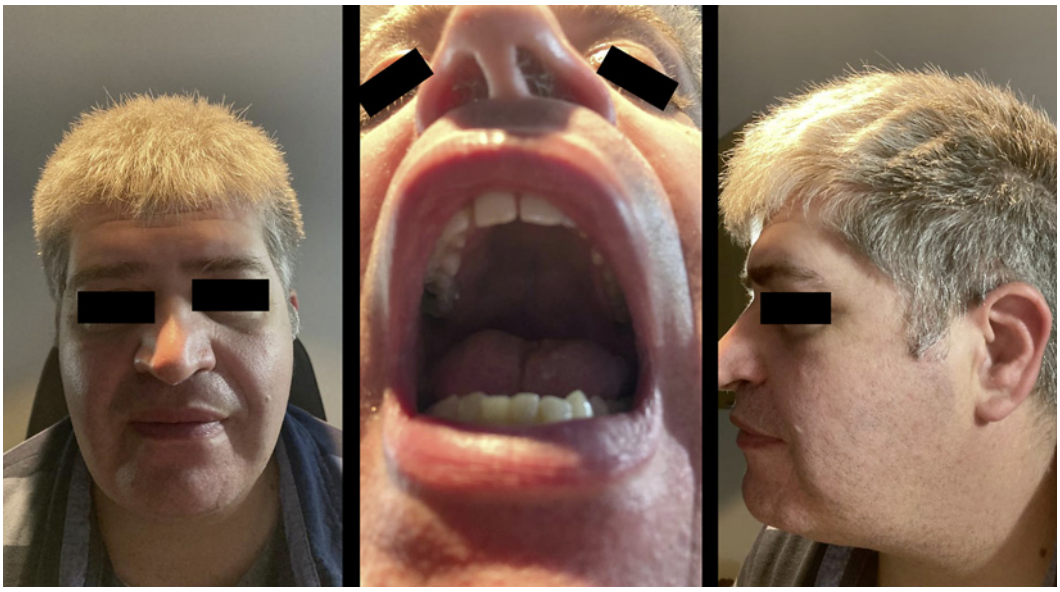

Fig. 1. Thick head of hair, bushy eyebrows, short, upturned philtrum, high nasal bridge, beak-shaped nose, and an ogival palate in the patient with Cohen syndrome.

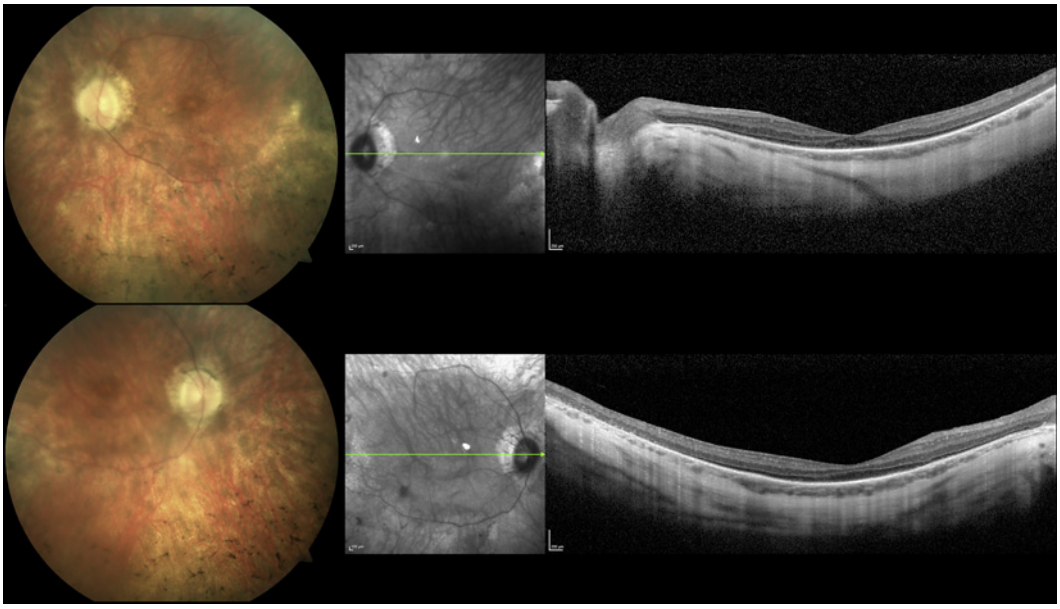

Fig. 2. Bilateral and symmetrical fundoscopic features of pigmentary retinopathy (disc pallor, generalized arteriolar narrowing, mid-peripheral "bone-spicule" pigmentary changes, and RPE atrophy), as well as tomographic bilateral diffuse RPE and outer retinal atrophy, which involved the subfoveal area, without concomitant CME, in the patient with Cohen syndrome.

(PCR), array comparative genomic hybridization (aCGH), and multiplex ligation-dependent probe amplification (MLPA) technology.

Currently, the patient is not experiencing any severe problems. He is regularly followed by a genetics specialist from our institution and undergoes regular complete blood count examinations to screen for de novo neutropenia. His verbal and motor abilities, as well as his

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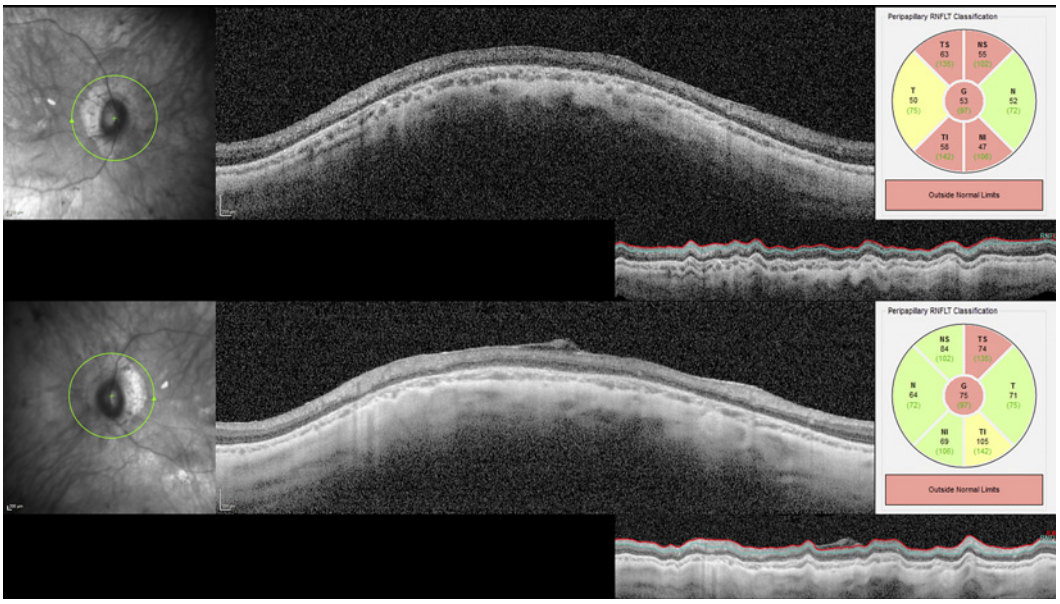

Fig. 3. Peripapillary optical coherence tomography of the patient with Cohen syndrome. There is bilateral peripapillary chorioretinal thinning with decreased peripapillary retinal nerve fiber layer (RNFL) thickness (global 3.5 mm peripapillary RNFL thickness of 53 μm in the right eye and of 75 μm in the left eye, though the RNFL segmentation is questionable due to the generalized chorioretinal thinning).

intellectual ability and social behavior, remain stable. He is regularly followed by our senior ophthalmologist responsible for the genetics section of our ophthalmology department (SES). BCVA remains stable in OU, as well as his multimodal retinal examinations (specifically, the fundus photography and the OCT, which have been repeated).

Discussion

We report two novel heterozygous variants in the *VPS13B* gene: 1) c.5138T>C p.(Leu1713Pro) and 2) c.10179del p.(Asn3393Lysfs*37). These heterozygous mutations led to a loss of function of the VPS13B protein, resulting in a Cohen syndrome phenotype in a 39-year-old Caucasian male patient with no history of parental consanguinity.

Chandler et al. [4] defined major and minor diagnostic criteria for Cohen syndrome. Major criteria include the characteristic facial gestalt (thick hair, eyebrows, and eyelashes; wave-shaped, downward-slanting palpebral fissures; prominent, beak-shaped nose; short, up-turned philtrum with a grimacing expression on smiling); pigmentary retinopathy; and the presence of neutropenia (defined as $<2 \times 10^{-9}/mm^3$). Minor diagnostic criteria include early onset progressive myopia, microcephaly, truncal obesity with slender extremities, and joint hyperextensibility [4]. In this case, the patient presented characteristic facial dysmorphism and bilateral pigmentary retinopathy. There was a history of transient neutropenia in his childhood, but recent complete blood count exams showed no alterations. He also presented high bilateral and symmetrical myopia, confirmed through axial length measurement. Microcephaly, truncal obesity, and joint hyperextensibility were also present. Thus, the patient presents most clinical features that characterize Cohen syndrome. Nonetheless, the genetic study remained essential to confirm our diagnosis. While performing our differential diagnosis to guide our genetic study, we considered diseases that could result in syndromic pigmentary retinopathy with concomitant obesity, intellectual disability, and facial

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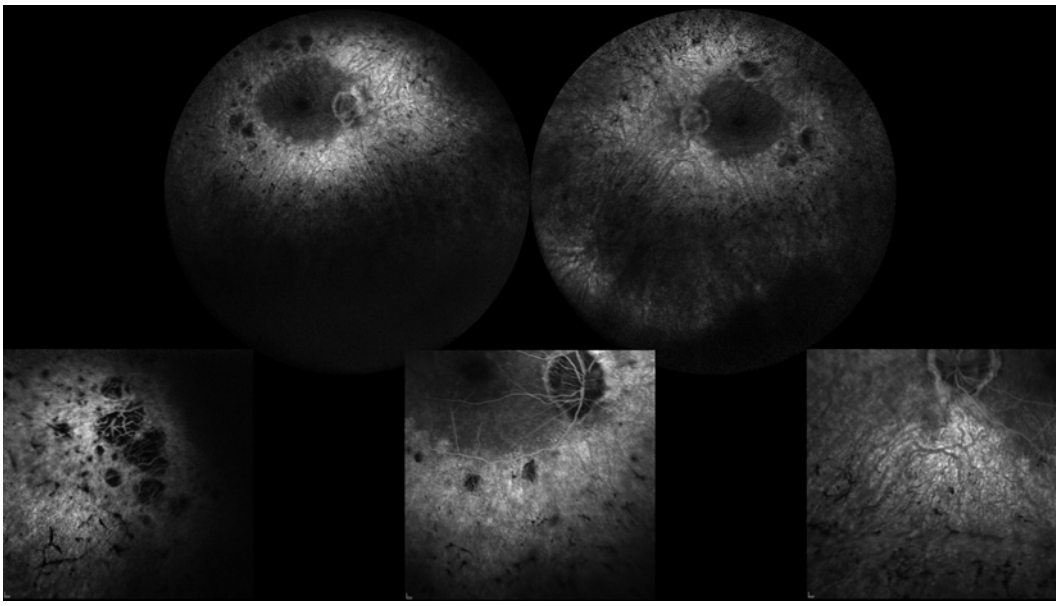

Fig. 4. FA of the patient with Cohen syndrome. There is diffuse RPE atrophy with prominent choroidal vessels, most evident in the mid and far peripheries, as well as "bone-spicule" pigment mobilization in the mid periphery.

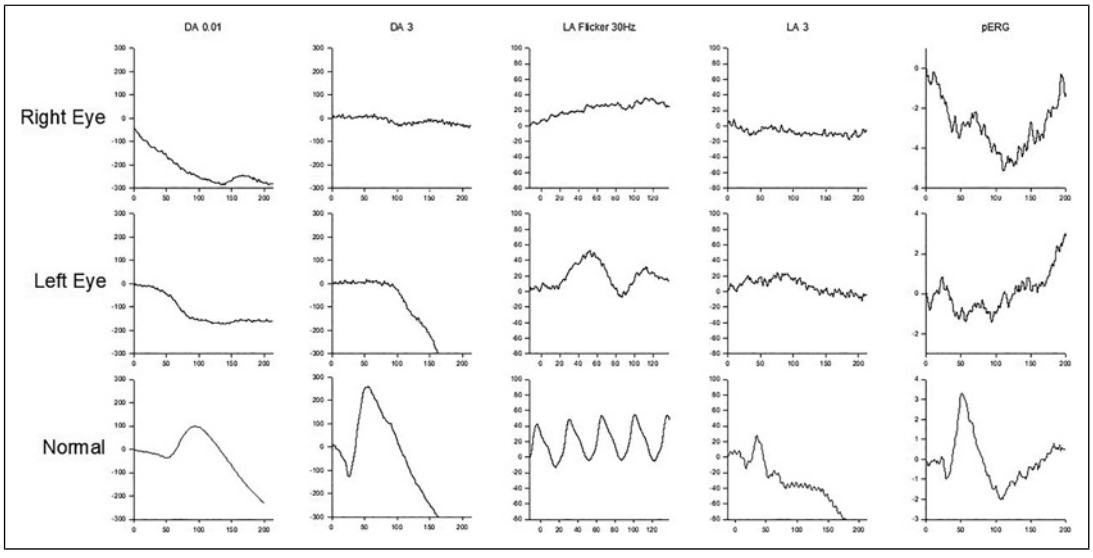

Fig. 5. Electrophysiologic study of the patient with Cohen syndrome. There were no identifiable a or b waves in dark-adapted (DA) or light-adapted (LA) phases of the full-field electroretinogram (ffERG). In addition, the P50 wave was not identified in the pattern ERG (pERG). These findings indicate rod-cone dystrophy with macular dysfunction.

dysmorphism. Therefore, besides Cohen syndrome, we also considered the possibility of Alström syndrome and Bardet-Biedl syndrome. However, regarding the possibility of Alström syndrome, the patient did not present a history of diabetes mellitus, short stature, bilateral hearing loss, cardiomyopathy, renal dysfunction, hepatic disease, or hypogonadism [19].

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Regarding the possibility of Bardet-Biedl syndrome, the patient did not present postaxial polydactyly, anosmia, congenital heart disease, renal dysfunction, or hypogonadism [20]. Thus, both syndromes were not as likely as Cohen syndrome and we only performed genetic testing for Cohen syndrome.

To date, 323 *VPS13B* variants have been reported [12, 13]. Systemic management of Cohen syndrome includes regular monitoring and rehabilitation. Recombinant human granulocyte colony-stimulating factor (rHG-CSF) can be used in neutropenia management. Moreover, since these patients are prone to develop insulin resistance, blood pressure, fasting blood sugar levels, lipid metabolism, and hemoglobin A1C levels should be monitored annually. Additionally, speech and physical therapy can help improve the speech and motor developmental delay, respectively [7]. Regarding ophthalmological complications, up to 1/3 of every Cohen syndrome patient are legally blind [4] due to the slowly progressive bilateral retinal dystrophy with nyctalopia, visual field constriction, and eventually central vision impairment as central macular RPE and outer retinal atrophy develop [4]. The delayed adulthood diagnosis in this case did not have an adverse impact on the subject himself, since the only therapeutic options we had for this patient was to treat his presenile posterior capsular cataracts with cataract surgery and monitor its retinal periphery for retinal lesions that can increase the risk of retinal detachment (being a high myope). There are no approved prognostic modifying therapies for the visual impairment caused by this syndrome. CME, when present, does not usually improve with topical or systemic carbonic anhydrase inhibitors (such as dorzolamide or acetazolamide) [15, 16]. In fact, findings of non-leaking macular cystoid spaces [16] suggest that Cohen syndrome may have anatomical findings similar to that seen in retinal dystrophies caused by mutations in the CHM, NR2E3, and XLRS1 genes [21]. This differs from classical *retinitis pigmentosa*, where cystoid macular edema usually demonstrates leakage on FA [22]. As stated by Huang et al. [15], cyst-like formation in Cohen syndrome is probably secondary to structural defects rather than the primary accumulation of fluid. Nonetheless, our patient did not present CME, only central RPE and outer retinal atrophy, as well as diffuse peripheral RPE atrophy, which resulted in a BCVA of 2/10 of the OD and of 2/10 of the OS despite no relevant disorders of the anterior segment (except for presenile cataracts which were corrected with uneventful cataract surgery with monofocal 13D IOL implantation). The delayed adulthood diagnosis could have had an adverse impact in family counseling, since this is an autosomal recessive genetic disease, which therefore can be inherited by other siblings of the study subject and can be transmitted to his descendants, but that was not the case for our subject, who had no siblings and did not present any descendants.

To conclude, novel variants in the *VPS13B* gene have been identified in a Caucasian 39-year-old male patient. He presented a characteristic facial gestalt with thick hair, a prominent, beaked shaped nose, and a short, upturned philtrum, as well as bilateral pigmentary retinopathy, intellectual disability, microcephaly, truncal obesity, and joint hyperextensibility. These are characteristic features of Cohen syndrome, caused by *VPS13B* mutations. This case highlights that Cohen syndrome should be considered in the differential diagnosis of patients with syndromic pigmentary retinopathy, truncal obesity, facial dysmorphism, and intellectual disability.

Statement of Ethics

This study protocol was reviewed, and the Ethics Committee of Centro Hospitalar Universitário de S. João waived the need for approval. This study adhered to tenets of the Declaration of Helsinki. The legal guardian of the patient (his mother) gave written informed consent to publish this case (including the publication of images). The patient's mother is permitted to provide consent on behalf of the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None of the authors have received any contribution for this submission.

Author Contributions

Rodrigo Vilares Morgado – ophthalmologist that observed the subject of the case report, redacted the manuscript, and contributed to its revision and final version. Ana Margarida Ferreira – ophthalmologist that also observed the subject of the case report and contributed to the revision of the manuscript. Renato Santos-Silva – ophthalmologist who performed the electrophysiologic study of the patient, oversaw the redaction of the case report, contributed to the revision process, and approved its final version. Rita Quental – medical geneticist who conducted the genetic study, oversaw the redaction of the case report, contributed to the revision process, and approved its final version. Ângela Carneiro – ophthalmologist who performed the multimodal retinal imaging of the patient, oversaw the redaction of the case report, contributed to the revision process, and approved its final version. Sérgio Estrela-Silva – senior ophthalmologist, responsible for the genetics section of our department, who observed and followed the subject of the case report, redacted the manuscript, and contributed to its revision and final version.

Data Availability Statement

All data generated or analyzed during this study are included in this case report and its online supplementary material. No other clinical data regarding this patient is available. Further inquiries can be directed to the corresponding author.

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