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Multimodal imaging reveals retinoschisis masquerading as retinal detachment in patients with choroideremia

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ABSTRACT

Purpose: To report three cases of retinoschisis in patients with intermediate to advanced choroideremia.
Observations: Three patients were referred for evaluation of retinal detachment in the context of an inherited retinal degenerative disease. In all three cases, patients carried variants in the *CHM* gene suspected to be pathogenic and exhibited the characteristic findings of choroideremia, including pigment clumping and chorioretinal atrophy with scleral exposure and prominent choroidal vessels. Interestingly, these patients were also found to have areas of typical retinoschisis and cystoid degeneration located in the outer plexiform layer of the mid periphery or macula. Retinoschisis was confirmed by spectral domain optical coherence tomography (SD-OCT).
Conclusions/Importance: This paper draws attention to the occurrence of retinoschisis in patients with choroideremia. OCT can be used to confirm the presence of retinoschisis rather than retinal detachment, as the clinical exam findings that distinguish the two conditions are not helpful in the setting of advanced chorioretinal atrophy. Although it remains unclear whether patients with choroideremia as a group are at increased risk of retinoschisis, it is possible that abnormal vesicular traffic in the RPE and photoreceptors could contribute to abnormalities in cell adhesion and the extracellular matrix. As gene therapy by subretinal injection of adeno-associated virus becomes the standard of care to slow down or arrest retinal degeneration in choroideremia, it will be critical to carefully screen these patients for retinoschisis prior to surgical intervention and to incorporate any such findings into surgical planning.

1. Introduction

Choroideremia is an X-linked, recessive, degenerative disease affecting the choroid, retinal pigment epithelium (RPE), and photoreceptor layer.[1,2] Its prevalence is approximately 1 in 50,000 males. Generally, patients experience night blindness in their first and second decade, which progresses to peripheral vision loss over their third decade, and central vision loss as early as their fifth decade.[2,3] Choroideremia has been associated with about 280 distinct mutations in the *CHM* gene (OMIM 303390), which codes for the Rab escort protein 1 (REP-1).[4–6] Almost all disease-causing pathogenic variants of CHM are considered null.[7] REP-1 is necessary for prenylation and membrane targeting of Rab proteins, which in turn regulate vesicular and membrane traffic in the golgi body, endoplasmic reticulum, and endosomes. In the absence of REP-1 function, Rab proteins accumulate in their unprenylated form, disrupting phagocytosis of photoreceptor outer segments and melanosome transport in the RPE.[8]

In this case series, we present three patients with a diagnosis of choroideremia who were found to have concurrent retinoschisis. Retinoschisis is a splitting of the retina, often confused clinically with retinal detachment. It occurs when cystoid spaces filled with mucopolysaccharide coalesce in the outer plexiform or nerve fiber layer.[9] Although a

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juvenile X-linked inherited form of retinoschisis has been described, the vast majority of cases are sporadic and arise in older patients without a known etiology. Senile retinoschisis is seen in 1–4% of the population over age 50, affects both sexes equally, is predominantly bilateral and inferotemporal, and is more common in hyperopes. It has typically been differentiated from retinal detachments by the presence of an absolute rather than relative scotoma, the appearance on ophthalmoscopy of a smooth rather than corrugated elevation of the retina, the inward displacement rather than flattening on scleral depression and the blanching rather than lack thereof elicited by application of laser.[10–12] However, these traditional clinical exam features may not be possible to ascertain in many choroideremia patients due to extensive retinal degeneration outside the fovea. Optical coherence tomography (OCT) is therefore important to make a definitive diagnosis in this context.

2. Methods

Study approval– The study was approved by the Stanford University and Columbia University Institutional Review Board and adhered to the tenets set forth in the Declaration of Helsinki (IRB: 201803853).

Patient testing– All patients in this case series had undergone genetic testing and had confirmed mutations in the *CHM* gene. Genetic testing was performed using Blueprint Genetics Retinal Dystrophy Panel and Prevention Genetics Comprehensive Ocular Disorders Panel. No patient had a mutation in the retinoschisin 1 *(RS1) gene.* Wide angle fundus photos were obtained following dilation with the Optos imaging system. Optical coherence tomography images were taken with the Zeiss Cirrus spectral domain OCT (SD-OCT) imaging system. For each patient, a 10mm b-scan line was obtained focusing on the area of suspected retinoschisis to definitively establish the presence of retinal splitting and absence of subretinal fluid.

3. Findings

3.1. Case 1

A 56-year-old man who presented with a history of nyctalopia and decreased peripheral vision since he was a teenager. He was originally diagnosed at 17 years of age. Previously performed genetic testing had identified a terminal deletion in the *CHM* gene (exons 9–15). At presentation, BCVA was 20/100 in the right eye and CF at 1 foot in the left eye. Anterior segment exam was notable for mild nuclear sclerotic cataracts in both eyes. Posterior segment exam revealed severe chorioretinal atrophy with a small central patch of preserved RPE in the macula, numerous pigment clumps in the midperiphery and prominent choroidal vessels, as well as elevation of the midperipheral superior retina in both eyes raising concern for retinal detachment (Fig. 1A–D). No retinal tears were evident in either eye after performing thorough scleral depressed exams. SD-OCT confirmed that these midperipheral areas of bullous elevation in both eyes represented retinoschisis without subretinal fluid (Fig. 1E). Although it is not possible to distinguish the retinal layer involved in these peripheral areas of schisis due to the advanced stage of degeneration, SD-OCT through the macula demonstrated cystoid degeneration in the inner nuclear layer (Fig. 1F). These areas of peripheral schisis remained stable on follow-up for two years.

3.2. Case 2

A 54-year-old man who presented with a history of longstanding nyctalopia and peripheral vision loss. He was previously diagnosed with choroideremia by a community ophthalmologist and presented to be screened for the Nightstar gene therapy clinical trial. Genetic testing revealed a novel likely pathogenic variant, c.1019C > A:p.Ser 340*, in the *CHM* gene. He had an unclear past ocular history of surgery in both eyes (presumably for treatment of the choroideremia). At presentation, BCVA was 20/50 in the right eye and HM in the left eye. Anterior

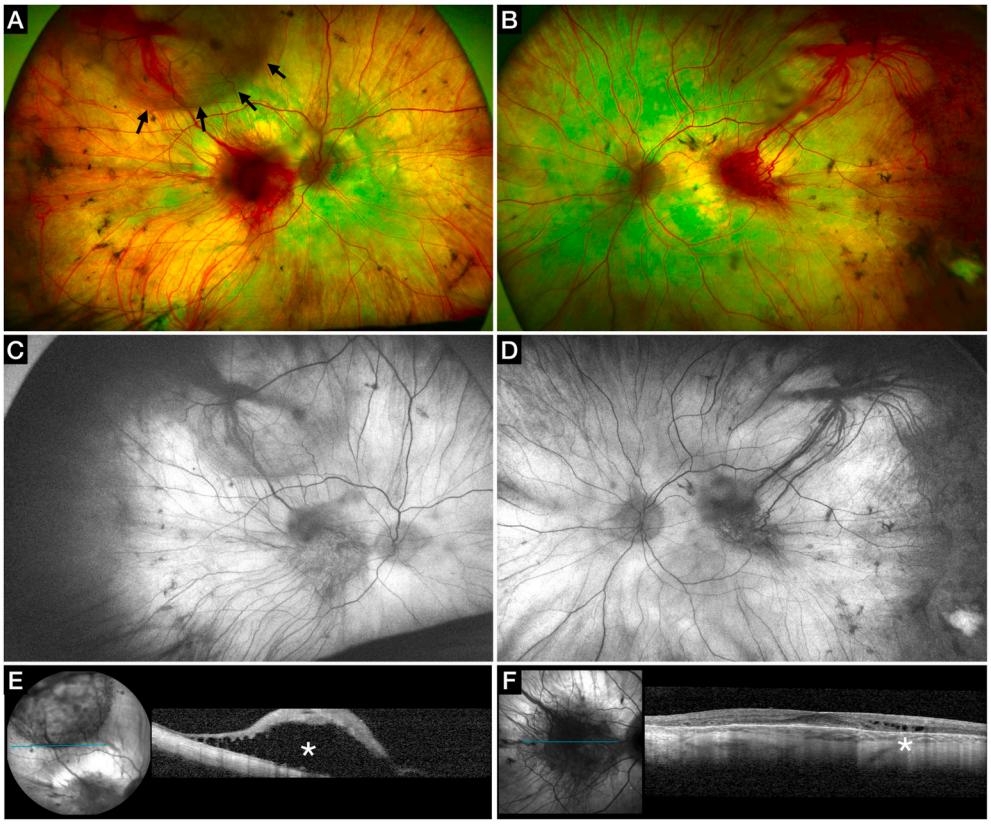

Fig. 1. Multimodal imaging of case 1: (A–B) Optos fundus photographs show extensive chorioretinal atrophy, numerous pigment clumps and prominent choroidal vessels in both eyes, as well as elevation of the superior retina in the right eye (arrows). **(C–D)** Optos fundus autofluorescence demonstrates a small central patch of preserved RPE in the macula in both eyes. **(E–F)** OCT through superior retina reveals splitting of the retina (asterisk), though it is not possible to discern the specific layer due to extensive atrophy. Within the macula, there is cystoid degeneration along the outer plexiform layer (asterisk).

segment exam was significant for posterior subcapsular cataracts in both eyes. Dilated fundus exam revealed significant chorioretinal atrophy with a spared central RPE island, with areas of schisis extending toward the macula, but no areas of isolated peripheral schisis (Fig. 2A–D). SD-OCT showed significant midperipheral bilateral cystoid degeneration in the inner nuclear layer and possible schisis in the outer plexiform layer without subretinal fluid that had proven resistant to a 3-month course of oral acetazolamide 250mg twice each day (Fig. 2E and F). Importantly, it is difficult to distinguish schisis from advanced cystic degeneration in areas of profound retinal atrophy, similar to what is seen in severe cases of geographic atrophy or subretinal fibrosis. In addition, some of these cavities could represent very large outer retinal tubulations, which have been reported in the setting of choroidal neovascularization in AMD patients and a number of inherited retinal diseases.[13,14]

3.3. Case 3

A 63-year-old man was clinically diagnosed with choroideremia eight years prior, and presented to consider enrollment in the Nightstar gene therapy trial. Genetic testing revealed a hemizygous pathogenic mutation in *CHM*, c.757C > T, p.(Arg 253*). His BCVA was 20/60 in the right eye and 20/40 in the left eye. Anterior segment exam was notable for PCIOL in the right eye and mild nuclear sclerotic cataract in the left eye. Posterior segment exam revealed chorioretinal atrophy with a patch of spared RPE in the central macula, as well as several pigment clumps and prominent choroidal vessels in the midperiphery (Fig. 3A–D). Areas concerning for schisis were noted to extend toward the macula, and there were no isolated areas of peripheral schisis. The patient also had midperipheral retinoschisis in the outer retina in both eyes, which was far more pronounced in the left eye, as demonstrated by SD-OCT scans (Fig. 3E and F).

4. Discussion

Although this case series cannot address whether patients with choroideremia are at increased risk of retinoschisis, it raises a number of important issues. First, OCT has become the imaging modality of choice to reliably distinguish not only between retinoschisis and retinal detachment, but also between its typical and reticular forms, and can identify midperipheral retinoschisis in choroideremia. Because retinoschisis was present in areas of prior degeneration, these *CHM* patients were asymptomatic. Long-term follow-up of these patients with wide field fundus imaging, as well as spectral domain OCT or swept-source OCT, will be necessary to ascertain whether these changes are progressive like X-linked retinoschisis or generally non-progressive like senile retinoschisis.

The laminar specificity of retinoschisis in CHM retinopathy appears to be similar to that of congenital X-linked retinoschisis, with cystoid degeneration first appearing in the inner nuclear layer before coalescing into larger schisis cavities. Senile retinoschisis, in contrast, tends to affect the nerve fiber layer or outer plexiform layer. These distinctive features might be related to the mechanisms underlying the formation of schisis cavities, which might predominantly affect cells in X-linked retinoschisis and neuropil in senile retinoschisis. Gene mutations underlying congenital X-linked retinoschisis have been mapped to the retinoschisin 1 (*RS1*) gene which encodes for a secreted protein involved in cell-cell adhesion. Interestingly, REP-1 is essential for prenylation and membrane targeting of Rab proteins, which in turn regulate vesicular and membrane traffic in the golgi body, endoplasmic reticulum, and endosomes. It is interesting to speculate that impaired secretory function as a result of impaired REP-1 function could disrupt trafficking of retinoschisin and other secreted proteins important for cell adhesion. However, profound retinal degeneration in choroideremia might outpace and preempt schisis cavity formation in most patients.

Another critical consideration is how the presence of retinoschisis in choroideremia patients might affect surgical planning for gene therapy

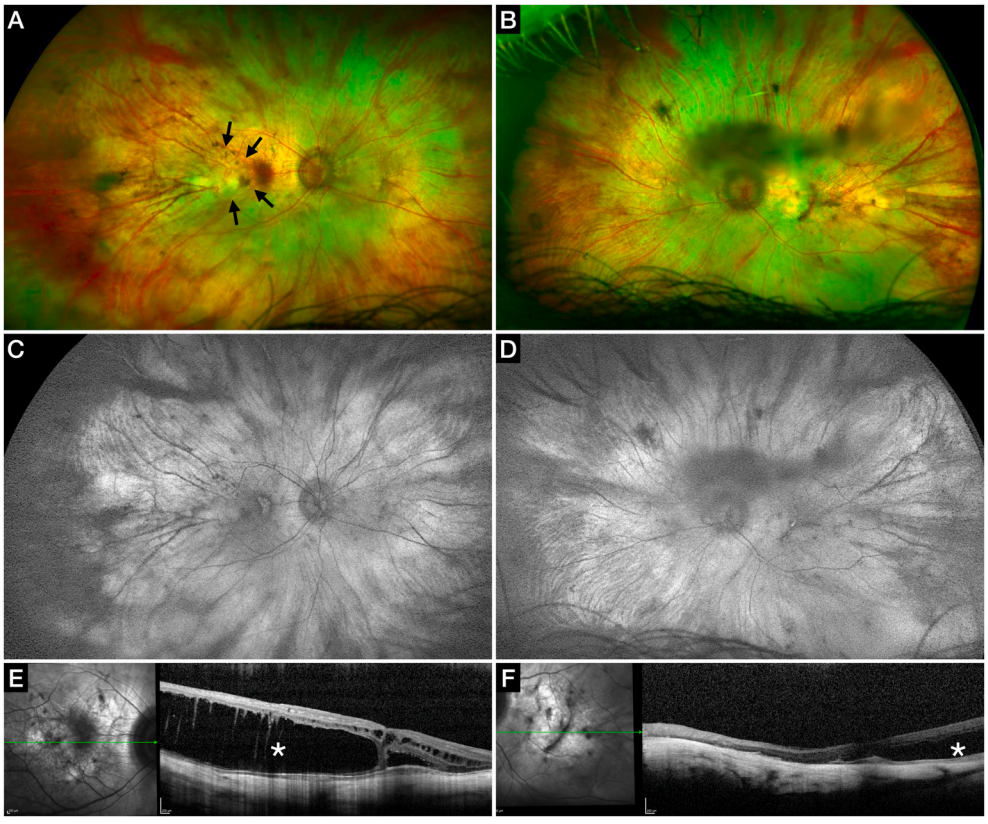

Fig. 2. Multimodal imaging of case 2: (A–B) Optos fundus photographs reveal significant chorioretinal atrophy, enlarged choroidal vessels and pigment clumps in both eyes, as well as elevation of the temporal macula more prominent in the left eye (arrows) than in the right eye. **(C–D)** Optos fundus autofluorescence demonstrates a small central island of spared RPE in the macula in both eyes. **(E–F)** OCT of the macula confirms schisis and cystoid degeneration (asterisks) in the outer plexiform layer of both eyes.

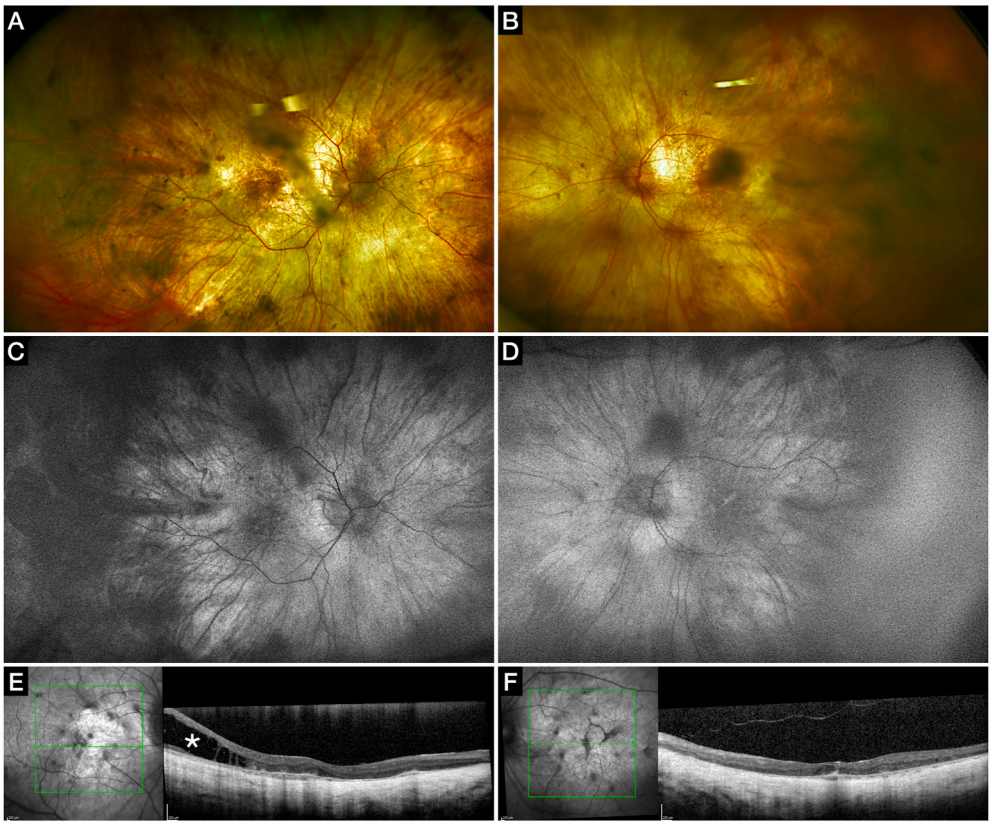

Fig. 3. Multimodal imaging of case 3: (A–B) Optos fundus photographs demonstrate extensive chorioretinal atrophy, numerous pigment clumps and prominent choroidal vessels in both eyes. **(C–D)** Optos fundus autofluorescence demonstrates a small central patch of preserved RPE in the macula in both eyes. **(E–F)** OCT of the macula reveals splitting of the retina along the outer plexiform layer in the temporal macula of the right eye (asterisk).

delivery. Subretinal injection of adeno-associated viral vector serotype 2 (AAV2) encoding REP1 may become an option for these patients, with a majority of participants in the original clinical trial experiencing visual acuity improvements through five years of follow-up.[15–18] However, a larger multi-center phase III clinical trial (NCT03496012) to investigate the long-term safety and efficacy of AAV2-REP1 for the treatment of choroideremia did not meet its endpoint of an improvement ≥15 ETDRS letters from baseline in best corrected visual acuity (BCVA) at month 12.[19] In these trials, standard surgical techniques for subretinal viral vector delivery\ were used. First, the retina is detached with an injection of basic saline solution (BSS) under intraoperative OCT guidance to create a subretinal bleb, and then AAV is injected into the bleb.[20] Multiple studies have shown that structural recovery occurs within one week and visual acuity improves despite this iatrogenic retinal detachment.[21] However, the presence of retinoschisis or severe cystic degeneration might result in communication of the bleb with a schisis cavity or may even cause a rhegmatogenous break secondary to the mechanical pressure induced by the subretinal bleb due to decreased structural integrity in these areas of thinned retina. Ongoing trials for gene therapy in patients with congenital X-linked retinoschisis exploit the breakdown of the ILM barrier in these patients and can sidestep these potential surgical complications by delivering viral particles using intravitreal injections. It is unclear whether this approach would be effective in patients with choroideremia. Given that subretinal injections have already shown promise, it might be preferable for surgeons to continue with the subretinal approach while being mindful of any areas of retinal thinning secondary to schisis or advanced cystic degeneration as they select the location for initiating the subretinal bleb and ensuring that the bleb does not extend toward these areas. If the areas of retinoschisis or severe cystic degeneration are too close to the macula for this to be feasible, prophylactic laser barricade could be considered prior to surgery to prevent extension of the bleb toward these areas.

5. Conclusions

This paper highlights three OCT-confirmed cases of retinoschisis in patients with choroideremia. Although it remains unclear if the latter has a causal relation to the former, we speculate that abnormal vesicular traffic in REP1 deficient retinal cells could weaken the extracellular matrix and impair cell adhesion leading to the formation of schisis cavities. Careful screening with wide filed Optos photos and SD-OCT should be performed in all patients with choroideremia, especially before pursuing surgical interventions for delivery of gene therapy.

Patient consent

Consent to publish this case report has been obtained from the patients in writing.

Declaration of competing interest

None reported.

Author contributions

Drs. Mahajan and Tsang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: VBM. Acquisition of data: VBM, SHT, EK, JKO and SRL. Analysis and interpretation of data: VBM, SHT, and LCG. Drafting of the manuscript: VBM, LCG and KGG. Critical revision of the manuscript for important intellectual content: VBM. Obtained funding: VBM. Administrative, technical, and material

support: VBM. Study supervision: VBM and SHT.

Role of the sponsor

The funding organizations had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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References

1. MacDonald IM, Russell L, Chan CC. Choroideremia: new findings from ocular pathology and review of recent literature. *Surv Ophthalmol*. 2009;54(3):401–407.
2. Pennesi ME, Birch DG, Duncan JL, Bennett J, Girach A. CHOROIDEREMIA: retinal degeneration with an unmet need. *Retina*. 2019;39(11):2059–2069. Philadelphia, Pa.
3. Roberts MF, Fishman GA, Roberts DK, et al. Retrospective, longitudinal, and cross sectional study of visual acuity impairment in choroideraemia. *Br J Ophthalmol*. 2002;86(6):658–662.
4. MacDonald IM, Hume S, Chan S, et al. Choroideremia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; 2003 Feb 21:1993–2020.
5. Mitsios A, Dubis AM, Moosajee M. Choroideremia: from genetic and clinical phenotyping to gene therapy and future treatments. *Ther Adv Ophthalmol*. 2018;10, 2515841418817490.
6. Sergeev YV, Smaoui N, Sui R, et al. The functional effect of pathogenic mutations in Rab escort protein 1. *Mutat Res*. 2009;665(1-2):44–50.
7. Simunovic MP, Jolly JK, Xue K, et al. The spectrum of CHM gene mutations in choroideremia and their relationship to clinical phenotype. *Investig Ophthalmol Vis Sci*. 2016;57(14):6033–6039.
8. Wavre-Shapton ST, Tolmachova T, daSilva ML, et al. Conditional ablation of the choroideremia gene causes age-related changes in mouse retinal pigment epithelium. *PLoS One*. 2016;8:1–11.
9. Straatsma BR, Foss RY. Typical and reticular degenerative retinoschisis. *Am J Ophthalmol*. 1973;75:551–575.
10. Byer NE. Long-term natural history study of senile retinoschisis with implications for management. *Ophthalmology*. 1986;93:1127–1136.
11. Byer NE. Clinical study of senile retinoschisis. *Arch Ophthalmol*. 1968;79:36–44.
12. Buch H, Vinding T, Nielsen N. Prevalence and long-term natural course of retinoschisis among elderly individuals. *Ophthalmol Times*. 2007;114:751–755.
13. Goldberg NR, Greenberg JP, Laud K, Tsang S, Freund KB. Outer retinal tubulation in degenerative retinal disorders. *Retina*. 2013 Oct;33(9):1871–1876. https://doi.org/10.1097/IAE.0b013e318296b12f. PMID: 23676993; PMCID: PMC4291318.
14. Xue K, Oldani M, Jolly JK, et al. Correlation of optical coherence tomography and autofluorescence in the outer retina and choroid of patients with choroideremia. *Invest Ophthalmol Vis Sci*. 2016 Jul 1;57(8):3674–3684. https://doi.org/10.1167/iovs.15-18364. PMID: 27403996; PMCID: PMC4959839.
15. Cehajic Kapetanovic J, Patrício MI, MacLaren RE. Progress in the development of novel therapies for choroideremia. *Expet Rev Ophthalmol*. 2019;14(6):277–285.
16. MacLaren RE, Groppe M, Barnard AR, et al. Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. *Lancet (London, England)*. 2014;383(9923):1129–1137.
17. Simunovic MP, Xue K, Jolly JK, MacLaren RE. Structural and functional recovery following limited iatrogenic macular detachment for retinal gene therapy. *JAMA Ophthalmol*. 2017 Mar 1;*135*(3):234–241.
18. Xue K, Jolly JK, Barnard AR, et al. Beneficial effects on vision in patients undergoing retinal gene therapy for choroideremia. *Nat Med*. 2018;24(10):1507–1512.
19. *Biogen Announces Topline Results from Phase 3 Gene THERAPY Study in Choroideremia*. Biogen Press Release; 14 June 2021. investors.biogen.com/news-releases/news-release-details/biogen-announces-topline-results-phase-3-gene-therapy-study.
20. Barnard AR, Groppe M, MacLaren RE. Gene therapy for choroideremia using an adeno-associated viral (AAV) vector. *Cold Spring Harbor Perspect Med*. 2014;5(3), a017293.
21. Xue K, Groppe M, Salvetti AP, MacLaren RE. Technique of retinal gene therapy: delivery of viral vector into the subretinal space. *Eye*. 2017;31(9):1308–1316.