

CE Credit - Case Report(s) & Topic Review

Adult Onset Foveomacular Vitelliform Dystrophy: A Case Report

Jonathan P. Christie, OD, MBA, FAAO

CRO (Clinical & Refractive Optometry) Journal

ABSTRACT

Introduction: Adult-onset foveomacular vitelliform dystrophy (AOFVD) is a rare pattern dystrophy that is frequently misdiagnosed and is characterized by subretinal lipofuscin accumulation at the macula in the subretinal space and is usually diagnosed after age 40. The lesions gradually increase and then decrease in size over the years, leaving atrophic retinal changes and a corresponding decrease in visual acuity.

Case Presentation: A 71-year-old male presents for a routine glaucoma follow-up and dilated fundus examination, which revealed recent macular changes in both eyes that resembled isolated large soft drusen. He reported that he recently underwent genetic testing and was a Complement Factor (CFH) mutation carrier, which put him at risk for age-related macular degeneration and cuticular drusen.

Management and Outcome: Further testing with ocular coherence tomography revealed a sub foveal lesion in both eyes with no inner segment/outer segment junction disruption, subretinal or intraretinal fluid. Patient was advised about AOFVD and sent for retina consult to confirm diagnosis.

Discussion: Adult-onset vitelliform maculopathy (AOFVD) is an uncommon retinal degeneration whose exact prevalence is unknown due to frequent confusion with other age-related conditions. This case demonstrates the importance of careful evaluation of macular changes in older adults to avoid misclassification and unhelpful management recommendations of this condition.

Keywords: Adult-onset Foveomacular Vitelliform Dystrophy, Adult-onset Vitelliform Dystrophy, Acquired Vitelliform Lesions, Best Disease, Pattern Dystrophy, Subretinal drusenoid deposit

INTRODUCTION

Adult Onset Foveomacular Vitelliform Dystrophy (AOFVD), or Adult Onset Vitelliform Maculopathy, is an uncommon pattern dystrophy that occurs later in life and usually results in slow vision loss. AOFVD is characterized by the accumulation of yellowish deposits beneath the macula, known as acquired vitelliform lesions, that are often confused with drusen. The term vitelliform is Latin for egg yolk, and while vitelliform lesions are most commonly associated with Best Disease (Best Vitelliform Macular Disorder), a disease of youth, these deposits can also occur in older patients¹. Functionally, the degree of vision loss can vary dramatically from mild to severe, depending on which stage of the disease the patient is presenting with and whether macular atrophy or neovascular membrane is present.

CASE REPORT

Initial Presentation

A white man aged 71 years old presented to the Optometry clinic for an annual eye exam and follow-up, including dilated eye examination, visual field testing, and optic nerve head imaging. The patient had been followed on a semi-annual basis since late 2020 as a glaucoma suspect and had been a regular patient in the clinic since 2007. His ocular history was significant for hyperopia, astigmatism, presbyopia, non-visually significant nuclear sclerotic cataracts, and he was a low-risk glaucoma suspect. His medical history at presentation was significant for hypertriglyceridemia, Barrett's esophagus, actinic keratosis, seborrheic keratosis, rosacea, and erectile dysfunction. The patient denied ever smoking or using smokeless tobacco. The patient was taking no ocular medications. Systemic medications were Zolpidem 10mg (Meda Pharmaceuticals, Somerset, NJ), Sildenafil 25mg (Teva Pharmaceuticals, Irvine, CA), Mupirocin 2% (Taro Pharmaceuticals, Hawthorne, NY), Fluorouracil

Residency Coordinator, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, USA;
Marshall B Ketchum University Southern California College of Optometry, Fullerton, California, USA

0.5% (Viartis, Canonburg, PA), and Calcipotriene 0.005% (Prasco Laboratories, Mason, OH). The patient had no known medication-related allergies. He reported that he had recently tested with 23andMe (South San Francisco, California) and was a Complement Factor H mutation carrier, putting him at higher risk for age-related macular degeneration and cuticular drusen.

Entering uncorrected visual acuity was 20/40 in the right eye, which pinholed to 20/25 and 20/25 in the left eye. Pupils, ocular motility, and confrontation visual fields were all normal. Intraocular pressure with Goldmann applanation tonometry was 18 mm Hg in both the right and left eyes. Blood pressure with a Mindray VS9 automated cuff (Mindray North America, Mahwah, MA) was 144/86.

Slit lamp examination of the anterior segment revealed normal lids/lashes, conjunctiva, cornea, anterior chamber and iris. Lenses had mild +1 mild nuclear sclerotic changes in both eyes. He was dilated with 0.5% Proparacaine and 1.0% Tropicamide (Amcon Laboratories, Inc, Greenpark, MI) in both eyes. Dilated Fundus Examination with a Volk Digital Wide Field and Volk Digital Clear lens (Volk Optical Inc, Mentor, OH) revealed round bilateral discs with a cup-to-disk ratio of approximately 0.45 and 0.6 in the right and left eyes, respectively, with lamina cribrosa showing in both eyes. Maculas in both eyes had what was initially described by the author as a large soft drusen, larger in the right vs the left eye, without pigment changes, blood, fluid, or lipid. Blood vessels had normal caliber, and the retinal periphery was unremarkable in both eyes. Ancillary testing was performed, including optical coherence tomography and widefield fundus photography. The infrared image revealed one hyperreflective round lesion at the macula in both eyes, the larger in the right eye (Figure 1). Optical coherence tomography with a Heidelberg Spectralis (Heidelberg Engineering, Franklin, MA) of the macula demonstrated a subfoveal lesion in both eyes with no inner segment/outer segment junction disruption, subretinal or intraretinal fluid (Figure 2). Widefield retinal photography with an Optos California (Optos Inc, Marlborough, MA) revealed round yellowish lesions at the macula of both eyes (Figure 3). The patient was diagnosed with suspected adult-onset vitelliform and referred for a retina consult to confirm the diagnosis and rule out age-related macular degeneration, especially in light of his genetic testing. The patient was seen within the week, and the diagnosis of AFOVD was confirmed. The retina specialist advised that no treatment was indicated and recommended that the patient follow up with optometry every three months with a repeat ocular coherence tomography, fundus autofluorescence, and dilated retinal examination.

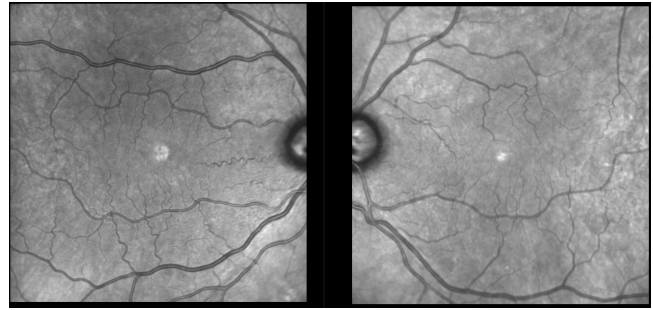


Figure 1. Heidelberg Infrared image reveals small, roundish, hyper-reflective areas at the macula in both eyes.

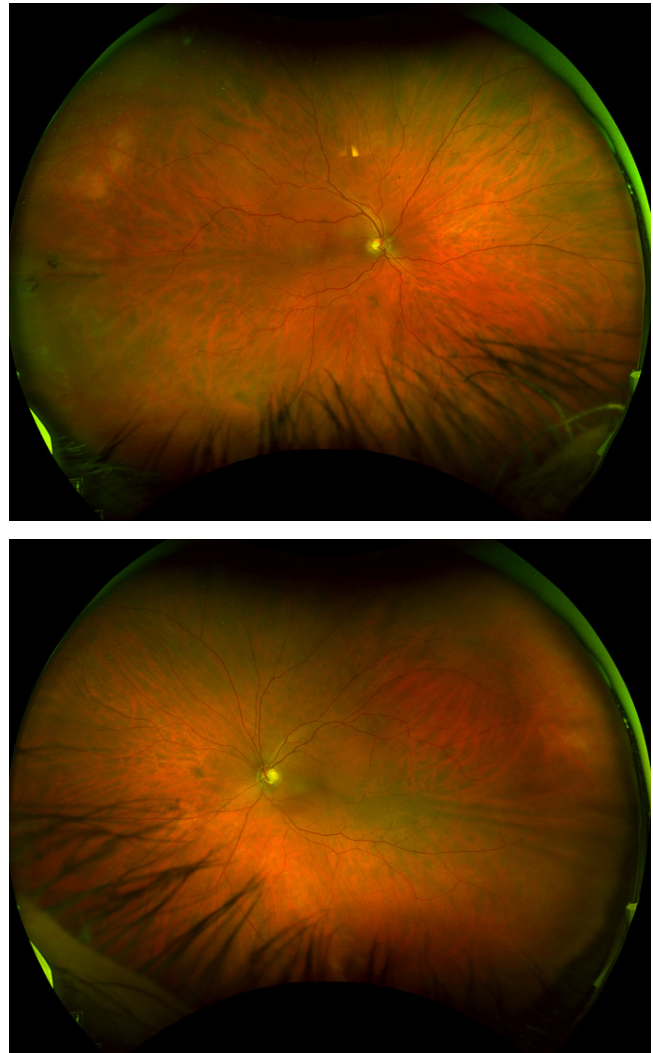


Figure 3. Widefield color retinal photography reveals yellowish lesions at the macula in both eyes. Artifacts from dust on the lens can also be seen.

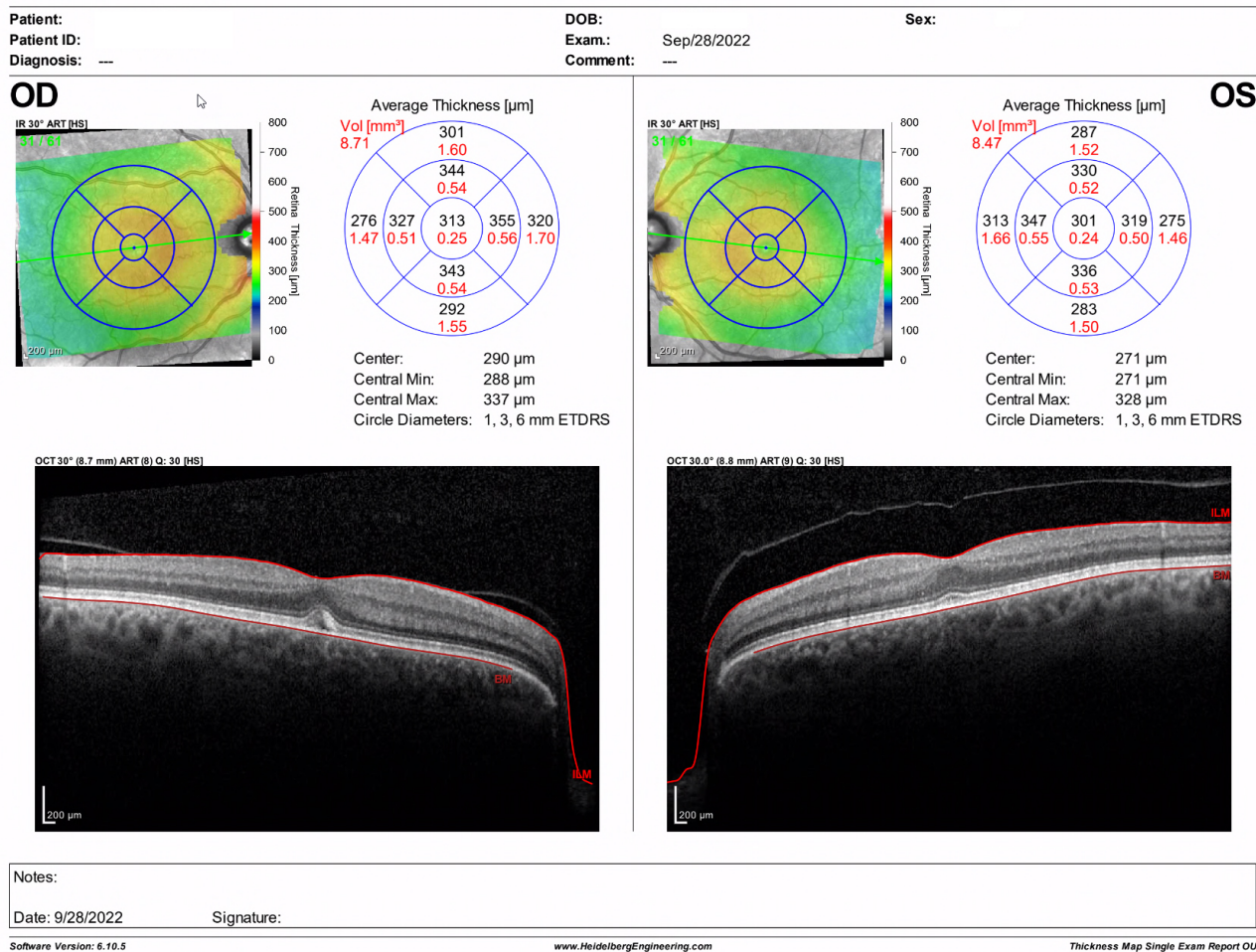


Figure 2. Optical coherence tomography of the macula shows bilateral asymmetric subfoveal lesions with no disruption of the inner segment/outer segment junction and no subretinal or intraretinal fluid.

DISCUSSION

Epidemiology & Histopathology

Adult-onset vitelliform maculopathy (AOFVD) is an uncommon retinal degeneration whose exact prevalence is unknown due to frequent confusion with other age-related conditions. The best guess is one frequently referenced study from Olmsted County, Michigan, which found the prevalence to be 1/7,400 people². AOFVD was first described in 1974 by Donald Gass as a "peculiar foveomacular dystrophy" and has been known by a number of names over the years, including adult macular vitelliform degeneration, adult vitelliform macular degeneration, pseudovitelliform macular degeneration, adult onset foveomacular pigment epithelial dystrophy, and adult vitelliform macular dystrophy³. Gass later classified it as one of the five autosomal dominant pattern dystrophies, which all have similarities related to RPE dysfunction and dark yellow lipofuscin deposition in the subretinal space, creating characteristic patterns in the macula³. Its classification as a pattern dystrophy has caused some debate, as the genetics of AOFVD do not align with those of other pattern

dystrophies. AOFVD is defined by the presence of yellowish, autofluorescent, egg-yolk-like deposits, known as acquired vitelliform lesions, which are usually 500-700 μm in size, localized beneath the central macula and contain a central pigmented spot. The deposits reside in the subretinal space above the retinal pigment epithelium, below the photoreceptor layer. These AOFVD lesions are made up of specifically melanosomes, lipofuscin, melanolipofuscin, and outer segment debris deposited between the photoreceptor and retinal pigment epithelium layers^{5,6}.

Mechanism

The mechanism of AOFVD lesion formation is not well understood and is thought to be due to impaired phagocytosis of photoreceptor outer segments by the retinal pigment epithelium, leading to the build-up of lipofuscin in the subretinal space⁷. AOFVD progresses through four distinct stages: the vitelliform stage, pseudohypopyon stage, vitelliruptive stage, and atrophic stage⁸. Because the stages visually present differently and similarly to other retinal conditions, AOFVD is easily confused with macular degeneration, retinal drusen, and other pattern dystrophies.

The vitelliform stage is characterized by a yellowish lesion with a well-defined edge in the macula, resembling the classic "egg yolk" appearance that is often associated with Best disease, making it the easiest stage for diagnosing AOFVD. In the pseudohypopyon stage, the material within the lesion starts to break down with sedimentation of denser lipofuscin deposits at the bottom and clearer fluid accumulating above⁹. As AOFVD progresses to the vitelliruptive stage, the material within the lesion becomes fragmented and unevenly dispersed, creating a "scrambled egg" appearance on imaging. This change results in variations in vision, reflecting the instability of the lesion during this stage. As the remaining material is reabsorbed, localized retinal thinning, RPE loss, and outer retinal degeneration develop, defining the atrophic stage. This final stage often correlates with a decline in visual function due to the loss of photoreceptor cells and structural damage in the macula.

Genetics

For many years, it was believed that AOFVD had an autosomal dominant inheritance pattern similar to other pattern dystrophies. Recent research has revealed that this only occurs in a minority of cases, which has caused some to question if AOFD is truly a pattern dystrophy. In most cases, AOFVD appears sporadically, and no consistent inheritance pattern has been identified⁵.

Mutations in several genes, BEST1, PRPH2, and IMPG1, have been linked to AOFVD⁵.

Mutations in the BEST1 gene cause dysfunction and a loss of attachment between the retinal pigment epithelium and the outer segment photoreceptors, leading to fluid and pigment accumulation and eventually, retinal atrophy¹⁰. In addition to BEST1, AOFVD is associated with mutations in the peripherin-2 (PRPH2) gene, which encodes a photoreceptor-specific glycoprotein necessary for creating and ongoing support of rod and cone outer segments¹¹. Mutations in the IMPG1 interphotoreceptor matrix proteoglycan gene, which encodes a protein that is a significant component of the retinal interphotoreceptor matrix, are also associated¹². While these mutations impact different genes, they all cause retinal pigment epithelium and phagocytic dysfunction. Genetic mutations are not found in all cases of AOFVD, and some are degenerative with characteristics that can overlap with age-related macular degeneration¹³.

Diagnosis

Before OCT imaging, it was difficult to distinguish AOFVD from other macular disorders due to a similar appearance unless it happened to present with the classic egg yolk lesion. Diagnosis is often made through a combination of fundoscopic examination, optical coherence tomography (OCT), and fluorescein angiography. On OCT, characteristic hyperreflective material is found above the retinal pigment epithelium, elevating a thinned overlying retina. Fluorescein angiography typically shows hypofluorescence or blockage

of the normal choroidal fluorescence¹⁴. Differential diagnosis includes Best Disease, retinal drusen, and age-related macular degeneration. While the deposits in AOFVD appear very similar to those found in Best disease, AOFVD usually develops in the fourth or fifth decade of life, whereas Best disease manifests in childhood. AOFVD can also be confused with age-related macular degeneration due to the similar appearance of vitelliform lesions and drusen. The main differences are that AOFVD lesions are often solid, yellowish in coloration, and larger than those seen in AMD and with retinal drusen. Also, AOFVD lesions are solitary, while drusen seen in AMD are usually multiple.

Prognosis

Visual acuity of patients may vary, with some patients experiencing minimal visual blur and or metamorphopsia while others may develop significant central vision impairment. The most important determinant of visual acuity is the condition of the outer retinal layers and it makes sense that worse vision is also associated with larger lesion size or if choroidal neovascular membrane or geographic atrophy is present^{14,15}. One study found that subretinal drusenoid deposits (SRDD), which disrupt the IS/OS junction, lead to a higher risk of macular atrophy and CNVM with poorer visual outcomes¹⁶.

Treatment

While there isn't a universally accepted treatment protocol, options typically address specific manifestations such as subretinal fluid accumulation or neovascularization. Asymptomatic or minimally symptomatic cases of AOFVD may be managed through regular monitoring similar to following age-related macular degeneration. Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents, such as ranibizumab or aflibercept, have been used off-label when associated with subretinal neovascularization or choroidal neovascularization (CNV) to limit angiogenesis and vascular permeability. Gene augmentation or gene editing aimed at restoring the function of calcium channels affected by mutations in Best1 gene is an area of current development.¹⁷ Development of an intervention to prevent or slow macular atrophy would be a future therapeutic strategy. Low vision consultation is appropriate in cases where macular atrophy or a neovascular membrane is causing a reduction in best corrected vision to recommend magnifying aids and/or electronic aids to mitigate reduced vision.

CONCLUSION

In summary, Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD) is an uncommon retinal condition marked by the accumulation of yellowish deposits beneath the macula, often leading to misdiagnosis. This case highlights key aspects of the disease, including its clinical presentation, diagnostic approaches, and available treatment options. AOFVD remains challenging due to its variable progression and the limited therapies currently

available. Accurate identification of this disorder is necessary to prevent unnecessary interventions or patient worry around age-related macular degeneration. Continued research is essential to improve treatment outcomes and develop more effective strategies for managing this condition. Gene therapy holds promise as one method of future treatment but more research is needed to fully exploit this as an option.

Conflicts of Interest

No identifiable health information was included in this case report. The author has no conflict of interest.

Take Home Points

- Adult-onset Foveomacular Vitelliform Dystrophy (AOFVD) is a pattern dystrophy similar to Best disease but with a later onset and smaller lesions.
- AOFVD also resembles age-related macular degeneration (AMD) and retinal drusen.
- Vision loss is due to areas of macular atrophy confined to the location of the vitelliform lesion or the development of a choroidal neovascular membrane.
- AOFVD progresses through four distinct phases each with a different retinal appearance.

REFERENCES

1. Benson WE, Kolker AE, Enoch JM, Van Loo JA Jr, Honda Y. Best's vitelliform macular dystrophy. *Am J Ophthalmol*. 1975;79(1):59-66. doi:10.1016/0002-9394(75)90457-2
2. Dalvin LA, Pulido JS, Marmorstein AD. Vitelliform dystrophies: prevalence in Olmsted County, Minnesota, United States. *Ophthalmic Genet*. 2017;38(2):143-147. doi:10.1080/13816810.2016.1175645
3. Gass JD. A clinicopathologic study of a peculiar foveomacular dystrophy. *Trans Am Ophthalmol Soc*. 1974;72:139-156.
4. Renner AB, Tillack H, Kraus H, et al. Morphology and functional characteristics in adult vitelliform macular dystrophy. *Retina*. 2004;24(6):929-939. doi:10.1097/00006982-200412000-00014
5. Chowers I, Tiosano L, Audo I, Grunin M, Boon CJ. Adult-onset foveomacular vitelliform dystrophy: a fresh perspective. *Prog Retin Eye Res*. 2015;47:64-85. doi:10.1016/j.preteyeres.2015.02.001
6. Arnold JJ, Sarks JP, Killingsworth MC, Kettle EK, Sarks SH. Adult vitelliform macular degeneration: a clinicopathological study. *Eye (Lond)*. 2003;17(6):717-726. doi:10.1038/sj.eye.6700460
7. Kennedy CJ, Rakoczy PE, Constable IJ. Lipofuscin of the retinal pigment epithelium: a review. *Eye (Lond)*. 1995;9(6):763-771. doi:10.1038/eye.1995.192
8. Nipp GE, Lee T, Sarici K, Malek G, Hadziahmetovic M. Adult-onset foveomacular vitelliform dystrophy: epidemiology, pathophysiology, imaging, and prognosis. *Front Ophthalmol*. 2023;3. doi:10.3389/fopht.2023.1237788
9. Shmueli O, Lender R, Shwartz Y, Chowers I, Tiosano L. The pseudohypopyon stage in adult-onset foveomacular vitelliform dystrophy. *Int Ophthalmol*. 2023;43(9):3107-3113. doi:10.1007/s10792-023-02710-5
10. Kane Dickson V, Pedi L, Long SB. Structure and insights into the function of a Ca²⁺-activated Cl⁻ channel. *Nature*. 2014;516(7530):213-218. doi:10.1038/nature13913
11. Boon CJ, Klevering BJ, Leroy BP, Hoyng CB, Keunen JE, den Hollander AI. The spectrum of ocular phenotypes caused by mutations in the BEST1 gene. *Prog Retin Eye Res*. 2009;28(3):187-205. doi:10.1016/j.preteyeres.2009.04.002
12. Salido EM, Ramamurthy V. Proteoglycan IMPG2 shapes the interphotoreceptor matrix and modulates vision. *J Neurosci*. 2020;40(20):4059-4072. doi:10.1523/jneurosci.2994-19.2020
13. Iovino C, Ramtohl P, Au A, et al. Vitelliform maculopathy: diverse etiologies originating from one common pathway. *Surv Ophthalmol*. 2023;68(3):361-379. doi:10.1016/j.survophthal.2023.01.009
14. Freund KB, Laud K, Lima LH, Spaide RF, Zweifel S, Yannuzzi LA. Acquired vitelliform lesions: correlation of clinical findings and multiple imaging analyses. *Retina*. 2011;31(1):13-25. doi:10.1097/IAE.0b013e3181ea48ba
15. Nipp GE, Sarici K, Lee T, Hadziahmetovic M. Risk factors for worsening morphology and visual acuity in eyes with adult-onset foveomacular vitelliform dystrophy. *Ophthalmol Retina*. 2024;8(8):804-812. doi:10.1016/j.oret.2024.03.004
16. Wilde C, Awad M, Giannouladis K, et al. Natural course of adult-onset vitelliform lesions in eyes with and without comorbid subretinal drusenoid deposits. *Int Ophthalmol*. 2020;40(6):1501-1508. doi:10.1007/s10792-020-01319-2
17. Sinha D, et al. Human iPSC modeling reveals mutation-specific responses to gene therapy in a genotypically diverse dominant maculopathy. *Am J Hum Genet*. 2020;107(2):278-292.