Published in final edited form as:

Am J Ophthalmol. 2018 April ; 188: 104–110. doi:10.1016/j.ajo.2017.12.011.

Peripheral pigmented retinal lesions in Stargardt disease

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Abstract

Purpose—To investigate the prevalence of peripheral pigmented retinal lesions and associated clinical findings in patients with Stargardt disease.

Design—Retrospective case series.

Methods—Records at a single academic institution were reviewed for patients with genetically confirmed Stargardt disease with peripheral pigmented retinal lesions on wide-field retinal imaging. For this cohort we described demographics, clinical features, and pathogenic variants.

Results—Out of 62 patients with Stargardt disease and wide-field retinal imaging, 14 had peripheral pigmented retinal lesions. These flat, subretinal lesions were located in the mid or far periphery and had well-defined borders, resembling CHRPE lesions. For this group of 14 patients, median age at initial diagnosis of Stargardt disease was 9.5 years, and the median duration of disease was 21.5 years. Median Snellen visual acuity was 20/200, and median central scotoma size was 20.0 degrees. All 14 patients had electroretinographic abnormalities. 4 out of 14 patients developed new lesions during clinical follow-up.

Conclusions—Wide-field retinal imaging revealed the presence of peripheral pigmented retinal lesions resembling CHRPE lesions in a subset of patients with genetically confirmed Stargardt disease. Presence of these lesions may be associated with severe phenotypes of the disease.

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The authors have no proprietary or commercial interest in any material discussed in this manuscript.

Stargardt disease (STGD1) is the most common inherited juvenile-onset macular dystrophy and is caused by pathogenic variants in the *ABCA4* gene. STGD1 predominantly affects the macula, leading to loss of central vision.^{1,2} There is significant phenotypic heterogeneity, and peripheral retinal changes may also be observed, such as pisciform flecks and retinal pigment epithelium (RPE) atrophy.³ Flecks may appear early in the course of disease and have been shown to progress over time by expanding outward from the fovea in a centrifugal pattern.⁴ RPE atrophy first occurs in the macula, but in later stages of disease atrophy can also develop outside the fovea with sparing of the peripapillary region.⁵ Other changes have been observed in individual patients but not well characterized, such as focal areas of fundus hyperpigmentation.^{6,7}

Fundus photography and fundus autofluorescence (FAF) have proven valuable in diagnosis and monitoring of STGD1, but these modalities are mostly used with 30- or 50-degree field imaging, limiting evaluation to the posterior pole. In the past decade, the development of ultra wide-field imaging has allowed more detailed study of the peripheral retina in a variety of diseases, including inherited degenerations such as gyrate atrophy and retinitis pigmentosa (RP).^{8–10} Recently, Klufas, *et al.*, showed that the majority of patients with STGD1 have changes in the peripheral retina on ultra wide-field autofluorescence (WF-FAF).¹¹

In this study, we describe the phenotype of a subset of patients with genetically confirmed STGD1 who have peripheral pigmented retinal lesions resembling CHRPE on wide-field fundus photography (WF-P) and wide-field fundus autofluorescence (WF-FAF). We evaluated their clinical characteristics in the context of their *ABCA4* pathogenic variants.

Methods

A retrospective chart review was performed on patients with both clinical and genetic diagnosis of STGD1. Clinical diagnoses were established by the presence of central visual dysfunction and bilateral macular atrophy, with or without surrounding flecks on fundus exam, by a retinal dystrophy specialist at the University of Michigan Kellogg Eye Center (J.R.H or T.J.). Genetic diagnosis was established by the presence of two or more variants in the *ABCA4* gene that were classified by the clinical genetic testing laboratory and/or *in silico* tools as either definitively or likely pathogenic. Genetic testing was performed as part of routine clinical care through commercial testing labs, the eyeGENE research project, or other collaborative research studies. For patients on whom segregation analysis was performed, variants were demonstrated to be *in trans*. The University of Michigan Institutional Review Board prospectively granted approval for this retrospective chart review.

We included patients with WF-P and WF-FAF, defined as either Optos 200-degree retinal imaging (Optos 200Tx, Optos PLC, Dunfermline, United Kingdom) or composites of 50-degree fundus photographs. Patients were excluded if they had any history of eye trauma or other concurrent eye disease affecting the fundus, visual acuity, or visual fields. WF-P and WF-FAF were reviewed according to a previously used classification scheme that is summarized here.^{7,11} After reviewing the patient demographics and finding that 13 out of 14 (93%) patients were under the age of 13 at initial onset of symptoms, we chose to use a

classification scheme that has previously been used for childhood-onset STGD1.⁷ For WF-P: grade 1, normal fundus; grade 2, macular and/or peripheral flecks (flecks outside the vascular arcades) in the absence of central atrophy; grade 3a, central atrophy without flecks; grade 3b, central atrophy with macular and/or peripheral flecks; grade 3c, paracentral atrophy only with macular and/or peripheral flecks in the absence of central atrophy; grade 4, multiple extensive atrophic changes of the RPE extending beyond the vascular arcades. For WF-FAF: type 1, central atrophy confined to the posterior pole with or without flecks confined to the posterior pole; type 2, central atrophy with flecks only extending outside the posterior pole; type 3, central atrophy with peripheral atrophy and flecks extending outside the posterior pole.

Age of onset (estimated by the age when patients first noticed visual impairment), disease duration (estimated by the time between age of onset and the date when imaging was acquired), Snellen visual acuity, and the size of scotoma on Goldmann visual field testing were recorded. Full-field electroretinogram (ffERG) studies were obtained at the first clinical visit following the International Society for Clinical Electrophysiology of Vision guidelines. Based on the ffERG responses, patients were classified into group 1 (normal ERG), group 2 (reduced photopic responses with normal scotopic responses), or group 3 (reduced scotopic and photopic responses).² Clinical characteristics were reported as counts, percentages, and median values with ranges.

Results

Patient Characteristics

Sixty-two patients met inclusion criteria and 14 (23%) showed peripheral pigmented retinal lesions. Five out of 14 (36%) patients were male, and the median age of first symptom onset was 9.5 years of age (range 7 – 28). Median duration of disease was 21.5 years (range 7 – 46). Of 14 patients, 13 (93%) were diagnosed with STGD1 at age 13 or younger. Median visual acuity was 20/200 (range 20/40 – counting fingers). Thirteen out of 14 (93%) had visual acuity worse than 20/100 in the better eye. Median size of central scotoma was 20.0 degrees (range 0 – 39). Eight out of 14 (57%) patients had a grade 3b fundus appearance, and 6 (43%) had a grade 4 fundus appearance. All patients had pisciform flecks extending outside of the vascular arcades. Six out of 14 (43%) had a type 2 FAF pattern, and 8 (57%) had a type 3 FAF pattern. All 14 patients had abnormal ffERG findings. Eleven (79%) patients presented with combined cone and rod dysfunction, and 3 (21%) patients presented with cone dysfunction only. Demographic and clinical characteristics of the 14 patients are shown in Table 1.

Genetic Variants

Figure 1 shows the pathogenic variants and their respective locations on the *ABCA4* gene for the 14 patients with peripheral pigmented retinal lesions. Ten (71%) patients had 2 pathogenic variants, 3 (21%) patients had 3 pathogenic variants, and 1 (7%) patient had 4 pathogenic variants. Among the 33 total detected variants, there were 23 (69%) missense variants, 8 (24%) splice site defects, and 2 (6%) nonsense variants. Three of the patients were siblings, and each had the p.A1773V missense mutation and the intronic variant c.

5461-10T>C. There were also 2 additional patients with the c.5461-10T>C intronic variant who were not related.

Lesion Characteristics

Representative images of the peripheral pigmented retinal lesions are shown in ultra wide-field photographs in Figure 2. All peripheral pigmented retinal lesions were flat, varied in size, and appeared in the mid to far periphery, resembling congenital hypertrophy of retinal pigment epithelium (CHRPE). All 14 patients had lesions with irregular but sharp borders. Seven (50%) patients had lesions containing retinal flecks, and 7 (50%) had lesions with a hypopigmented halo. Ten (71%) patients had lesions containing areas that were non-pigmented. WF-FAF imaging was available for all 14 patients. On WF-FAF, 11 (79%) of patients had lesions that were heterogeneously hypoautofluorescent. Lesions were unilateral in 8 (57%) patients. Follow-up images were available for 9 patients, and in 4 of those patients, (44%) development of new lesions was observed. Figure 3 and Figure 4 show development of new lesions in two different patients during clinical follow-up. The patient eye shown in Figure 3 initially had pigmented lesions in the temporal, inferior, and inferonasal periphery at age 14. Two years later, new lesions developed in the temporal and inferotemporal periphery. The lesion in the temporal periphery appears hyperautofluorescent compared with most other lesions observed in the cohort of 14 patients. The patient eye shown in Figure 4 initially had a pigmented lesion in the superotemporal macula at age 12. Two years later, a second lesion developed in the superotemporal periphery along the border of advancing retinal flecks. Out of these 4 patients with documented lesion development, 2 were siblings with identical pathogenic variants, and the others were not genetically related.

Discussion

Peripheral pigmented retinal lesions resembling atypical CHRPE lesions in patients with STGD1 have not previously been characterized. We described the phenotypic characteristics of these patients with lesions that may be mistaken for CHRPE, and also show the emergence and growth of lesions.

Patients with peripheral pigmented lesions had markedly decreased visual acuity, large central scotomas, abnormal fERGs, and widespread involvement of the peripheral retina on WF-P and FAF. The spectrum of phenotypes for STGD1 is broad, ranging from mild macular changes to severe degeneration involving the peripheral retina.³ While there are few published longitudinal studies of STGD1, the existing literature shows that retinal changes and loss of visual function both begin in the macula and then progress outward in a centrifugal pattern.^{4,12,13} Photographic and functional evidence of progression is also accompanied by progressive electrophysiologic dysfunction. Patients with peripheral pigmented retinal lesions all had WF-P and FAF patterns and fERG changes consistent with progression to an advanced form of STGD1. Of note, patients enrolled in the ProgStar study had milder stages of STGD1 because the study excluded patients with large areas of RPE atrophy.¹⁴ We observed pigmented lesions developing along the border of advancing peripheral retinal flecks, suggesting that these lesions only develop after the disease progresses to involve the peripheral retina. Development of peripheral pigmentation has

been previously described in the natural history of other retinal dystrophies caused by pathogenic variants in *ABCA4*, including RP and cone-rod dystrophy.^{15,16} The lesions shown here have a different morphology compared to the bone-spicule and patchy hyperpigmentation that can appear in *ABCA4*-associated RP and cone-rod dystrophy. Further studies with wide-field imaging will be needed to determine whether peripheral pigmented lesions with the morphology described here can also be found in other *ABCA4*-associated retinal dystrophies.

The peripheral pigmented retinal lesions described in this study resemble CHRPE, although some characteristics of the lesions were atypical for CHRPE. Lesions were acquired in nature, lesion borders appeared more irregular, and the lesions contained pisciform flecks. A majority of lesions had a heterogeneous pigmentation pattern. Typical CHRPE are congenital, have smooth, well-defined borders, and are darkly pigmented, except where lacunae are present (Figure S1).¹⁷ We found that a subgroup of patients with STGD1 have CHRPE-like lesions. These lesions should not be mistaken for true CHRPE lesions, which have a prevalence of 1.2% in the general population.¹⁸ There is a known association between mutations on the *APC* gene causing familial adenomatous polyposis and development of multiple bilateral CHRPE-like lesions, often with a hypopigmented comet tail.¹⁹ However, none of the 14 patients with STGD1 had a known diagnosis of familial adenomatous polyposis. The presence of pigmented lesions in a STGD1 patient was previously described by Fujinami, *et al.* in a 15 year-old patient, but those lesions were observed in the posterior pole.⁷ Histologically, true CHRPE lesions contain enlarged RPE cells with large, densely packed melanosomes.²⁰

We observed lesions developing along the border of advancing retinal flecks, suggesting that lesion development is linked to the natural history of STGD1. One patient (Figure 3) had a predominantly hyperautofluorescent lesion emerge at a follow-up visit, suggesting that lesions may have a hyperautofluorescent phase preceding the hypoautofluorescent state. FAF abnormalities in STGD1 have been previously characterized for the posterior pole. The ProgStar study has shown that flecks expand centrifugally outward from the macula, and that each fleck reaches a peak hyperautofluorescence before becoming progressively more hypoautofluorescent.^{21,22} Hyperautofluorescence is initially observed due to accumulation of lipofuscin containing the toxic metabolite A2E and other fluorophores³. After reaching peak hyperautofluorescence, flecks become progressively more hypoautofluorescent due to RPE cell death. Peripheral pigmented lesions appear at the expanding edge of flecks and are predominantly hypoautofluorescent, containing hyperautofluorescent foci corresponding to flecks and lacunae. True CHRPE lesions are hypoautofluorescent due to lack of lipofuscin.²³ We therefore hypothesize that there is decreased lipofuscin production or accumulation within these lesions, either due to RPE loss of function and/or metaplasia, or due to RPE cell death and release of pigment into the subretinal space. One case report showed examples of subretinal fibrosis in STGD1, suggesting that under some circumstances, RPE cells do undergo epithelial-mesenchymal transition in STGD1 while retaining variable amounts of pigment.²⁴ It is not clear whether peripheral pigmented lesions are a separate entity from subretinal fibrosis, or whether they may be a precursor to subretinal fibrosis.

The most frequent pathogenic variants in patients with peripheral pigmented retinal lesions were the missense mutations p.A1038V and p.A1773V, and the splice site defect c.5461-10T>C. p.A1038V causes retention of protein in the photoreceptor inner segment and absence of *ABCA4* activity.²⁵ p.A1773V is a known founder variant in Mexican patients and was present in 3 Mexican descendent siblings in this study.²⁶ c.5461-10T>C is the third-most frequent variant overall and causes exon skipping leading to protein truncation and complete absence of *ABCA4* activity. c.5461-10T>C is associated with rapidly progressive disease.²⁷ Due to small sample size and also to the high number of variants described in STGD1, we cannot definitively attribute lesion development to any specific pathogenic variants.

In this study, we described peripheral pigmented retinal lesions and associated clinical findings in a proportion of patients with clinical and genetic diagnoses of STGD1. Clinicians and researchers should be aware that CHRPE-like lesions may develop in patients with STGD1, and that these STGD1-associated lesions do not appear to be related to the CHRPE-like lesions associated with familial adenomatous polyposis. We anticipate that with increasing use of wide-field fundus imaging, longitudinal data from the ProgStar prospective cohort study, and implementation of wide-field optical coherence tomography, additional observations on the natural history and significance of these peripheral pigmented retinal lesions will be possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Foundation Fighting Blindness CF-CL-0616-0698-UMICH grant awarded to M.F.A., and the National Institutes of Health K23 EY026985 grant awarded to T.J. The authors would like to thank Trudy Kukuk, David Murrel, and Tim Olsen for their assistance with preparing ophthalmic images for publication, Mark Johnson and Cagri Besirli for generously providing the images for supplemental figure S1, and Victor Elner for his insightful comments.

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Domain numbering based on Tsybovsky and Palczewski, 2014

Figure 1.

Location of 33 *ABCA4* pathogenic variants in 14 patients with peripheral pigmented retinal lesions.

Figure 2.

Ultra wide-field Optos fundus imaging showing peripheral pigmented retinal lesions. *Top left*, multiple confluent pigmented lesions along the advancing border of peripheral retinal flecks in a 30 year-old. *Top right*, geographic pigmented lesion in an 18 year-old. A second stellate shaped lesion is visible in the far inferotemporal periphery. *Bottom left*, single pigmented lesion in a 15 year-old. *Bottom right*, ovoid pigmented lesion in the inferotemporal periphery of a 16 year-old.

Figure 3.

Development of two pigmented lesions over time in a 14 year-old. *Top left and bottom left*, wide-field fundus photographs and wide-field fundus autofluorescence showing the pigmented lesions (black arrows) in the temporal and inferior periphery. *Top right and bottom right*, photographs of the same patient at two-year follow-up showing development of two new lesions (white arrows), including one temporally that is predominantly hyperautofluorescent with a hypoautofluorescent center.

Figure 4.

Development of a pigmented lesion in a 12 year-old. *Top left and bottom left*, wide-field fundus photographs and wide-field fundus autofluorescence showing a flat, pigmented lesion in the superotemporal retina (black arrow) and diffuse retinal flecks extending past the vascular arcades. *Top right and bottom right*, photographs of the same patient eye at two-year follow-up showing development of a new lesion (white arrow) with expansion of surrounding peripheral retinal flecks.

Table 1

Individual characteristics of the 14 patients with peripheral pigmented retinal lesions

#	Gender	Age of Onset	Disease Duration (years)	Visual Acuity	Size of Central Scotoma (degrees)	Color Grade	FAF Type	ERG Group
1	F	10	20	20/150	16	3b	2	2
2	M	11	20	20/250	21	4	3	3
3	F	13	32	20/500	18.5	4	3	3
4	F	7	7	20/100	21	3b	2	3
5	M	9	7	20/150	31	3b	3	3
6	F	10	8	20/200	5	3b	2	2
7	F	11	46	20/150	18	4	3	3
8	M	8	29	20/400	22	4	3	3
9	F	7	15	20/200	11.5	3b	2	2
10	M	9	23	20/400	25	3b	2	3
11	F	10	24	20/1000	30	3b	3	3
12	F	9	44	20/200	33.5	4	3	3
13	M	28	41	20/40	0	4	3	3
14	F	7	9	20/150	19.5	3b	2	3

* Visual acuity and central scotoma were recorded for the eye with better visual acuity. If both eyes had equal visual acuity with different central scotoma sizes, the scotoma sizes were averaged.