THE **RETINA** PARTNERS

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Case of the Month – June 2021

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A 40 year-old asymptomatic male was referred for "macular degeneration" in both eyes. He had a personal history of moderate myopia and underwent LASIK refractive surgery 10 years prior. His vision was correctable to 20/20 in each eye, and intraocular pressures were within normal limits. Anterior segment examination was unremarkable. Color fundus photos, autofluorescence and OCT images are shown below.

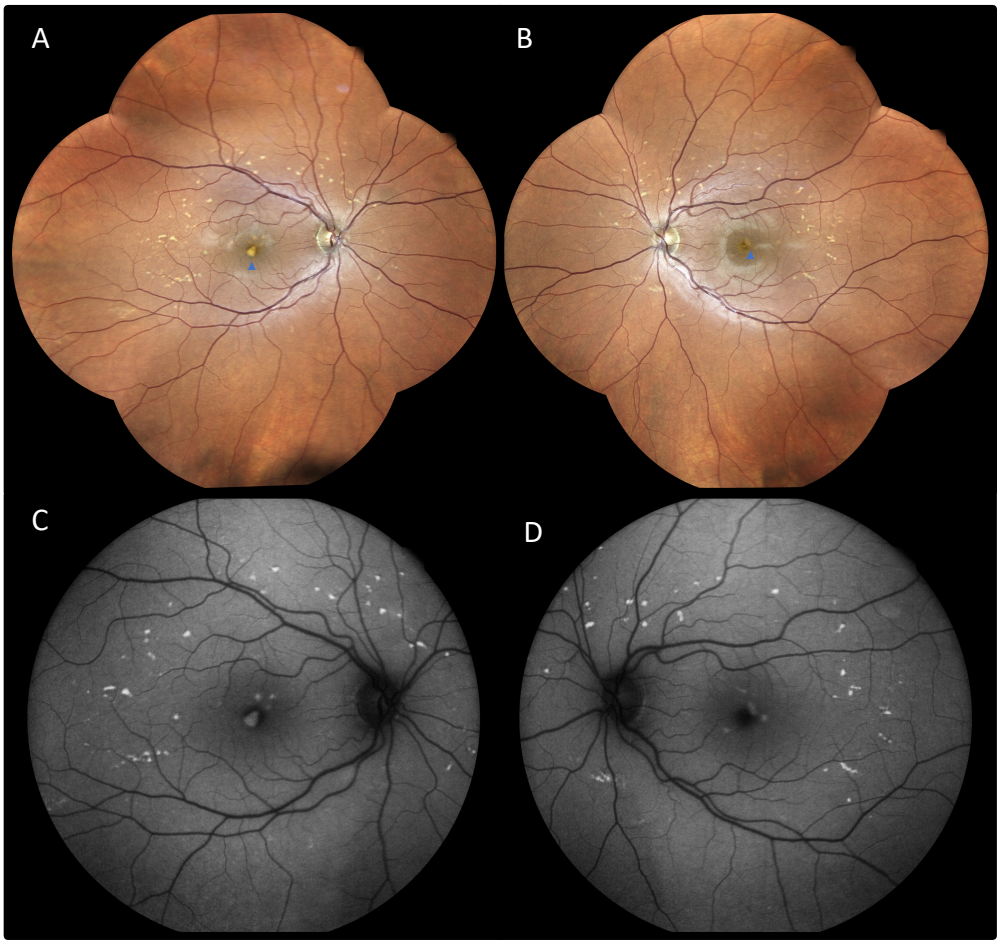

Figure 1: Color fundus photographs of the right (A) and left (B) eyes are remarkable for scattered yellow subretinal, fleck-like deposits scattered throughout the posterior pole and near periphery. The right eye has a prominent yellow lesion within the fovea, and the left eye shows a similar, though much less pronounced lesion (arrowheads). Autofluorescence images of the right (C) and left (D) eyes show hyperfluorescence of the central and more peripheral deposits.

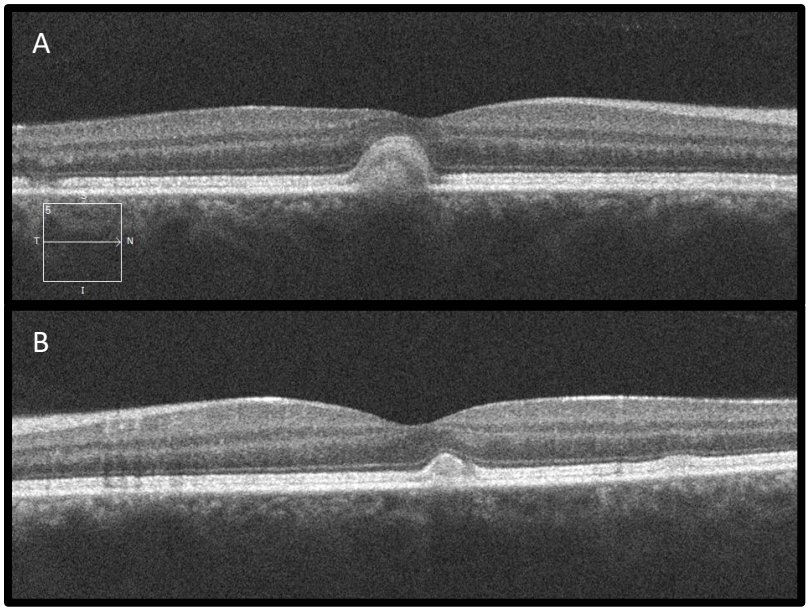

Figure 2: SD-OCT of the right (A) and left (B) eyes shows subfoveal hyper-reflective lesions predominantly located within the subretinal space. These are consistent with vitelliform deposits.

Differential Diagnosis: Stargardt Disease, Best's Disease, Autosomal Recessive Best's Disease, adult-onset foveomacular vitelliform dystrophy, multifocal pattern dystrophy simulating fundus flavimaculatus

Additional History: After examination, a more detailed family history was obtained. The patient endorsed a history of progressive vision loss in his father beginning in his 40's. His symptoms were predominantly nyctalopia with some component of central vision loss. The exact diagnosis was not known at the time of our consultation. The patient also believes that his paternal grandmother had similar vision problems.

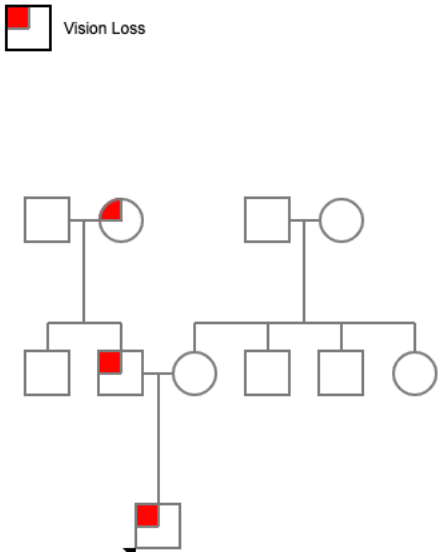

Figure 3: A pedigree constructed from the patient's family history shows three affected individuals (including the patient) in three successive generations. The trait affects both male and females. This suggests an autosomal dominant mode of inheritance.

Clinical Course: The examination, imaging and history was consistent with an inherited retinal dystrophy. Multifocal pattern dystrophy simulating fundus flavimaculatus, was high on the differential. After a long discussion regarding the benefits and drawbacks of genetic testing, we decided to go forward with testing which revealed a pathogenic mutation in peripherin-2 (PRPH2). The clinical presentation alongside of the confirmed mutation solidified the diagnosis of pattern dystrophy most consistent with multifocal pattern dystrophy simulating fundus flavimaculatus. The patient was referred for genetic counseling, and continues to be monitored under our care.

Discussion:
Pattern dystrophies represent a group of disorders characterized by yellow subretinal deposits and RPE clumps distributed throughout the posterior pole. Five subclassifications of pattern dystrophies exist – adult onset foveomacular vitelliform dystrophy (AOVMD), Sjogren reticular dystrophy, butterfly-shaped pattern dystrophy, fundus pulverulentus and multifocal pattern dystrophy simulating fundus flavimaculatus. These subclassifications are based upon the particular pattern of distribution of RPE change and subretinal deposits.

Pattern dystrophies are variable in presentation. Clinical findings usually manifest in the 3rd to 5th decade of life. Patients may complain of mild decrease in central vision, or, like our patient, be completely asymptomatic. Fortunately, the disease tends to progress slowly, with many patients remaining asymptomatic or mildly symptomatic for their entire lives. However, in some cases, late stages of pattern dystrophy may be indistinguishable from age related macular degeneration with up to 50% of patients developing atrophic macular lesions or choroidal neovascularization.

Pattern dystrophies are most frequently caused by mutations in the peripherin-2 gene (PRPH2), which encodes a structural transmembrane protein present on photoreceptor outer segments. Mutations in this gene (which was previously known as the RDS gene), are responsible for several retinal degenerative phenotypes including pattern dystrophy, cone-rod dystrophy, retinitis pigmentosa and central areolar chorioretinal dystrophy. These mutations are most frequently transmitted in an autosomal dominant inheritance pattern. However, mutations in PRPH2 display a significant variability in penetrance and phenotypic expression. The very same mutation may therefore cause very different disease in the same family. In our patient, a PRPH2 mutation caused a pattern dystrophy with no perceivable functional impact thus far. In contrast, the patient described significant night vision and central vision deficits in his father beginning at the same age. It is likely that his father was affected with a more severe phenotype, perhaps even retinitis pigmentosa caused by the same PRPH2 mutation.

The phenotypic variability can present challenges to making the diagnosis. Our patient's clinical appearance was most consistent with multifocal pattern dystrophy simulating fundus flavimaculatus. However, he also had central vitelliform deposits similar to what could be seen in adult-onset foveomacular vitelliform dystrophy or autosomal recessive Best's disease. The family history may also be misleading in that the same mutation can cause different symptoms in the same family. Fortunately, genetic testing is now widely available and may yield a definitive diagnosis. Information obtained from genetic testing can help patients understand their disease and its implication on their future and their family. Furthermore, while few treatments for hereditary retinal dystrophies currently exist, there are many ongoing clinical trials, and it is likely that specific therapies will slowly enter the marketplace in the coming decades. Knowing which genetic mutation a patient carries unlocks the ability to participate in clinical trials or receive a targeted genetic therapy when available.

However, the decision to pursue genetic testing may not always be straight forward. First, patients must understand that our knowledge of the genetics of retinal disease is rapidly evolving. A test is not a guarantee of a diagnosis since there are undoubtedly many disease causing genetic variants which are yet to be identified. Even when a causative mutation is found, knowing the specific genetic mutation is not a crystal ball since the same gene can express itself in different ways in different people. Furthermore, since very few targetted treatments are currently available, some clinicians argue that there is little practical value in testing. Finally, some worry that genetic information could be used to discriminate against individuals. This sounds far-fetched,

but until the 2008 passage of the Genetic Information Nondiscrimination Act (GINA), health insurance companies could use genetic information to deny coverage, and even now, GINA does not apply to life insurance, disability insurance or long term care insurance coverage. Ultimately, the decision to pursue genetic testing is a personal one which should be explored with the help of the clinician when hereditary disease is suspected.

Take Home Points

- Pattern dystrophies are a set of inherited retinal degenerations most frequently caused by autosomal dominant mutations in the PRPH2 gene
- The disease manifests in the 3rd to 5th decade of life with subretinal yellow deposits and pigmentary changes in the posterior pole
- Vision loss from pattern dystrophy tends to be mild and slowly progressive, but up to 50% of affected individuals may eventually develop secondary CNVM or macular atrophy
- Genetic testing for inherited retinal degenerations is widely available and may give a definitive diagnosis. However, the potential benefits and drawbacks should be discussed prior to testing.

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