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BETA-PERIPAPILLARY ATROPHY AND GEOGRAPHIC ATROPHY IN THE COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENTS TRIALS

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Purpose: To determine associations between beta-peripapillary atrophy (B-PPA) and incidence and growth of geographic atrophy (GA) in eyes treated with anti–vascular endothelial growth factor agents in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Methods: We included 245 cases with incident GA and 245 controls matched by baseline demographics and characteristics associated with development of GA in the CATT. Baseline color images were graded for the type of B-PPA, defined as presence of hypopigmentation with visible choroidal vessels and sclera that is adjacent to the optic disk. Beta-peripapillary atrophy was further classified as scleral ring, sclera, sclera/choroidal blood vessels, or combination. Areas of each type of B-PPA and the circumferential extent of B-PPA were measured.

Results: Beta-peripapillary atrophy was present in 58% of eyes developing GA and in 52% without GA ($P = 0.17$). The greater circumferential extent of sclera/choroidal blood vessels B-PPA in relation to the optic disk was associated with incident GA ($P = 0.02$) and the GA size at first observation ($P = 0.047$). Beta-peripapillary atrophy was not associated with GA growth rates ($P > 0.05$). Patients without B-PPA had a higher number of GA-associated risk alleles of *ARMS2* ($P = 0.0003$) and *HTRA1* ($P = 0.001$).

Conclusion: The extent of sclera/choroidal blood vessel B-PPA was associated with the GA incidence and size but not with the growth rate in eyes treated for neovascular age-related macular degeneration. Beta-peripapillary atrophy and GA may share some common pathophysiologic pathways unrelated to the GA-associated risk alleles evaluated.

RETINA 41:125–134, 2021

Peripapillary atrophy (PPA) can be detected on clinical examination, has been defined using several imaging modalities, and is associated with several clinical conditions, most commonly myopia and glaucoma.[1,2] Several subtypes of PPA have been described. Alpha-PPA is an irregular retinal pigment epithelium (RPE) hyperpigmentation or hypopigmentation that is farther away from the optic nerve than beta-PPA (B-PPA), which is itself characterized by hypopigmentation with visible choroidal vessels and sclera that is adjacent to the disk.[3] Gamma-PPA is B-PPA but without the presence of the RPE or Bruch membrane (BM)[4] as assessed through optical coherence tomography (OCT).[5] Furthermore, "delta zone" has been defined as part of gamma-PPA where blood vessels are >50 μm in diameter and <300 μm in length.[5]

Depending on the patient population and ocular pathology, alpha-PPA may be present in up to 100% of eyes and B-PPA in up to 75% to 80% of eyes.[6,7] Several studies have focused on changes in the PPA area and morphology over the course of time.[8] For example, B-PPA has been found to expand on the order of 10 μm^2/year[9] and is associated with increasing age.[10]

Typical OCT-defined characteristics in the area subtending B-PPA include a preserved retinal nerve fiber layer (RNFL), RPE and photoreceptor loss, RPE disruption, and inner/outer retinal thinning.[11,12] Other findings may include a RNFL plaque, intraretinal cystoid changes, and abnormal retinal sloping. Progressive outer retinal/RPE/BM changes are characteristic of geographic atrophy (GA) as well.[13]

Several previous studies explored the relationship between B-PPA, choroidal thickness, pseudodrusen, and age-related macular degeneration (AMD).[14–17] For example, presence of broad B-PPA was associated with AMD; however, age may have been a confounding variable.[17] In another study, B-PPA was associated with reticular pseudodrusen in early AMD, although the relationship was attenuated when subfoveal choroidal thickness was taken into account.[14] Using data from the Geographic Atrophy Progression (GAP) study, Chang et al[18] showed that PPA (type not defined) was identified at presentation in 86.4% of eyes with macular GA. However, we are unaware of any studies analyzing the relationship between B-PPA and GA, in particular, in eyes with neovascular AMD treated with anti–vascular endothelial growth factor (anti-VEGF) agents. Based on the above data, we surmised that there might be an association between B-PPA and GA. To test this hypothesis, we investigated the relationship between B-PPA at baseline and development of GA during five years in the study eyes with anti-VEGF treatment for neovascular AMD in the Comparison of AMD Treatments Trials (CATT).

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Supported by cooperative agreements U10 EY017823, U10 EY017825, U10 EY017826, and U10 EY017828 from the National Eye Institute, National Institutes of Health, and Department of Health and Human Services. Supported by the Heed Ophthalmic Foundation. ClinicalTrials.gov number, NCT00593450.

No conflicting relationships or proprietary interests exist for any author as it pertains to the current manuscript. The following commercial relationships include: A. M. Kolomeyer is a consultant to Alimera Sciences and Allergan. B. J. Kim is a consultant to Allergan, Synergy Research, Inc, and Apellis Pharmaceuticals. G.-S. Ying is a biostatistical consultant for Chengdu Kanghong Biotechnology Co Ltd, Ziemer Ophthalmic Systems AG, Synergy Research, Inc, and Apellis Pharmaceuticals. M. G. Maguire serves on data and safety monitoring committees for Genentech-Roche.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

A full listing of the CATT Research Group in the supplemental appendix, http://links.lww.com/IAE/B225.

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Methods

Comparison of Age-Related Macular Degeneration Treatments Trials Study Population

This is a secondary analysis of the data from the CATT study. Design, methods, study population, treatment, and outcomes for CATT during five years of follow-up have been previously published.[19–21] Eligibility criteria for the trial included presence of neovascular AMD as evidenced by leakage on fluorescein angiography and fluid on OCT, visual acuity between 20/25 and 20/320, and no previous treatment for the neovascularization. Study eyes were randomly assigned to treatment with either intravitreal ranibizumab or bevacizumab and to one of three treatment regimens as follows: monthly treatment for two years, pro re nata treatment for two years, or monthly treatment for one year and pro re nata treatment for the second year. The study was approved by institutional review boards at each center and was Health Insurance Portability and Accountability Act compliant. The study is registered on http://www.clinicaltrials.gov (no. NCT00593450, accessed July 24, 2018).

Selected Patient Population

To assess the association between B-PPA at baseline with incident GA during five years in the study eye, we conducted a matched case–control study. The cases were from 266 patients who developed GA in the study eye at any point during the five years of CATT follow-up.[22] After excluding those with GA at baseline, poor photograph quality, and no follow-up, 245 (92.1%) study eyes with incident GA were included. 245 controls without incident GA were 1:1 matched with cases based on demographics and characteristics shown to be associated with the development of GA in CATT, which included GA in the fellow eye, subretinal tissue complex thickness at the foveal center, and subretinal and intraretinal fluid.[23,24] Two additional case–control matched pairs were excluded because of inability to reliably determine the area of B-PPA in one of the eyes, leaving 243 (91.4%) case–control pairs for analysis. The baseline characteristics of this subset of CATT cases and matched controls are shown in Table 1. In addition, we characterized the association between B-PPA at baseline and the GA size at Year 1, 3, and 5, as well as GA growth during 5 years of CATT.[22]

Grader Training and Initial Grading

Graders (A.M.K. and E.S.) were trained by E.D. from the Reading Center of the Center for Preventive

Table 1. Comparison of Baseline Characteristics Between Eyes With Versus Without Development of GA During Follow-up*

Baseline Characteristics	Incident GA		*P*
	No (n = 243)	Yes (n = 243)	
Age (years), mean (SD)	79.4 (7.9)	79.8 (7.0)	0.57
Smoking status			0.66
Never	101 (41.6%)	110 (45.3%)	
Quit	127 (52.3%)	117 (48.1%)	
Current	15 (6.2%)	16 (6.6%)	
Hypercholesterolemia, yes	129 (53.1%)	154 (63.4%)	**0.02**
Drug group, Avastin	127 (52.3%)	111 (45.7%)	0.15
Regimen groups			0.18
Pro re nata	123 (50.6%)	112 (46.1%)	
Switched	64 (26.3%)	57 (23.5%)	
Monthly	56 (23.0%)	74 (30.5%)	
Baseline visual acuity in the study eye			0.55
20/200-320	12 (4.9%)	18 (7.4%)	
20/100-160	64 (26.3%)	57 (23.5%)	
20/50-80	89 (36.6%)	96 (39.5%)	
20/25-40	78 (32.1%)	72 (29.6%)	
Baseline choroidal neovascularization area (disk areas)			0.42
≤1	109 (44.9%)	106 (43.6%)	
>1 to ≤2	50 (20.6%)	38 (15.6%)	
>2 to ≤4	42 (17.3%)	48 (19.8%)	
>4	18 (7.4%)	27 (11.1%)	
Unknown	24 (9.9%)	24 (9.9%)	
Retinal angiomatous proliferation, yes	24 (9.9%)	49 (20.2%)	**0.002**
Glaucoma in the study eye, yes	32 (13.2%)	27 (11.1%)	0.49
Cataract status in the study eye			0.42
No history	14 (5.8%)	11 (4.5%)	
Pseudophakic/aphakic	125 (51.4%)	139 (57.2%)	
Ongoing	104 (42.8%)	93 (38.3%)	
Spherical equivalent in the study eye†			0.56
Pseudophakic/aphakic	125	139	
Myopia −5 to −0.5 D	19 (16.1%)	12 (11.5%)	
Emmetropia −0.49 to 0.49 D	11 (9.3%)	15 (14.4%)	
Hyperopia 0.5 to 5 D	85 (72.0%)	74 (71.2%)	
Hyperopia ≥5 D	3 (2.5%)	3 (2.9%)	

*The eyes were matched by GA in the fellow eye, subretinal tissue complex thickness at foveal center, and subretinal and intraretinal fluid in the fovea.

†Excluding pseudophakic/aphakic eyes.

Ophthalmology and Biostatistics to recognize B-PPA on multiple disk-centered color fundus images (Figure 1). We did not use OCT images in this study because baseline OCT images in CATT were all time-domain rather than spectral-domain OCT, which would make it difficult to delineate the BM. Furthermore, these OCT images were fovea-centered scans, so the area adjacent to the disk was not visualized typically. Guided by definitions used in previous studies,[3,5] B-PPA was defined as a hypopigmented area with absence of the RPE/BM resulting in visible choroidal vessels and/or sclera that was adjacent to the scleral ring or disk margin.[3] Representative images were selected and agreed on by all graders (A.M.K. and E.S.) and an adjudicator (E.D.) and were used in the study for reference during the adjudication process.

Qualitative and Quantitative Characterization of Beta-Peripapillary Atrophy

Disk-centered images for all 243 case–control matched pairs were independently double-graded for presence of B-PPA (A.M.K. and E.S.). The graders were masked to all demographics, clinical characteristics, and status of case or control. For each image, confidence of B-PPA presence (0—not confident, 1—probable, and 2—definite) and image quality (0—poor, 1—fair, and 2—good) were graded. Images with poor quality were excluded from analysis. Among eyes with presence of B-PPA, we determined different subtypes of B-PPA as follows: 1) thick scleral ring, 2) sclera only, 3) sclera/choroidal blood vessels, and 4) combination (Figure 2) [3,25] and performed the following area

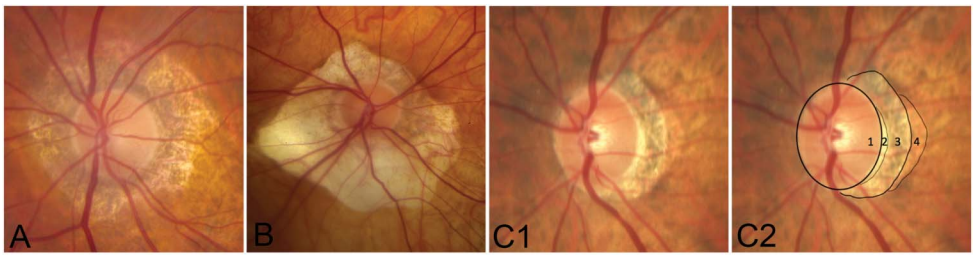

Fig. 1. Different examples of PPA. **A** and **B.** Examples of 360° circumferential B-PPA with a normal thickness scleral ring and no obvious alpha-PPA. **C1** and **C2.** Original image (**C1**) and image with tracings (**C2**) outlining optic disk (1), thick scleral ring (2), B-PPA (3), and alpha-PPA (4).

measurements: 1) optic disk, 2) optic disk plus scleral ring, and 3) optic disk plus scleral ring and total B-PPA using the drawing tool in Image J software (available for download from https://imagej.nih.gov/ij/download.html). Because the images were obtained with different cameras and magnifications, we measured the areas in pixels rather than mm^2. To account for the differences in image magnification, we reported the PPA area in pixels as a percent of the optic disk area or optic disk plus scleral ring area.[25] For "scleral ring" and "sclera/choroidal blood vessel" subtypes of B-PPA, we also graded "extent" of PPA with "extent" being defined as the percent of circumference of the optic disk encompassed by the specific subtype of B-PPA (e.g., 360° would represent 100%). These were graded as <25%, 26% to 74%, and >75%. All quantitative measurements were adjudicated if the difference was >20% of the mean of the two graders, and all qualitative differences were adjudicated. There is no consensus in the literature regarding inclusion of the scleral ring as part of the total B-PPA area.[3,25] To account for this, we performed two separate statistical analyses with and without the inclusion of the scleral ring as part of the B-PPA area.

Pseudodrusen and Genetic Analysis

The presence of pseudodrusen in the study/fellow eye and detailed genetic analysis was previously assessed.[26] In CATT, only 835 of the 1,185 (70.5%) participants consented to genetic testing.[27] Geographic atrophy–associated single nucleotide polymorphism alleles included *CFH* rs1061170, *ARMS2* rs1049092, *HTRA1* rs1120063, *C3* rs2230199, and *TLR3* rs3775291.[28,29] The risk alleles are C for *CFH*, T for *ARMS2*, A for *HTRA1*, and G for *C3*, whereas the protective allele is T for *TLR3*.

Statistical Analysis

We used two-sample *t*-tests for comparison of means and Chi-square tests for comparison of proportions between two groups. We used univariate and multivariate logistic regression models to assess the associations between presence of B-PPA and characteristics of B-PPA with incidence of GA during five years of follow-up. Correlation from pairings between GA cases and controls was accounted for by using generalized estimating equation. In multivariate analyses, the models were adjusted by age, smoking status, treatment drug, regimen, hypercholesterolemia, retinal angiomatous proliferation (RAP) lesion, glaucoma, cataract status, and refractive error. The association of ordered categorical variables with GA was assessed using linear trend tests. Analysis of variance was used to evaluate the association of B-PPA with the GA size, when first observed. Linear mixed effects models were used to evaluate the association of B-PPA with the rate of GA growth. In the mixed effects model, the square root of the GA area (in mm) was modeled as a function of time (relative to the first observation of GA). Linear trend tests were used to determine the association of the area of sclera/choroidal blood vessels B-PPA as a percent of the optic disk or optic disk plus scleral ring area with incidence, initial size, and growth rate of GA. For the above, the area of B-PPA was categorized

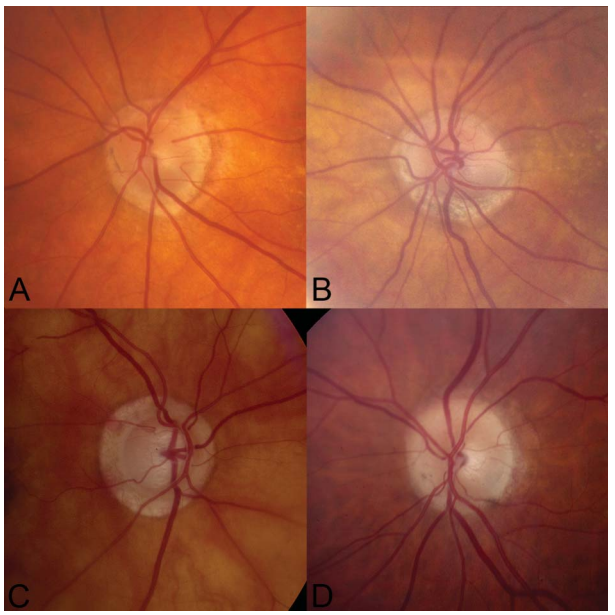

Fig. 2. Different subtypes of B-PPA. **A.** Thick scleral ring. **B.** Sclera only. **C.** Sclera/choroidal blood vessels. **D.** Thick scleral ring and sclera/choroidal blood vessels. Note that alpha-PPA is present in (**A**, **B**, and **D**).

into three equally sized groups, whereas those without B-PPA were considered as another separate group. All statistical analyses were performed using SAS v9.4 (SAS Institute Inc, Cary, NC), and two-sided P value < 0.05 (without correction for multiple comparisons) was considered to be statistically significant.

Results

Demographics and Baseline Characteristics

Demographic and baseline study eye characteristics for the 243 incident GA cases during the 5-year CATT follow-up and their matched controls are shown in Table 1. Geographic atrophy cases and controls were similar in age, smoking status, treatment drug group and regimen, baseline visual acuity and choroidal neovascularization size, history of glaucoma, lens status, and refractive error in the study eye. However, participants with GA in the study eye were more likely to have hypercholesterolemia ($P = 0.02$) and a RAP lesion ($P = 0.002$).

Presence of B-PPA on disk-centered color fundus photographs was identified in 267 (54.9%) patients. Patients with B-PPA were significantly older ($P = 0.0003$) than those without B-PPA, but did not differ significantly in sex, smoking status, and presence of pseudodrusen at baseline in the study/fellow eye (Table 2).

Beta-Peripapillary Atrophy Grading Agreement and Data Adjudication

Preadjudication intergrader agreement for categorical variables—B-PPA type, extent of scleral ring, and extent of B-PPA sclera/choroidal blood vessels—was 61.2% (kappa, 0.27), 58.6% (kappa, 0.21), and 52.2% (kappa, 0.32), respectively. Intraclass correlation coefficients (ICC) for continuous variables—area of optic disk and optic disk plus scleral ring and B-PPA—were 0.97 (95% confidence interval [CI], 0.97–0.98) and 0.57 (95% CI, 0.48–0.64), respectively. Adjudication was performed on 3.6% to 49.4% of measurements depending on previously outlined criteria (see "Qualitative and quantitative characterization of B-PPA" in the Methods section).

Association of Beta-Peripapillary Atrophy With Development of Geographic Atrophy

Beta-peripapillary atrophy was present in 58.0% of eyes with GA and in 52.0% of eyes without GA (adjusted odds ratio = 1.35, $P = 0.12$; Table 3). The greater area of B-PPA as a percent of the disk size was weakly associated with the development of GA ($P = 0.08$). The type of B-PPA was not associated with the risk of GA ($P = 0.30$). The greater circumferential extent of sclera/choroidal blood vessels B-PPA was significantly associated with a higher incidence of GA during the CATT 5-year follow-up period ($P = 0.02$). In relation to GA development, a trend toward statistical significance was detected for an increasing area of sclera/choroidal blood vessels B-PPA (including scleral ring) as a percent of the disk area ($P = 0.10$) and an increasing area of sclera/choroidal blood vessels B-PPA as a percent of the optic disk plus scleral ring area ($P = 0.08$).

Association of Beta-Peripapillary Atrophy With the Geographic Atrophy Size and Rate of Growth

The extent of sclera/choroidal blood vessels B-PPA in relation to the optic disk was significantly (P

Table 2. Comparison of Demographics and Pseudodrusen Between Eyes With Versus Without B-PPA at Baseline

Characteristics	Beta-Peripapillary Atrophy		P
	No (n = 219)	Yes (n = 267)	
Age (years), mean (SD)	78.2 (7.6)	80.7 (7.1)	**0.0003**
Gender, female	142 (64.8%)	163 (61.1%)	0.39
Smoking status			0.42
Never	102 (46.6%)	109 (40.8%)	
Former	103 (47.0%)	141 (52.8%)	
Current	14 (6.4%)	17 (6.4%)	
Pseudodrusen in the fellow eye*, yes	52 (26.0%) (n = 201)	81 (32.1%) (n = 260)	0.18
Pseudodrusen in either eye†, yes	61 (31.0%) (n = 197)	94 (37.6%) (n = 250)	0.16

*Pseudodrusen could not be determined in 25 fellow eyes because of poor image quality or presence of fluid, which prevented pseudodrusen assessment.

†Pseudodrusen could not be determined in either study or fellow eye of 39 patients because of poor image quality or presence of fluid, which prevented pseudodrusen assessment.

Table 3. Univariate and Multivariate Analyses for the Association Between Baseline B-PPA and Incident GA

	Geographic Atrophy		Univariate Analysis		Multivariate Analysis*	
Beta-Peripapillary Atrophy	No (n = 243)	Yes (n = 243)	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Presence of B-PPA				0.17		0.12
No	117 (48.1%)	102 (42.0%)	1.00 (Ref)		1.00 (Ref)	
Yes	126 (51.9%)	141 (58.0%)	1.28 (0.90, 1.83)		1.35 (0.92, 1.99)	
B-PPA areas as % of the disk area				0.08†		0.08†
No B-PPA	117 (48.1%)	102 (42.0)	1.00 (Ref)		1.00 (Ref)	
≤50%	49 (20.2%)	44 (18.1%)	1.03 (0.65, 1.64)		1.10 (0.66, 1.81)	
51%–75%	31 (12.8%)	41 (16.9%)	1.52 (0.89, 2.59)		1.65 (0.92, 2.95)	
76%–100%	16 (6.6%)	18 (7.4%)	1.29 (0.65, 2.58)		1.27 (0.60, 2.69)	
>100%	30 (12.3%)	38 (15.6%)	1.45 (0.84, 2.52)		1.56 (0.86, 2.82)	
B-PPA types				0.36		0.30
No B-PPA	117 (48.1%)	102 (42.0%)	1.00 (Ref)		1.00 (Ref)	
Scleral ring only	4 (1.6%)	8 (3.3%)	2.29 (0.68, 7.79)		2.40 (0.71, 8.16)	
Scleral ring + sclera/ChBV	35 (14.4%)	35 (14.4%)	1.15 (0.68, 1.93)		1.19 (0.68, 2.10)	
Sclera/ChBV only	87 (35.8%)	98 (40.3%)	1.29 (0.87, 1.92)		1.36 (0.88, 2.09)	
B-PPA sclera/ChBV circumferential extent				**0.03**†		**0.02**†
None	117 (48.1%)	102 (42.0%)	1.00 (Ref)		1.00 (Ref)	
≤25%	37 (15.2%)	32 (13.2%)	0.99 (0.60, 1.64)		1.06 (0.63, 1.79)	
26%–74%	67 (27.6%)	68 (28.0%)	1.16 (0.75, 1.80)		1.25 (0.77, 2.01)	
>75%	22 (9.1%)	41 (16.9%)	2.14 (1.18, 3.88)		2.39 (1.26, 4.53)	
B-PPA sclera/ChBV area as % of the disk area‡§				0.07†		0.10†
No B-PPA	117 (49.0%)	102 (43.4%)	1.00 (Ref)		1.00 (Ref)	
<30%	44 (18.4%)	42 (17.9%)	1.09 (0.69, 1.75)		1.13 (0.68, 1.88)	
30%–70%	40 (16.7%)	46 (19.6%)	1.32 (0.80, 2.16)		1.38 (0.80, 2.37)	
>70%	38 (15.9%)	45 (19.1%)	1.36 (0.81, 2.27)		1.39 (0.79, 2.43)	
B-PPA sclera/ChBV as % of the disk plus scleral ring area‡§				0.06†		0.08†
No B-PPA	117 (49.0%)	102 (43.4%)	1.00 (Ref)		1.00 (Ref)	
<25%	42 (17.6%)	43 (18.3%)	1.17 (0.74, 1.86)		1.27 (0.77, 2.09)	
25%–55%	42 (17.6%)	42 (17.9%)	1.15 (0.71, 1.86)		1.13 (0.67, 1.91)	
>55%	38 (15.9%)	48 (20.4%)	1.45 (0.86, 2.43)		1.52 (0.86, 2.68)	

*Adjusted by age, smoking status, treatment drug, regimen, hypercholesterolemia, retinal angiomatous proliferation lesion, glaucoma, cataract, and spherical equivalent.
†From test of linear trend.
‡Area of B-PPA could not be determined in 12 patients with B-PPA (four in the no GA group and eight in the GA group).
§The subjects were divided into three equal groups.
CI, confidence interval; ChBV, choroidal blood vessels.

= 0.047) associated with the GA size at first observation during follow-up (Table 4). The presence and type of B-PPA and the area of sclera/choroidal blood vessels were not significantly associated with the initial size or growth rate of GA ($P>0.08$ for all comparisons, Table 4).

Genetic Analysis of Geographic Atrophy–Associated Alleles

Genetic data were available on 155 of the 219 (70.8%) patients without B-PPA and on 179 of the 267 (67.0%) patients with B-PPA (Table 5). Patients without B-PPA had a significantly higher likelihood of the T-risk allele in *ARMS2* rs1049092 ($P = 0.0003$) and the A-risk allele in *HTRA1* rs1120063 ($P = 0.001$). There were no statistically significant differences in the C-risk allele for *CFH* rs1061170, the G-risk allele for *C3* rs2230199, or the protective T allele for *TLR3* rs3775291.

Discussion

In the current study, we examined the relationship between B-PPA at baseline and incident GA in the study eye during five years of CATT follow-up. We found that B-PPA was present at baseline in 58% of study eyes that developed GA throughout five years of follow-up versus 52% that did not. This difference was not statistically significant. Interestingly,

Table 4. Univariate Analysis for the Association Between Baseline B-PPA and the Size of GA Area and Growth Rate of GA

	Geographic Atrophy Size at First Observation During Follow-Up*			Geographic Atrophy growth†		
	n	Mean (SD) in mm^2	*P*	n	mm/year (SE)	*P*
Presence of B-PPA			0.32			0.46
No	102	3.47 (0.41)		44	0.277 (0.037)	
Yes	141	4.21 (0.56)		77	0.312 (0.030)	
B-PPA area as % of the disk area			0.16‡			0.28‡
No B-PPA	102	3.47 (0.41)		44	0.291 (0.036)	
≤50%	44	3.87 (1.00)		26	0.318 (0.047)	
51%–75%	41	4.07 (1.02)		21	0.309 (0.060)	
76%–100%	18	2.89 (0.98)		6	0.164 (0.107)	
>100%	38	5.39 (1.26)		24	0.390 (0.052)	
B-PPA types			0.56			0.71
No B-PPA	102	3.47 (0.41)		44	0.291 (0.037)	
Scleral ring only	8	6.05 (3.72)		5	0.210 (0.116)	
Scleral ring + sclera/ChBV	35	4.47 (1.03)		20	0.346 (0.055)	
Sclera/ChBV only	98	3.97 (0.66)		52	0.330 (0.037)	
B-PPA sclera/ChBV circumferential extent			**0.047**‡			0.29‡
None	102	3.47 (0.41)		44	0.258 (0.036)	
≤25%	32	3.93 (1.11)		21	0.304 (0.061)	
26%–74%	68	2.80 (0.55)		34	0.245 (0.043)	
>75%	41	6.78 (1.41)		22	0.370 (0.057)	
B-PPA sclera/ChBV area as % of the disk area§			0.16‡			0.22‡
No B-PPA	102	3.47 (0.41)		44	0.265 (0.036)	
≤23%	42	3.32 (0.80)		24	0.312 (0.050)	
23%–79%	46	4.07 (0.97)		21	0.223 (0.057)	
>79%	45	4.86 (1.09)		27	0.377 (0.052)	
B-PPA sclera/ChBV as % of the disk plus scleral ring area§			0.08‡			0.31‡
No B-PPA	102	3.47 (0.41)		44	0.267 (0.036)	
<25%	43	2.86 (0.70)		24	0.322 (0.052)	
25%–55%	42	4.27 (1.05)		20	0.237 (0.058)	
>55%	48	5.07 (1.06)		28	0.355 (0.051)	

*GA was first observed at Year 1 in 111 eyes, at Year 3 in 37 eyes, and at Year 5 in 95 eyes.
†Among those with two or more measurements of the GA size during follow-up (those with baseline GA were excluded from this study).
‡From test of linear trend.
§The subjects were divided into three equal groups.
ChBV, choroidal blood vessels.

the 58% prevalence of B-PPA was considerably lower than the 86% reported in the GAP study among eyes with GA; however, Chang et al[18] did not specify the type of PPA. Although presence of B-PPA was not associated with development of GA, there was a weak trend ($P = 0.08$, Table 3) for an association between a larger B-PPA area and a higher incidence of GA. Presence of B-PPA was also significantly associated with older age, which has been previously shown.[10]

We separated B-PPA into different morphologic categories—thick scleral ring, sclera, sclera/choroidal blood vessels, or combination (Figure 2). In previous studies, the scleral ring has not been considered as a separate subcategory of B-PPA and was usually incorporated into the overall area of B-PPA because it was assumed that it was so thin that it would not significantly affect the overall area of B-PPA measurement.[1,25] However, we felt that in certain patients the ring was "too thick" to be included and wanted to separate it out (Figure 1, C1 and C2). In addition, to be consistent with the literature, we also performed data analysis with the area of the scleral ring incorporated into the area of sclera/choroidal blood vessels B-PPA. We found that the scleral ring (scleral ring only vs. scleral ring/sclera/choroidal blood vessels) did not significantly affect any of the comparisons performed in the study, and it was not independently associated with development of GA (Table 3).

Table 5. Comparison of Genetic Characteristics Between Eyes With Versus Without Beta-Peripapillary Atrophy at Baseline

Gene Alleles*	Beta-Peripapillary Atrophy		P
	No (n = 155)	Yes (n = 179)	
CFH rs1061170			0.29
CC	47 (30.3%)	48 (26.8%)	
TC	78 (50.3%)	88 (49.2%)	
TT	30 (19.4%)	43 (24.0%)	
ARMS2 rs1049092			**0.0003**
GG	37 (23.9%)	61 (34.1%)	
GT	68 (43.9%)	93 (52.0%)	
TT	50 (32.3%)	25 (14.0%)	
HTRA1 rs1120063			**0.001**
AA	47 (30.3%)	25 (14.0%)	
AG	70 (45.2%)	94 (52.5%)	
GG	38 (24.5%)	60 (33.5%)	
C3 rs2230199			0.41
CC	86 (55.5%)	114 (63.7%)	
CG	61 (39.4%)	51 (28.5%)	
GG	8 (5.2%)	14 (7.8%)	
TLR3 rs3775291			0.31
CC	86 (55.5%)	88 (49.2%)	
CT	58 (37.4%)	77 (43.0%)	
TT	11 (7.1%)	14 (7.8%)	

*The risk alleles are C for *CFH*, T for *ARMS2*, A for *HTRA1*, and G for *C3*.
The protective allele is T for *TLR3*.

In addition to the type and area of PPA, the circumferential extent of PPA has been evaluated in several previous studies. For example, eccentric (<270°) versus concentric (>270°) PPA in myopic glaucomatous eyes was shown to associate with glaucoma worsening and PPA progression.[8] We found that the circumferential extent (>75% or >270°) of sclera/choroidal blood vessels B-PPA was significantly associated with the development of GA during five years of CATT follow-up (Table 3) and the size of GA at first observation (Table 4). The sclera/choroidal blood vessels B-PPA subtype was not significantly associated with GA development probably because the smaller areas/lesions of this type of B-PPA do not seem to be associated with GA development. Overall, these data suggest that an enlarging area and extent of sclera/choroidal blood vessels B-PPA may indicate a widespread outer retina/RPE/BM susceptibility to degeneration, including the macula. In addition, a relationship between peripapillary strain, mechanical stress, and changes in the lamina cribrosa as related to age and development of glaucoma has been explored.[30,31] These findings imply that the peripapillary area may have a preexisting susceptibility to degeneration due to mechanical stress.

Numerous AMD and GA-associated alleles have been identified.[32] Genetic testing is not yet recommended as part of routine patient management because allele-specific treatments are not currently available, but may in the future influence the choice of therapy.[33,34] Although select alleles are associated with a higher or lower incidence of GA,[22] they were not associated with GA growth in CATT.[27] In the current study, patients without B-PPA had significantly higher likelihood of the risk alleles in *ARMS2* and *HTRA1* genes (Table 5). Although the development of B-PPA is strongly genetically inherited,[35] these data imply that any associations between B-PPA and GA may not be mechanistically related to GA-specific risk alleles evaluated in this study. In addition, the results indicate that the known association of the T-risk allele for *ARMS2* and the A-risk allele for *HTRA1* with advanced AMD may be specifically related to the neovascular type. This finding may warrant further validation in future studies with a much more robust sample size.

The strengths of this study include: 1) our matched case–control approach using a well-characterized clinical trial cohort with five years of follow-up, 2) rigorous double-grading of images with adjudication, and 3) thorough analysis of different aspects of B-PPA as they relate to incident GA. Our data regarding GA development is most applicable to eyes with neovascular AMD treated with anti-VEGF agents. Therefore, the results may be different if GA of nonexudative AMD eyes were to be studied. The use of anti-VEGF agents, which themselves have been implicated in development/progression of atrophy,[23] may have affected our results. Differences in the vascular supply

and structural/biochemical characteristics between the peripapillary and macular areas may have also had an effect.[30,36]

Our study also has several limitations. These include subjective assessment of B-PPA and outlining the margins on color photographs for B-PPA area quantification. This may explain the low intergrader agreement for the type and extent of B-PPA. Use of OCT technology may aid in more reliable determination of B-PPA presence and delineation for area measurement.[12] However, disk-centered spectral-domain OCT images were not available, as they were not routinely performed under CATT methodology. In addition, spectral-domain OCT has recently been used to differentiate B-PPA from gamma-PPA,[37] which cannot be performed on color photographs, and so the area of B-PPA represented in this study could have included gamma-PPA. Using flattened photographs representing a curved fundus may result in measurement errors, especially if the patients have significant refractive errors. However, we used previously reported approaches for area measurements on color photographs.[25] Assessment of pseudodrusen and genetic testing data were not available for all patients. The B-PPA area was represented as a percent of the disk (or disk plus scleral ring) area rather than mm^2 because of differences in cameras and image acquisition methods. Because we did not measure areas of the optic disk or B-PPA in mm^2, potential comparisons to future studies may be difficult. We did not perform any corrections for multiple comparisons in this secondary data analysis study. Finally, these data are exploratory and hypothesis generating; additional studies would be needed to confirm the association of sclera/choroidal blood vessel B-PPA with incident GA.

In summary, we identified a statistically significant association between the circumferential extent of sclera/choroidal blood vessels B-PPA and incidence as well as the size of GA during five years of CATT follow-up. Although there remains an urgent need to investigate biomarkers for incident GA, the exact mechanisms for development of GA and B-PPA still remain unclear. Our results suggest that further investigation of B-PPA could be meaningful, especially as a biomarker in clinical trials focusing on GA. With the advent and application of artificial intelligence and deep learning algorithms in medicine, and especially ophthalmology, this technology might be adapted to aid in identification of such biomarkers in future endeavors.

Key words: age-related macular degeneration, geographic atrophy, beta-peripapillary atrophy, CATT.

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