Article • Low Vision Rehabilitation of a Stargardt-Like Macular Dystrophy Linked to a Novel ELOVL4 Heterozygous Mutation in a Hispanic Family

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ABSTRACT

Background: Stargardt disease (STGD), the most common juvenile form of macular degeneration, is typically autosomal recessive, inherited from an ABCA4 gene mutation. With advancements in genetic testing, novel potentially pathogenic variants have been phenotypically linked to STGD. We will discuss the low vision (LV) management of a patient with an initial unspecified retinal dystrophy diagnosis leading to the discovery of an ELOVL4 genetic mutation found within his family.

Case Report: A 57-year-old male presented to the LV clinic for a second opinion with a diagnosis of an unspecified retinal dystrophy. Despite being diagnosed 7 years prior, a severe decrease in vision within a year initiated several visits to different eye care providers with an uncertain diagnosis. The LV examination addressed his goals of reading large print with eccentric viewing, training, and electronic magnification; reducing glare sensitivity with filter lenses; and genetic testing for a molecular diagnosis. Genetic testing identified a novel mutation in the *ELOVL4* gene previously linked to an autosomal-dominant form of macular dystrophy. Seven additional genetic variants with uncertain clinical significance were identified. Due to limited clinical data available for these variants, the patient's five children also completed genetic testing to assess whether any of these variants co-segregated with retinal disease in the family. The same *ELOVL4* variant was confirmed in his five currently asymptomatic children. Genetic counseling, lifestyle recommendations, and information on the importance of an annual eye exam were provided based on genetic findings.

Conclusions: Genetic testing plays a role in LV for the identification of ocular conditions outside the textbook presentation. Our case demonstrated more evidence to support the correlation of this *ELOVL4* variant to a possibly novel form of autosomal-dominant STGD. Genetic testing can identify others with the same variant and aid in determining pathophysiology to advance gene therapy options. LV rehabilitation has the tools to maximize patients' remaining vision.

Keywords: autosomal dominant, *ELOVL4*, genetics, low vision, macular dystrophy, Stargardt disease

Introduction

STGD is the most prevalent hereditary maculopathy (1 in 10,000) and typically manifests during the 1st to 2nd decade of life, but it can also start in adulthood.[1,2] Symptoms begin with bilateral progressive central vision loss, light sensitivity, and impaired color vision. Earlier-onset types have a poorer prognosis, with typical visual acuities of 20/200 before stabilizing.[3] Typical presentation includes yellow pisciform (fish-tailed) flecks of accumulated lipofuscin within the posterior pole or midperiphery and macular mottling with a "beaten-bronze" appearance that progresses to macular atrophy, resulting in a "bull's-eye" configuration.[1-4] STGD can be clinically diagnosed

with the presence of a hypofluorescent choroid or a dark or silent choroid on fluorescein angiogram (FA), which is considered the gold standard diagnostic modality. This dark appearance occurs because the accumulation of lipofuscin in the subretinal layers blocks the choroidal fluorescence.[1-3] Additional tests, such as optical coherence tomography (OCT), fundus autofluorescence (FAF) imaging, visual fields, and electrophysiologic testing, should be considered to aid in diagnosis.[1]

Since there is no cure or Federal Drug Administration-approved treatment for STGD, management should be focused on low vision rehabilitation to assess visual function and to provide proper training and devices. Low vision rehabilitation aims to optimize the remaining vision and to teach new skills in order to enable adaptation to vision loss and enhance quality of life. Studies focused on different types of low vision rehabilitation for patients with STGD show positive responses to optical devices that provide magnification and methods to learn how to fixate eccentrically.[5-7] Low vision rehabilitation for STGD patients tends to be very successful because they have often grown up learning how to adapt to their reduced vision, which stabilizes at around 20/200 to 20/400.[8]

To date, there are 3 genotypically major types of STGD described. Pathogenic variants in the *ABCA4* gene (1p22.1) account for most autosomal-recessive (AR) forms of STGD type 1.[1] *ELOVL4* (6q14.1) and *PROM1* (4p15.32) are known loci involved in autosomal-dominant STGD3 and STGD4, respectively.[4,9] The ELOVL4 (elongation of very-long-chain fatty acid-4) gene encodes an enzyme involved in the synthesis of the lipids of the photoreceptor outer segment membrane, and certain gene variants have been reported to manifest like STGD1.[9-11] However, there is significant variability in the clinical presentation of STGD; therefore, genetic confirmation is useful to provide a definitive diagnosis for patients with a Stargardt-like disease. With genetic testing becoming more accessible, novel gene mutations have been discovered that are linked to atypical cases of STGD, specifically the *ELOVL4* gene. To our knowledge, there is only a single report of a patient with macular dystrophy linked to the same *ELOVL4* genetic variant, which presented phenotypically differently from our patient.[12] In this case report, we present a Hispanic family with a novel mutation in the *ELOVL4* gene potentially linked to a novel late-onset type of autosomal-dominant adult macular (cone-rod) dystrophy.

Case Report

A 57-year-old male presented to the low vision clinic for a second opinion with an ocular history of an unspecified retinal dystrophy. Despite receiving a diagnosis 7 years prior, a severe decrease in his vision over the past year initiated several visits to different eye care providers that left him with an uncertain diagnosis. He had undergone electrodiagnostic testing at an ophthalmology clinic a year before, at which an electroretinogram (ERG) showed moderate to severe dysfunction of overall retinal neural response OD>OS. At the current visit, his vision was measured as 20/400 OD and 20/80 OS without correction. Retinal findings were specified as "pigment mottling, perimacular chorioretinal atrophy involving posterior pole OU with a chorioretinal scar temporal to fovea OD." The differential diagnoses were central areolar choroidal dystrophy (CACD), rod-cone dystrophy, or STGD disease. He had no pertinent medical history and denied any history of trauma. He was not taking any ocular or systemic medications, had no known allergies, and denied tobacco, alcohol consumption, or recreational drug use. He denied any family history of vision loss or any family members experiencing similar visual symptoms. He last reported seeing a low vision specialist in 2018 but could not remember what services he had received. His current accommodations consisted of using magnifying software on the computer such as ZoomText, as well as speech-to-text applications on his phone.

Uncorrected Feinbloom distance visual acuities were 10/200 OD (Snellen equivalent 20/400) with a preferred retinal locus (PRL) at 3:00 and 10/200 OS (Snellen equivalent 20/400) with PRLs at 7:00 and 10:00. With his single-vision reading glasses of +5.25-1.00x100 OD and +5.00-0.75x110 OS, single-letter near acuities were 0.15/2.5M (Snellen equivalent 20/333) OD and 0.15/5.0M (Snellen equivalent 20/666) OS. Continuous-text reading acuities with his reading glasses were OU 0.15/8.0M (Snellen equivalent 20/1066) at critical print size and OU 0.15/5.0M (Snellen equivalent 20/666) at threshold size. MARS contrast sensitivity was profoundly reduced to 0.15 log CS OD and was unable to be tested OS. Full and central visual fields were assessed with the monocular Esterman on the Humphrey Visual Field Analyzer and the Central Visual Field Test, respectively. The monocular Esterman visual

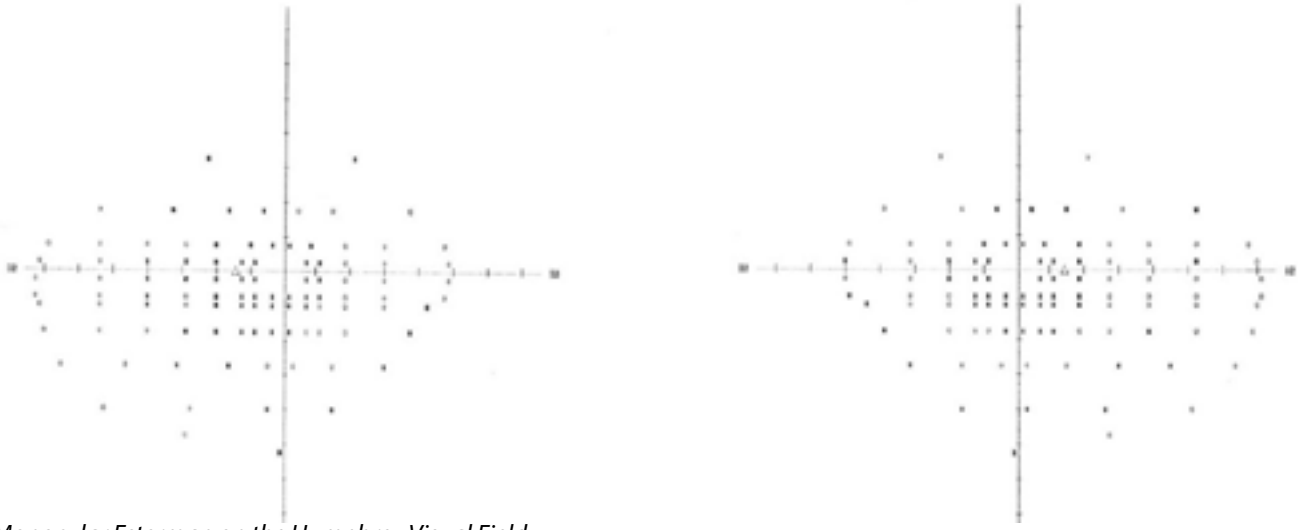

Figure 1. *Monocular Esterman on the Humphrey Visual Field*

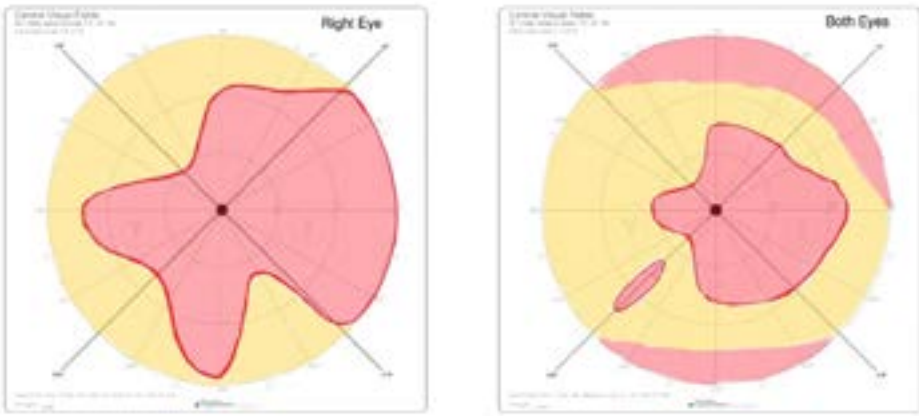

Figure 2. *Central Visual Field Test OD/OU*

field revealed that he missed a little more than half of the points in each eye, with the left eye having a slightly larger scotoma (Figure 1). The Central Visual Field Test measures the central 30 degrees of field at 50 cm with a +2.00 effective add, if appropriate, and can be done monocularly and binocularly (Figure 2). We were unable to determine the left eye's scotomas because our patient reported that he could not see the lines and the target on the paper. The right eye demonstrated a moderately size scotoma of 20-30 degrees sparing the superior nasal quadrant; binocularly, there was a smaller scotoma that was about 20 degrees in each direction, sparing most of the nasal quadrant.

Dilated fundus examination of the right eye revealed large optic nerves and cupping, arteriolar attenuation, indiscrete scattered white flecks, areas of pigmented hypertrophy within the posterior pole and along retinal vessels, mild epiretinal membrane, and perimacular chorioretinal atrophy with a chorioretinal scar temporal to the fovea (Figure 3). The left eye revealed similar findings, with slightly larger nerves but without the epiretinal membrane and chorioretinal scar (Figure 4). FAF imaging in each eye showed more areas of scattered hypoautofluorescence than hyperautofluorescence, suggesting retinal cell loss (Figure 5). Macular OCT imaging confirmed thinning of the inner and outer retinal layers at the macula OU (Figure 6).

The functional vision evaluation was completed over two visits. During the initial visit, we did a low vision device evaluation, and the second visit was a follow-up to dispense the recommended devices with further education of each device. The patient's ultimate goals included being able to read large print like the Bible, determining whether any glasses prescription would improve his vision, and having comfortable vision under bright conditions. The 20-item Veteran Affairs Low Vision Visual Functioning Questionnaire (VFQ-20) revealed that most tasks were impossible, but he was still able to prepare meals, watch TV on a 32-inch screen about 2-3 ft away, and use the speech applications on his phone.[13]

When determining a prescription in low vision, the just-noticeable difference (JND) is usually calculated by placing the patient's Snellen denominator/100 and then dividing by 2 to determine the sphere lens power to present as a starting point for the trial-frame refraction. After a trial-frame refraction, our patient accepted a final glasses prescription of +2.00-1.00x100 OD (Snellen equivalent 20/400) and +1.00-0.75x110 OS (Snellen equivalent 20/400). With a +4.00D effective add (EA) and good direct overhead lighting, his single-letter near acuities were 0.15/2.5M OD (Snellen equivalent 20/333) and 0.15/5.0M OS

Figure 3. *Color Fundus Photo OD*

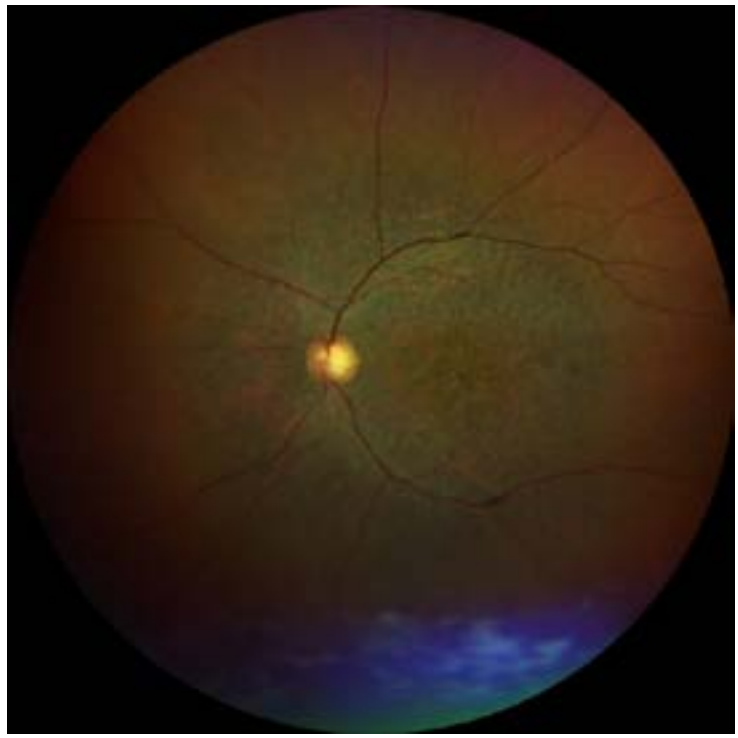

Figure 4. *Color Fundus Photo OS*

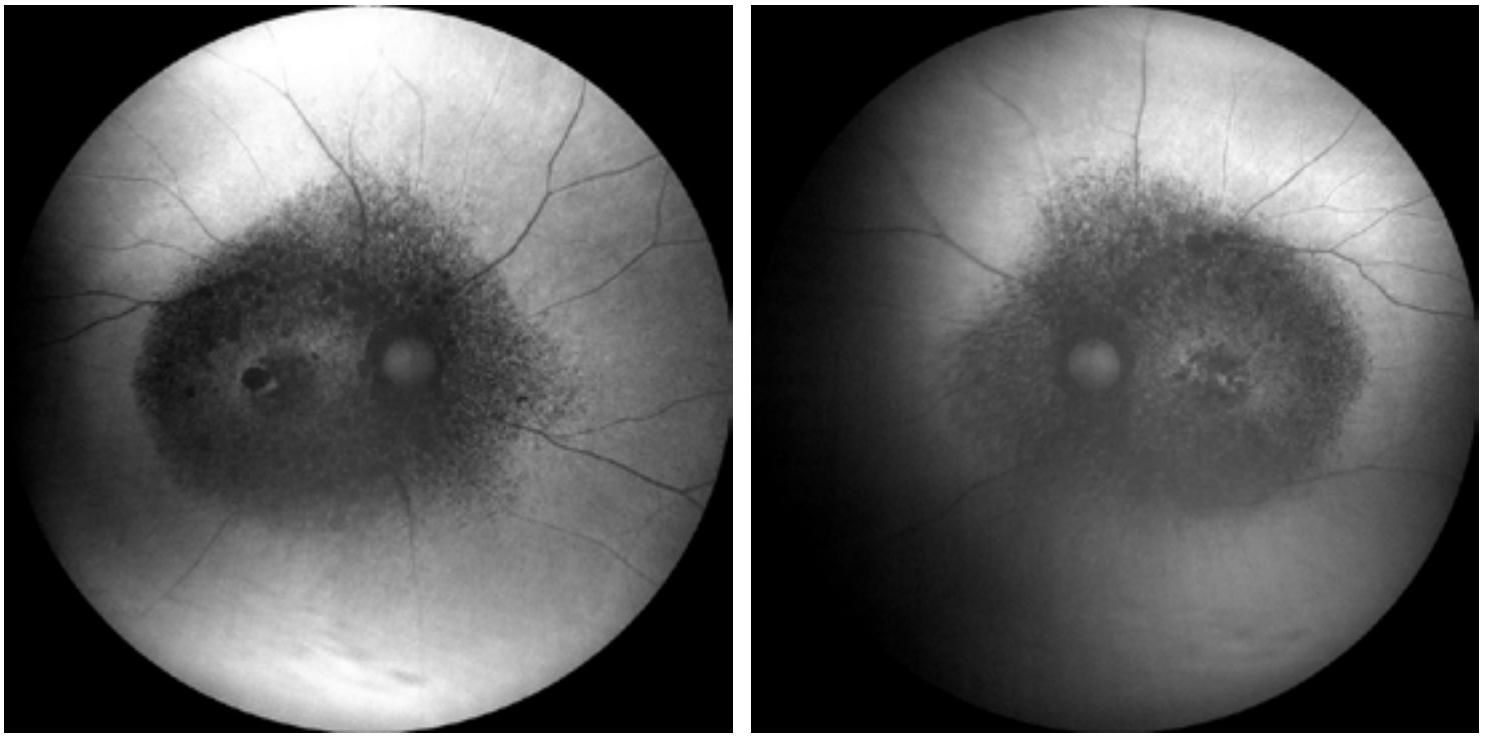

Figure 5. *Fundus Autofluorescence (FAF) Photos OD,OS*

(Snellen equivalent 20/666). Although his acuity did not improve, as we expected, he subjectively appreciated a slight increase in clarity with a thorough in-office demonstration comparing the prescription in the trial frame to being uncorrected.

The patient had multiple PRLs, at 3:00 OD and 7:30 & 10:00 OS, due to his larger central scotomas and had not been taught how to use the functional part of his retina to displace the scotomas. Eccentric viewing (EV) training was performed by using an EV clock straight ahead (Figure 7) and having the patient look at one clock hour at a time to determine where he would see the central dot the clearest. He reported that his clearest vision was within the 6:00-9:00 clock hours EV position, but he had more success binocularly at 6:00. Traditionally, we would initiate EV training with the better-seeing eye (in this case it would be the right) and have the patient patch the fellow eye (the left) to make it easier. This was offered, but our patient preferred not to be

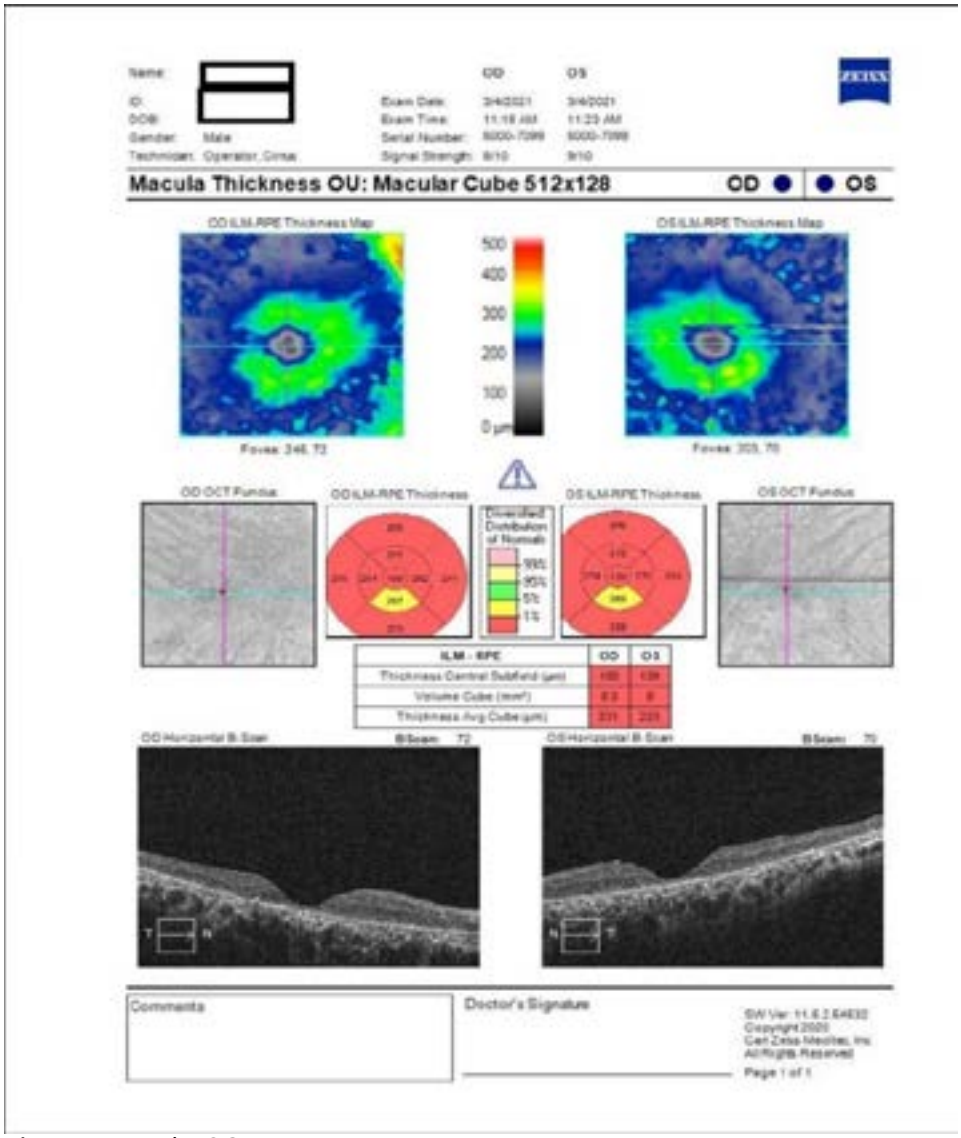

Figure 6. *Macular OCT*

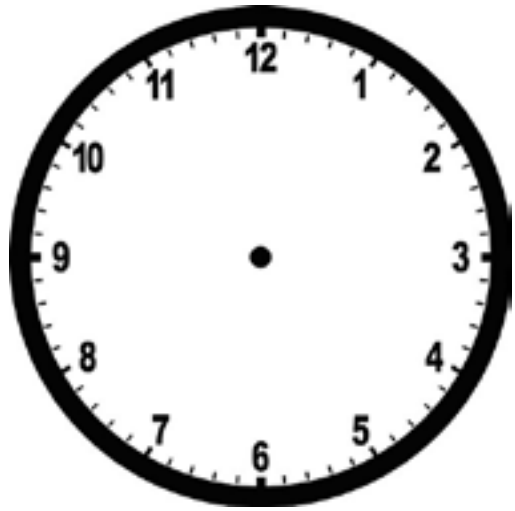

Figure 7. *Eccentric Viewing (EV) Clock*

Figure 8. *Eccentric Viewing (EV) Training Text*

patched and wanted to train binocularly so that he could establish, in his words, "muscle memory" faster. Therefore, we started EV training at 6:00 binocularly and tried to emphasize the right eye since it had better acuity. Once the concept was understood, the patient was tasked with EV training homework using an EV clock and a sheet of single spaced, 7M, random san serif letters (Figure 8). This size font was selected because it was above his critical print size, which would give him confidence to start with. As his EV improved, our goal was to reduce the single-letter print to threshold size, then to 3-5 letter words, and eventually to 5-7 letter words for reading. He was instructed to practice EV training 2-3x per day by using a high-contrast marker; he would point to the letter, look at 6:00 spot (towards the bottom of the letter), and read it out loud. He was also instructed to circle the letters coordinating with the days of the week (i.e., M for Monday, T for Tuesday, etc.), and he would do this for 10-15 minutes each time that he practiced. The accuracy of how well he circled the entire letter would determine how successful he was with eccentric viewing.

For viewing large print, an Eschenbach SmartLux Digital portable video magnifier was evaluated. The patient was able to read single-letter print size of 2M, which met his goal of wanting to read large print (typically 2M). Although he had multiple PRLs, he still appreciated magnification with a +4.00 effective add (EA) and an enlargement ratio (ER) of 2.3x, which meant that his equivalent viewing power (EVP = EA * ER) was +9.33D. With an EVP of +9.33D, the patient was able to read 2.0M at threshold and 2.5M print comfortably. This was better than what we expected based on his predicted EVP of +26.67D, determined by taking the inverse of the equivalent viewing distance that would allow him to read 2.0M print. He appreciated contrast enhancement with a preference for reverse polarity.

Table 1.Genetic Results Summary through Invitae

Gene	Gene Variant	Zygosity	Variant Classification	Inheritance Pattern of Linked Condition	Predicted Effect
BEST1	c. 1560T>A (p.A sp520Glu)	Heterozygous	Uncertain Significance	AD	Likely tolerated but insufficient evidence
ELOVL4	c. 931G>A (p.Ala311Thr)	Heterozygous	Uncertain Significance	AD, AR	Possibly damaging but insufficient evidence
INPP5E	c. 1159+7_1159+8ins54 (intronic)	Heterozygous	Uncertain Significance	AR	May affect RNA sequence changes but insufficient evidence
NPHP4	c. 34G>A (p. Val12Met)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence
PEX3	c. 841A>T (p.Asn281Tyr)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence
PRPF8	c. 3709A>G (p. Met1237Val)	Heterozygous	Uncertain Significance	AD	Likely tolerated but insufficient evidence
TRPM1	c. 4385C<T (p. Thr1462Met)	Heterozygous	Uncertain Significance	AR	Likely tolerated but insufficient evidence
VPS13B	c. 5497A>C (p.Asn1833His)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence

Table 2.Summary of Familial Variant Testing in the children

Age/Sex	Gene	Gene Variant	Zygosity	Variant Classification	Inheritance Pattern of Linked Condition	Predicted Effect
13M*	*ELOVL4*	c. 931G>A (p.Ala311Thr)	Heterozygous	Uncertain Significance	AD, AR	Possibly damaging but insufficient evidence
22M*						
19M**						
23F**						
21F**						

*Patients were tested under VUS Resolution Program from Invitae

**Patients were tested under Blueprint Genetics Familial Variant Testing where only one gene variant was requested to be detected

Table 3.Summary of Clinical Findings in the Children

Age/Sex	VA OD & OS	Clinical Notes
13M	20/20	Unremarkable ocular exam
22M		Unremarkable ocular exam
19M		Unremarkable ocular exam
23F		Dry eyes OU, Congenital Hypertrophy of Retinal Pigmented Epithelium OS
21F		Dry eyes OU

In order to address the patient's glare sensitivity in bright conditions, we evaluated different colored filters. He subjectively appreciated the yellow NoIR 450nm clip-on filters that allow 87% light transmission for reducing glare and enhancing contrast in all lighting conditions.

Genetic Testing

Genetic testing was sponsored through the Spark Therapeutics' ID YOUR IRD program. The patient's saliva sample was collected and his DNA sequenced using Invitae's Inherited Retinal Disease Panel. This panel analyzed 248 genes associated with inherited retinal disorders using sequence analysis and copy number variation testing. Table 1 lists the eight heterozygous genetic variants identified in our patient.

Currently, there is not enough clinical data to demonstrate the effect of each of these variants; therefore, they were classified as variants of uncertain significance (VUS). *TRPM1* and *VPS13B* were variants linked to autosomal-recessive forms of stationary congenital night blindness and retinitis pigmentosa, and these were unlikely to explain the loss of vision seen in the patient. However, three of the identified genes (*ELOVL4, BEST1*, and *PRPF8*) have been associated with autosomal-dominant forms of retinal dystrophies. The genetic variant identified in *ELOVL4* qualified for sponsored familial testing within the VUS Resolution Program from Invitae. We informed the patient that parental testing or offspring testing might assist in elucidating the role of these variants in his retinal condition. Parental testing was not an option since his parents were not living in the country. However, he had three sons and two daughters, four of them either adolescents or young adults, all of whom were asymptomatic for any visual conditions. He expressed interest and consent

for his underage children to be tested. His motivation was dual: first, to find out whether they inherited any variants, and second, to contribute to research efforts in the genetics of retinal disease. Therefore, each of his children underwent a comprehensive dilated eye exam and genetic testing.

A summary of the genetic and clinical findings for each child is listed in Tables 2 and 3, respectively. None of the children had clinical findings suggestive of STGD that could be seen from the compilation of the fundus and FAF photos compared to their father (Figure 9). It is important to note that two of the patient's children had their genetic sample analyzed with Invitae, while the other three children were analyzed with Blueprint Genetics, a second testing company. There was no significant reason why the family was tested with two different companies other than logistics and the fact that sponsored funding was starting to run low with both programs. The Familial Variant Testing offered through Blueprint Genetics for the three children targeted one specific gene variant (ELOVL4) because the other identified variants, BEST1 and PRPF8, caused a minor change in the encoded proteins predicted to be tolerated based on bioinformatic analysis (i.e., how conserved the amino acid was and the biochemical properties of the amino acids involved). The algorithms used to predict the effect of the missense changes suggested that the changes were unlikely to be pathogenic. However, there is no clinical evidence or published studies that prove or rule out the effect of these *BEST1* and *PRPF8* variants in macular dystrophy. Tables 4 and 5 list the genetic variants identified in the two sons who were tested with the Inherited Retinal Disorders Panel (Invitae). Genetic testing revealed that the patient's five children expressed the same *ELOVL4* genetic variant previously described in our patient with a novel autosomal-dominant form of macular dystrophy.[12] Given that currently none of the children were symptomatic and had no relevant clinical findings indicative of retinal disease, we educated them on the importance of annual dilated eye exams for early disease detection, UV-blocking sunglasses, and the importance of avoiding smoking to prevent unnecessary retinal damage. Since this was a novel genetic variant, and there has been no definitive clinical condition associated, it is difficult to predict the children's risk of developing a retinal condition in the future. We will continue to monitor each of the family members yearly with an eye exam and to gather more baseline data (i.e., OCT, electrodiagnostic testing) that we were unable to complete during the initial visit due to time and cost constraints. We advised them to follow a healthy diet rich in antioxidants and omega-3 fatty acids (e.g., DHA and EPA) since there is evidence that the synthesis of these polyunsaturated fatty acids may be impaired in patients with pathogenic ELOVL4 variants.[14]

Discussion

To the best of our knowledge, this is the first finding of this heterozygous missense mutation in the *ELOVL4* gene within a family and the second finding of this gene variant in an individual with late-onset macular dystrophy. This genetic variant was initially discovered with whole-exome sequencing of DNA after no molecular diagnosis was found from direct sequencing of the *ABCA4* gene.[12] The first reported individual was a 61-year-old male with a visual acuity of 20/25 OD/OS and only a horseshoe pattern of perifoveal geographic atrophy. There was also an unconfirmed family history that the father might also have been affected with the same retinal condition. This study proposed a novel form of AD STGD linked to a missense mutation in the *ELOVL4* gene. Our patient was a 57-year-old with much worse acuity and more extensive retinal findings. This case suggested that despite expressing the same genetic mutation, additional genetic, epigenetic, and/or environmental factors may affect the phenotypic expression in this form of late-onset macular dystrophy. For instance, the initial individual did not express the other genetic variants as our patient did. Nevertheless, there is still insufficient clinical data to establish a definitive genotype/phenotype correlation between the *ELOVL4 c.931G>A, p.*(Ala311Thr) variant and late-onset macular dystrophy.

STGD is a heterogeneous disease, and having a genetic diagnosis together with a comprehensive clinical assessment can help to expand our understanding of SRGD's genotype/phenotype correlations. A recent meta-analysis identified more than 1000 pathogenic variants in the *ABCA4* gene alone, leading to wide clinical variability, from macular dystrophy to retinitis pigmentosa, which is explained by the residual function still present in the mutated ABCA4 protein.[15] In comparison, there are only nine reported variants of *ELOVL4*, four of which are associated with Stargardt disease (STDG3) due to their similar clinical presentations.[9,10,16-19] Still, novel genetic variants are being discovered that are rarely reported.[12,17] Our case is evidence that although two patients are affected by the same variant, phenotypic expression can still vary. It will also be interesting to

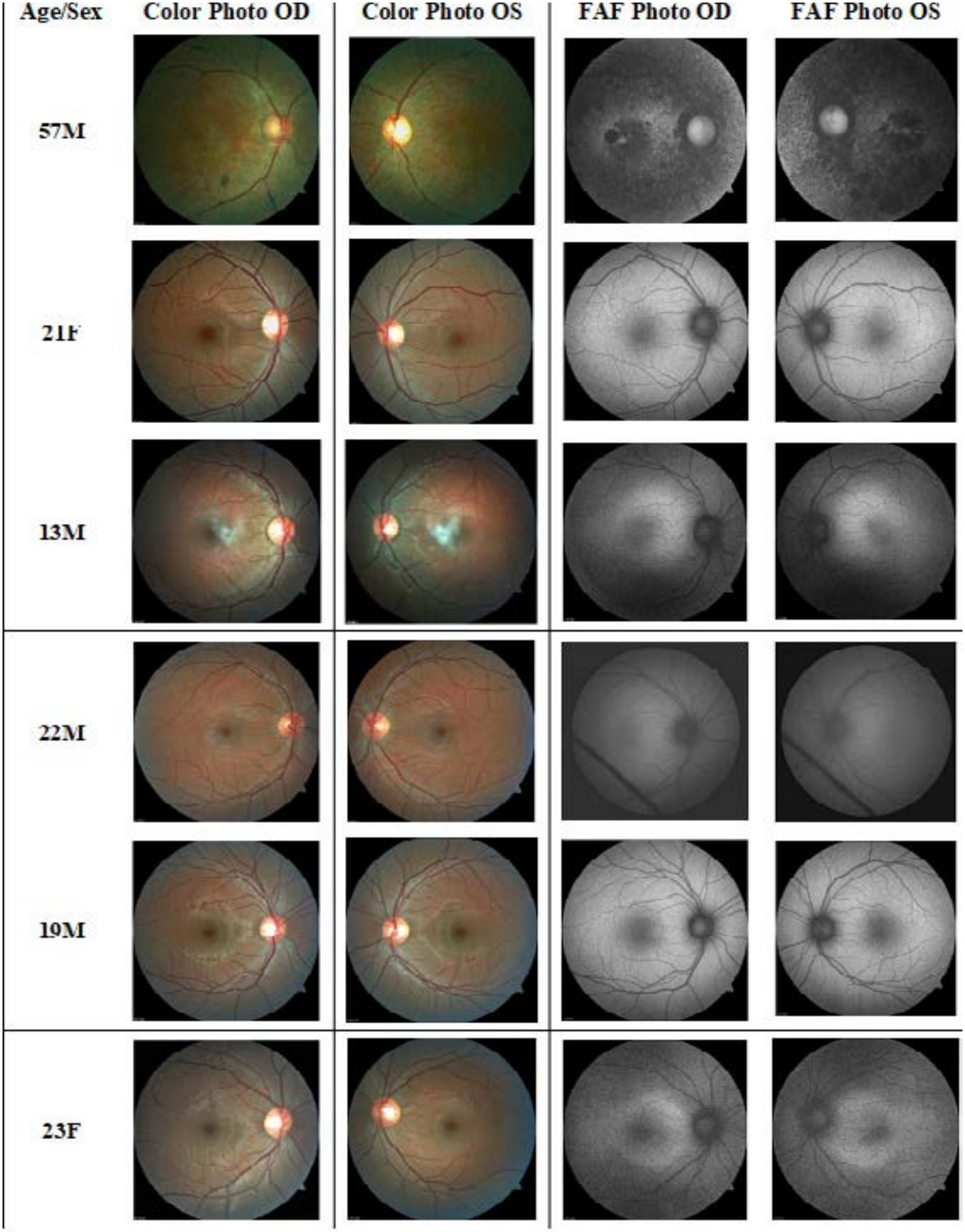

Figure 9. *Pictorial collage of the funduscopic findings from the family*

Table 4. Summary of All Genetic Variants for 13M – Invitae IRD 248 gene panel

Gene	Gene Variant	Zygosity	Variant Classification	Inheritance Pattern of Linked Condition	Predicted Effect
ELOVL4	c. 931G>A (p.Ala311Thr)	Heterozygous	Uncertain Significance	AD, AR	Possibly damaging but insufficient evidence
TRPM1	c. 4385C<T (p. Thr1462Met)	Heterozygous	Uncertain Significance	AR	Likely tolerated but insufficient evidence
VPS13B	c. 5497A>C (p.Asn1833His)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence

Table 5. Genetic Results Summary for 22M through Invitae

Gene	Gene Variant	Zygosity	Variant Classification	Inheritance Pattern of Linked Condition	Predicted Effect
BEST1	c. 1560T>A (p.Asp520Glu)	Heterozygous	Uncertain Significance	AD	Likely tolerated but insufficient evidence
ELOVL4	c. 931G>A (p.Ala311Thr)	Heterozygous	Uncertain Significance	AD, AR	Possibly damaging but insufficient evidence
NPHP4	c. 34G>A (p. Val12Met)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence
PEX3	c. 841A>T (p.Asn281Tyr)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence
PRPF8	c. 3709A>G (p. Met-1237Val)	Heterozygous	Uncertain Significance	AD	Likely tolerated but insufficient evidence
*ARHGEF18**	c. 2615A>G (p.Gln872Arg)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence
TRPM1	c. 4385C<T (p. Thr1462Met)	Heterozygous	Uncertain Significance	AR	Likely tolerated but insufficient evidence
VPS13B	c. 5497A>C (p.Asn-1833His)	Heterozygous	Uncertain Significance	AR	Unknown due to insufficient evidence

*This variant was not identified in patient JA

see the natural progression of this variant as we follow the asymptomatic family members and perhaps help to classify a new type of STGD.

The *ELOVL* enzyme family is responsible for catalyzing the formation of long-chain fatty acids.[11,14,20] *ELOVL4* specifically is expressed in the retina, cerebellum, and hippocampus and is crucial in the production of very-long-chain saturated fatty acids (VLC-SFA) and very-long-chain polyunsaturated fatty acids (VFC-PUFA), which are important lipids in the central nervous system.[19] Therefore, mutations in the ELOVL4 gene in humans have been reported to cause central nervous system disorders such as spinocerebellar ataxia 34 (SCA34) and a neuro-ichthyotic syndrome, in addition to STGD3. In the retina, ELOVL4 mainly produces VLC-PUFA, a component of the photoreceptor outer segment that is crucial to the health and survival of photoreceptors. There are six different heterozygous ELOVL4 mutations associated with STGD3 that are caused by frameshift or nonsense variants, which result in a truncation of the ELOVL4 protein, rendering the enzyme inactive.[9,16,18,21-23] This specific *ELOVL4* [c.931G>A, (p. Ala311Thr), AD] variant (PMID22864181; ClinVar database ID281603) causes a missense mutation that replaces the amino acid alanine with threonine at position 311 in the ELOVL4 protein, within its reticulum endoplasmic binding domain. As stated above, it is unknown how this missense mutation may contribute to the pathogenesis of a macular dystrophy. Based on the bioinformatic analysis, although there is a moderate physicochemical difference between these two amino acids, this alanine residue is conserved across species. This would suggest that the variation may not be tolerated and could interfere with normal ELOVL4 protein function.

As this is a novel genetic variant without a definitive clinical diagnosis, it would be prudent to conduct intravenous fluorescein angiography (IVFA or FA) and electrodiagnostic testing to rule out differentials such as retinitis pigmentosa or widespread cone-rod dystrophy. Unfortunately, FA was not conducted since we did not have access to this technology. Although the classic dark choroid sign on FA is known to aid in the diagnosis of STGD, it is only present in 85% of patients and may not be as useful in the late stages.[4] Stone et. al reported on a family of 23 affected by an autosomal-dominant macular dystrophy with Stargardt-like clinical signs that did not reveal the classic dark choroid feature on FA.[24] The widespread dark choroid appearance may be blocked by the confluent lipofuscin flecks that appear hyperfluorescent on FA, so a peripapillary dark choroid ring around the optic nerve head could be a better diagnostic sign.[4,25] In addition, this patient presented to our low vision clinic; therefore, our primary focus was on vision rehabilitation to maximize

the remainder of his vision and on providing genetic counseling to the family.

According to the 2016 recommendations on the clinical assessment of inherited retinal degenerations, the American Academy of Ophthalmology recommends the multifocal ERG (mfERG) to be used in the diagnosis and management of macular dystrophies like STGD.[26] Although the traditional full-field ERG offers more insight with regard to diffuse retinal dystrophies, it should still be considered to complete the diagnostic picture. We did not conduct electrodiagnostic testing since our patient already had both the mfERG and ERG performed at an ophthalmology clinic a year earlier and was not interested in repeating them. The mfERG showed evidence of reduced amplitudes, with delayed time responses around the mid-peripheral region of the macula OD>OS. The ERG also recorded reduced responses, but they were near normal, leading to the conclusion that the OD had a moderate to severe dysfunction of overall retinal neural response compared to the OS with mild to moderate dysfunction. Typically, the mfERG shows a significant reduction in central retinal function and minimal latency in patients with STGD; however, presentation can vary depending on the severity.[27]

OCT has revolutionized how we evaluate and understand retinal dystrophies, particularly at the macula. We can structurally see how the individual layers are affected and how that correlates to retinal function. Most clinicians can use the spectral-domain OCT (SD-OCT) to visualize the loss of the photoreceptor integrity line (junction of inner and outer segments of photoreceptors) and the thinning of the outer retina that allows increased choroidal reflectivity.[27] At our clinic, we only have the SD-OCT available; however, the latest invention of Enhanced Depth Imaging (EDI-OCT) may provide more insight into how the outer retinal layers and choroid are changing in STGD. EDI-OCT allows the clinician to visualize and to analyze the choroidal layers in more detail: for example, with the ability to measure choroidal thickness (CT). The average CT was measured in small groups of STGD patients but was found not to be significantly different compared to the average CT measured in healthy, normal patients.[28] Although this group was a small sample size without many severe STGD patients, the research can be applied in a clinical setting knowing that average CT could be an additional value used to monitor the progression of STGD.

Because of the late onset and novelty of this genetic variant, penetrance and expressivity for the *ELOVL4* variant are unknown at this point. Therefore, we are unable to predict whether the children who have inherited the same *ELOVL4* variant will develop similar symptoms of vision loss in the future, and thus, close monitoring is a dire need in order to identify visual changes in our patient's children as early as possible. Rare cases like these highlight the importance of genetic testing and have implications for providing a more accurate diagnosis for those "atypical" inherited retinal conditions. Typical genetic testing for STGD would screen for ABCA4 gene mutations and any already identified genes related to STGD; therefore, it might miss these novel mutations. As the previous study suggests, exome sequencing to detect novel or confounding genetic mutations will allow further research into how these novel mutations manifest clinically and progress.[8] Being able to identify these individuals can qualify them for new clinical trials investigating potential treatment options for STGD.

Having genetic testing in a clinical setting, especially in low vision clinics, connects scientists and clinicians with a better understanding of these inherited conditions. As a result, clinicians can educate and rehabilitate these patients so that they can understand why they may have developed vision loss at a later age. Our patient had what we presumed to be a "late-onset" case of STGD since he was not symptomatic for vision loss until his early 50s. It is possible that he may have developed clinical findings earlier than 50 years old, but we cannot confirm this since it had been several decades since he had an eye exam. Although there is currently no cure for most of these inherited retinal dystrophies, a low vision examination to rehabilitate patients' vision properly is crucial in restoring their independence and easing them back to their daily activities.

In order to maximize the remainder of their vision and to use certain low vision devices successfully, individuals with larger central scotomas should be taught how to use a new PRL. EV training should be implemented, where patients are taught to realign the image to a new area on the retina away from the damaged area.[29] Those who are affected by macular conditions often have central scotomas, blur, and distortion, which makes most daily activities difficult.[30,31] Several factors play a role when training patients in how to use the new PRL during EV training. The size, shape, and location of the scotoma can affect the success of EV training.[32] If there is a dominant eye or binocular rivalry, occluding an eye will make training easier. However, our patient

preferred to train binocularly; this is not uncommon, as binocular viewing can reduce the size of central scotomas due to binocular summation. If the scotoma is closer to or involves the fovea, patients are more likely to have trouble when reading. It is also not uncommon for those with central scotomas to have more than one PRL when reading. One study looked at how five patients with central scotomas, two of them with STGD, used their various PRLs while reading.[33] The authors concluded that the PRL used when reading is dependent on the size and length of a word, and there are different strategies developed when reading paragraphs depending on the layout of the text. This is because reading involves more than just a recognition acuity. When patients use an alternative spot away from the fovea, the acuity is expected to decrease, but they may use that location to have a broader view of the text while maintaining accurate eye movements for active scanning if there is sufficient functional retina. Another case study reported an individual also affected by STGD to have variable PRLs that did not necessarily affect him from completing certain tasks.[34] The authors found that not having a well-defined PRL did not hinder the patient from doing things such as making a sandwich or catching a ball, and having multiple PRLs would be dependent on the task and stimuli involved. There is currently no standard of care on how to approach EV training, and most of it is based on experience and what is available. A study conducted by the Department of Veteran Affairs (VA) surveyed optometrists and visual skills instructors at their rehabilitation centers and found that the amount of time spent training varied amongst practitioners, and various training techniques were used in EV training.[30] Nevertheless, EV training in low vision patients with central scotomas can help to maximize their functional vision and should always be considered as part of the rehabilitation plan.

Reading is considered to be the toughest challenge for most low vision patients, and there are different factors that play a role in reading.[35,36] These variables include, but are not limited to, the viewing distance, viewing angle, the material of the text (i.e., print vs. digital), and properties of the text such as color, contrast, font size, and font style. One survey conducted with the assistance of organizations such as the American Council of the Blind and Foundation Fighting Blindness reported that low vision subjects relied on a combination of decreasing their working distance and increasing the physical letter size in order to read better.[36] Our patient's initial reading acuity was worse than his single-letter acuity, likely to due to multiple reasons: 1) the crowding effect, 2) bilateral central scotomas of varying sizes, and 3) not having the optimal reading conditions such as good lighting and reverse polarity for enhancing contrast. When we evaluated the electronic magnifier with our patient for reading, his acuity improved, and he needed less magnification, likely because of the combination of relative size magnification and enhanced contrast using reverse polarity that regular optical magnifiers do not provide. A Cochrane Review from 2018 evaluated different reading aids for adults with low vision, which ranged from simple optical magnifiers to high-magnification video magnifiers, and found that reading speed might be higher with CCTVs compared to optical devices (hand or stand magnifiers). Low vision patients also preferred electronic devices because they were easy to use, and they were able to read longer with such devices.[37] Occupational therapists should also be involved in the care of low vision patients because they can spend more time with patients to conduct EV training and teach them to read more efficiently. A systematic review also looked at the effectiveness of different interventions that were used to improve the reading abilities of low vision patients in occupational therapy. Interestingly, the review also encouraged the integration of electronic magnification, EV training, and comprehensive low vision services into routine care to improve reading performance in low vision patients.[38]

Conclusion

To the best of our knowledge, this is the second report of an individual with Stargardt-like macular dystrophy expressing the *ELOVL4 p.* (Ala311Thr) missense variant in heterozygosity, consistent with a novel autosomal-dominant form of STGD. However, ours is the first report of this *ELOVL4* variant identified in six members of the same family. Our patient presented with a late-onset macular dystrophy, and his five children were all currently asymptomatic.

The *ELOVL4* variant was classified as being of uncertain significance and thus did not provide a definitive molecular diagnosis for our patient. Intriguingly, this mutation has been described in the context of macular dystrophy, and the amino acid change is predicted to be deleterious by bioinformatic analysis. Despite not having a molecular diagnosis, the discovery of another affected individual and

asymptomatic carriers with the same genetic variant will help to advance further research into identifying this variant as pathogenic for future potential individuals. Familial variant testing has also proven beneficial as now we can educate family members who are found to be carriers of suspected or confirmed pathogenic variants about the early signs and symptoms of expected vision loss associated with the condition. Carefully monitoring the visual function of our patient's five children will be crucial in establishing whether the variant co-segregates with the disease. This will allow us to provide the family with a definitive molecular diagnosis compatible with his vision loss, as well as to intervene if his children show early symptoms of retinal disease.

This case highlights the importance of low vision rehabilitation in maintaining one's functional vision that does not necessarily include achieving "20/20" vision. Specifically, those with suspected inherited retinal conditions should be referred as soon as a diagnosis is made, even before any vision loss occurs, in order to equip and prepare them better for their visual prognosis. The earlier the referral is made, the longer the patient can stay functional with the resources to remain independent, especially after providing them with a grim diagnosis. With this assistance and interdisciplinary collaboration between clinicians, geneticists, and researchers, larger metagenomic databases can be analyzed for novel mutations that will hopefully provide more accurate diagnosis and treatment options for patients with atypical forms of retinal disease.

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