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Stargardt Disease

Stargardt disease is the most prevalent inherited macular dystrophy in both adults and children often associated with a mutation in the ATP-binding cassette A4 (ABCA4) gene found on chromosome 1. The prevalence ranges from 1 in 8000 to 10,000 and most commonly has an autosomal recessive mode of inheritance. Autosomal dominant forms of Stargardt disease exist with mutations found in PRPH2, ELOVL4 and PROM1 genes.¹

Clinical Presentation

Patients present with bilateral central visual loss with complaints of dyschromatopsia (difficulty with color vision) and central scotomas. Disease onset is triphasic, most commonly in childhood, next occurring in early adulthood, and least likely in later adulthood. The later the disease onset, the better the general prognosis. The initial fundus exam may only show mild retinal abnormalities such as a blunting of the foveal light reflex or mild retinal pigment epithelium (RPE) abnormalities. The diagnosis of Stargardt disease can be delayed as a result of these mild findings unless additional retinal imaging is pursued, including fundus autofluorescence (FAF) or optical coherence tomography (OCT).

Clinical Exam, Multimodal Imaging, and Functional tests

Atrophic appearing lesions within the macula become prominent and are associated with decreased central vision. Macular atrophy can present in conjunction with yellow-white lesions at the level of the RPE, referred to as pisciform (fish-like) flecks (Figure 1). These flecks are a result of excessive accumulation of lipofuscin in the RPE.² Lipofuscin is a mix of lipid, protein, and fluorescent visual fluorophores such as A2E which can be hyper-autofluorescent on FAF. The macular atrophy will manifest as dark, hypo-autofluorescent lesion on the FAF which may not be overtly visible on fundus exam (Figure 2). This hypo-autofluorescence may appear as a bull's eye and therefore Stargardt Disease should be on the differential for bull's eye maculopathy. OCT demonstrates atrophy of the outer retina, including loss of the photoreceptor layers with collapse of the normal retinal architecture (Figure 3). Fluorescein angiography demonstrates a characteristic 'dark choroid' (Figure 4) while the pisciform flecks will be hyperfluorescent.¹

Electroretinograms (ERG) may be performed to help determine prognosis for these patients. Three groups of patients have been isolated with regards to ERG-testing: 1) those with macular dysfunction with normal full-field ERG, 2) those with isolated cone dysfunction with normal rod function, and 3) those with both cone and rod dysfunction. Patients that fall under the first category were found to have the best prognosis, while those with frank cone, or combined cone and rod dysfunction were found to have worse visual prognosis.³

Genetic Testing

Genetic testing can be offered to patients when an inherited retinal degeneration may be suspected. Our offices currently utilize the Invitae panel of 293 genes to evaluate for an underlying mutation that may lead to a retinal degeneration, including Stargardt disease. Despite this testing, not all mutations are known, and therefore not all pathogenic variants may be identified. The patient provides a saliva specimen which is sent to the laboratory and a detailed report is provided listing the various mutations from the genes that were tested. The patient's genes are compared to those in the database and any differences between the two will be listed. Although there may be many identified mutations, this data must be clinically correlated as many mutations may not be clinically relevant or pathologic. The patient has access to a genetic counselor through Invitae where additional information can be provided on whether other family members should be tested as well as discussing reproductive ramifications if the patient chooses to have biologic children in the future.

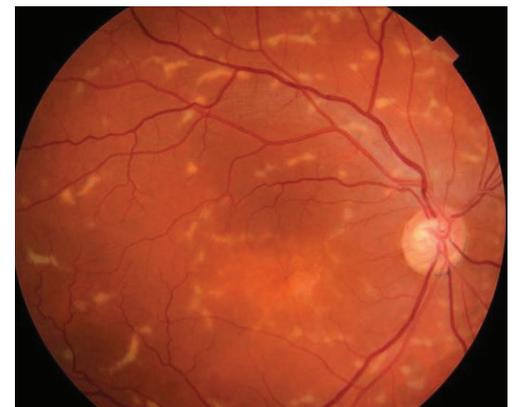


Figure 1:
Fundus photograph with scattered yellow pisciform flecks

Case 1

A 46-year-old white male presents with a several month history of decreased vision. He denies nyctalopia, dyschromatopsia, hemeralopia, or family history of vision loss. Visual acuity measured 20/80 OD and 20/160 OS with normal intraocular pressure. Anterior segment was normal. Posterior segment and multimodal imaging (Figures 1-4) demonstrate findings consistent with Stargardt disease. The patient underwent genetic testing and was found to have a single mutation in ABCA4 among other mutations on his genetic report. This patient was deemed to have Stargardt disease, however with an unknown second mutation resulting in the Stargardt phenotype. The patient declined additional full gene sequencing to identify the second mutation as it was unlikely to change the management for his condition.

Case 2

A 16-year-old white male presents with a two week history of vision loss. The patient denies nyctalopia, hemeralopia and dyschromatopsia and there is no family history of vision loss. Vision measured at 20/160 OD and 20/40 OS. Anterior segment exam was normal with the findings of pisciform flecks on posterior segment exam (Figure 5). Fundus autofluorescence demonstrated mixed hypo and hyper-autofluorescence throughout the posterior pole with central macular hypo-autofluorescence consistent with macular atrophy (Figure 6). OCT demonstrated significant outer retinal thinning within the subfoveal area (Figure 7). ERG testing demonstrated both rod and cone dysfunction indicating a likely poor prognosis. The patient underwent genetic testing and was found to have two mutations in the ABCA4 gene, confirming a diagnosis of Stargardt disease.

Treatment Horizon

Several investigations are underway to identify potential treatment options for patients with Stargardt disease, however none are approved by the US Food and Drug Administration. A clinical trial based out of the United Kingdom attempted to transplant human embryonic stem cells derived from the RPE into the subretinal space however was found to be of limited benefit to patient's vision.⁴ As of May 2021, several phase II and III studies are underway in hopes to reduce rate of progression of macular atrophy compared to placebo (emixustat in phase III by Acucela, ALK-001 in phase II by Alkeus and Zimura in phase II by Iveric Bio).⁵ Many of these investigational products aim to reduce the toxicity of A2E and other byproducts found in the retina to reduce progression of atrophy.

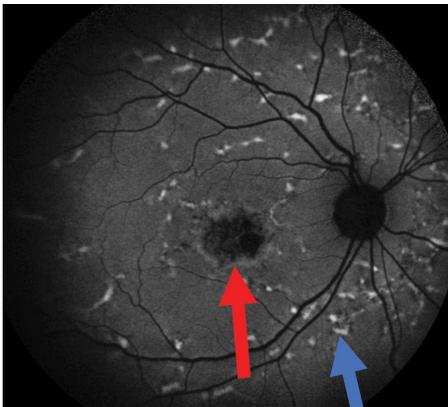


Figure 2:

Fundus autofluorescence demonstrating central macular atrophy (red arrow) and hyper-autofluorescent pisciform flecks (blue arrow)

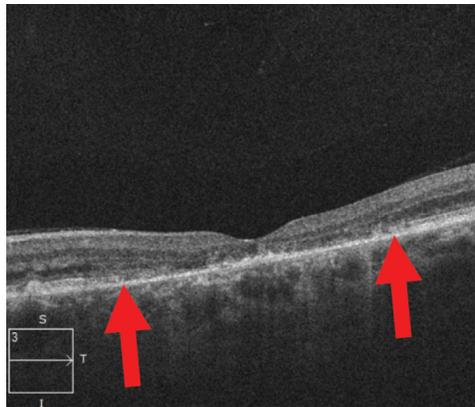


Figure 3:

Loss of ellipsoid layer and outer retinal thinning between the red arrows



Figure 4:

Dark choroid on fluorescein angiography with hyperfluorescent flecks

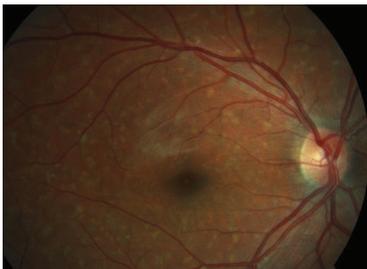


Figure 5:

Fundus photos

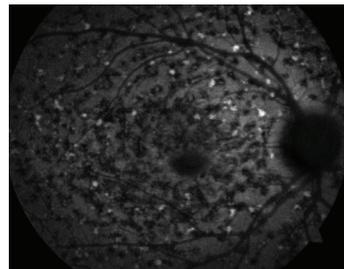
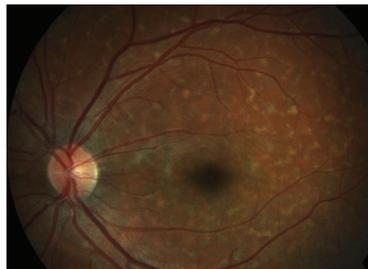
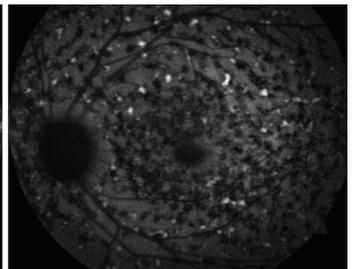


Figure 6:

Autofluorescence images



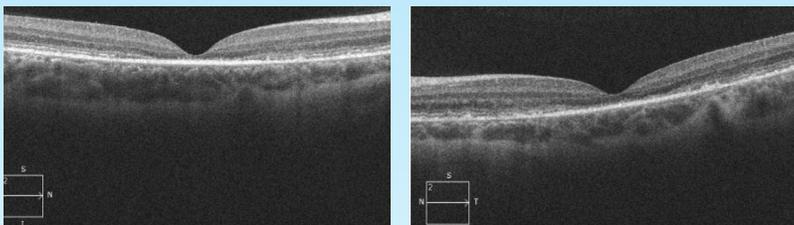


Figure 7:
OCT images

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5. Oakl FFBP-5555 6925, Road M, #701, et al. Stargardt Disease Research Advances. Foundation Fighting Blindness. Accessed April 29, 2021. <https://www.fightingblindness.org/research/stargardt-disease-research-advances-6>

Online Appointment Booking Now Available *at* NJRetina



We are pleased to announce that all our NJ Retina offices now offer an option for patients to schedule an appointment online. Patients can schedule their appointment with one of our physicians in real time by simply visiting our website, selecting an office and the physician they would like to see. It's a great way for us to improve access to care by making it easier, faster, and more convenient for patients to schedule an appointment.

At the forefront of clinical research

NJRetina continuously conducts clinical trials at key locations. Our clinical research coordinators will be happy to discuss the inclusion/ exclusion criteria or any other aspect of these studies with you or your patients. If you have any questions, please feel free to contact:

Joe Martinez - [Teaneck: 201-837-7300](tel:201-837-7300)

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Enrolling Studies:

Dry AMD

[Vauxhall](#)

GTSCOPE: A Study of Disease Progression in Genetically Defined Subjects With Geographic Atrophy Secondary to Age-Related Macular Degeneration

[Teaneck](#)

Catalina: A Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled Study of the Safety and Efficacy of Intravitreal Injections of NGM621 in Subjects with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

[Teaneck and Toms River](#)

Gallego: A phase II, multicenter, randomized, single-masked, sham-controlled study to assess safety, tolerability, and efficacy of intravitreal injections of FHTR2163 in patients with geographic atrophy secondary to age-related macular degeneration (Gallego)

Wet AMD

[Edison](#)

Pulsar: Randomized, Double-Masked, Active-Controlled Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration

Diabetic Macular Edema (DME)

[Teaneck](#)

Gleam: A prospective, randomized, double-masked, active comparator-controlled, multi-center, two- arm, phase 3 study to evaluate the efficacy and safety of intravitreal KSI-301 compared with intravitreal aflibercept in participants with visual impairment secondary to treatment- naive diabetic macular edema.

Diabetic Retinopathy

[Teaneck](#)

Pavilion: A Phase III, Multicenter, Randomized Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Diabetic Retinopathy

[Teaneck](#)

Altitude: A Phase 2, Randomized, Dose-escalation, Observation-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of RGX-314 Gene Therapy Delivered via One or Two Suprachoroidal Space (SCS) Injections in Participants with Diabetic Retinopathy (DR) Without Center Involved-Diabetic Macular Edema (CI-DME) (ALTITUDE)

Soon to Enroll Studies:

Retinal Vein Occlusion

• **Balaton:** A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-controlled Study To Evaluate The Efficacy And Safety Of Faricimab In Patients With Macular Edema Secondary To Branch Retinal Vein Occlusion – Toms River

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