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Prevalence and factors associated with optic disc grey crescent in the Primary Open-Angle African Ancestry Glaucoma Genetics (POAAGG) Study

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ABSTRACT

Aim To investigate the prevalence and factors associated with optic disc grey crescent (GC) in African Americans with glaucoma.

Methods Stereo optic disc image features from subjects with glaucoma in the Primary Open-Angle African Ancestry Glaucoma Genetics Study were evaluated independently by non-physician graders and discrepancies adjudicated by an ophthalmologist. Risk factors for GC were evaluated by logistic regression models with intereye correlation accounted for by generalised estimating equations. Adjusted ORs (aORs) were generated.

Results GC was present in 227 (15%) of 1491 glaucoma cases, with 57 (3.82%) bilateral and 170 (11.4%) unilateral. In multivariable analysis, factors associated with GC were younger age (aOR 1.27, 95% CI 1.11 to 1.43 for every decade younger in age, p=0.001), diabetes (aOR 1.46, 95% CI 1.09 to 1.96, p=0.01), optic disc tilt (aOR 1.84, 95% CI 1.36 to 2.48, p<0.0001), a sloping retinal region adjacent to the outer disc margin (aOR 2.37, 95% CI 1.74 to 3.32, p<0.0001) and beta peripapillary atrophy (aOR 2.32, 95% CI 1.60 to 3.37, p<0.0001). Subjects with GC had a lower mean (SD) value of the ancestral component q0 than those without GC (0.22 (0.15) vs 0.27 (0.20), p=0.001), consistent with higher degrees of African ancestry.

Conclusions More than 1 in 10 glaucoma cases with African ancestry have GC, occurring more frequently in younger subjects, higher degrees of African ancestry and diabetes. GC was associated with several ocular features, including optic disc tilt and beta peripapillary atrophy. These associations should be considered when evaluating black patients with primary open-angle glaucoma.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Misdiagnosis of rim thinning in glaucomatous discs with grey crescent has been well documented. In black populations with glaucoma, no other associations have been reported.

WHAT THIS STUDY ADDS

⇒ This study, with much larger numbers than previous studies, reports on the hitherto unknown associations of grey crescent with other concurrent ocular characteristics in African Americans.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These associations, especially beta peripapillary atrophy and tilted optic discs, must be accounted for when investigating glaucoma in high-risk black populations.

INTRODUCTION

Grey crescent (GC) of the optic nerve head, first described nearly four decades ago, is defined as a crescent-shaped, slate grey pigmentation in the periphery of the neuroretinal rim that is completely inside the scleral ring. GC appears to be a relatively common finding in patients with glaucoma, especially among individuals of African ancestry.[1 2] GCs have been reported to be commonly bilateral and predominantly occur along the temporal or inferotemporal disc margins. There have been no histopathological studies related to GCs, but observations on spectral domain optical coherence tomography (SD-OCT) images with enhanced depth imaging suggest that the anatomical correlate of GC is pigmentation of the externally oblique border tissue of Elschnig.[3]

Clinically, the identification of GC is important because a faulty assumption that the pigmentation of the GC is peripheral to the disc margin can lead to a mistaken identification of rim thinning when rim thinning was not present. In a white population aged 50 years or older, GC was more commonly observed in women and was associated with hyperopic eyes and larger optic discs and cups, and its prevalence was inversely related to the presence of peripapillary atrophy.[4] No such associations have been reported from black populations.[2] Although more prevalent in black participants with glaucoma, GCs have

not been associated with glaucomatous damage in either the black or white populations.[2 4]

The Primary Open-Angle African American Glaucoma Genetics (POAAGG) Study has recruited more than 10 200 individuals of African ancestry from Philadelphia, making it the largest African ancestry primary open-angle glaucoma (POAG) cohort recruited from a single city.[5] The optic disc images from these study participants have been evaluated using stereoscopy for various quantitative and qualitative features.[6] From the accrued dataset, we evaluated the prevalence of GC among glaucoma cases and their possible associations with baseline demographic, ocular and genetic characteristics.

METHODS

Participants

The study population included self-identified African ancestry participants (black, Afro-Caribbean or African American), aged 35 years or older, recruited from Philadelphia, Pennsylvania. These participants were initially identified from comprehensive and subspecialty ophthalmology clinics at the University of Pennsylvania and two neighbouring ophthalmology clinics in Philadelphia, Pennsylvania (Windell Murphy; Temple University).

Every participant was interviewed on-site and received a comprehensive ophthalmic evaluation. The examination data were recorded on case report forms, which were entered into the REDCap (Research Electronic Data Capture) database and Microsoft access database. Related ophthalmic and systemic health data were extracted from the UPenn EPIC and MERGE databases. A glaucoma specialist classified each subject as a glaucoma case.

Details on eligibility criteria, phenotyping and baseline characteristics have been described previously.[7] All participants signed an informed consent form and provided a genomic DNA sample.

Patient and public involvement

Patients and the public were not involved in any way with this research publication.

Genetic analysis

Genomic DNA for enrolled participants was extracted from peripheral blood or saliva, both of which have demonstrated excellent performance in array-based genotyping.[8] The genotyping and quality control were performed as explained previously.[9] The fastSTRUCTURE, the software designed to infer population structure from genotyped data, was used to estimate the proportion of ancestry in POAAGG cases. A detailed description of the ancestry analysis of the POAAGG cases has been described by our group previously.[9]

Grading of colour images

To be eligible for analysis, participants were required to have 30° colour stereo disc fundus photographs of both eyes taken using the Topcon TRC 50EX retinal camera (Topcon Corp of America). These stereo colour images were uploaded to the Ophthalmology Reading Center at the University of Pennsylvania using a secure server. The images were taken between 13 January 2004 and 25 June 2019; uploaded to the Reading Center server between 22 January 2016 and 20 April 2021; and graded at the Reading Center between 6 June 2016 and 19 November 2021.

Three non-physician graders trained by two glaucoma specialists in grading digital stereo colour images of the optic disc using a stereo viewer (Screen-Vu stereoscope) independently performed quantitative and qualitative assessments on the best stereo colour image of the pair. Details on the training of the graders have been described elsewhere.[6] Discrepant results in grading from the two independent graders were adjudicated by an ophthalmologist, the Director of the Reading Center.

Qualitative grading of the optic nerve head

For qualitative image grading, two graders completed a standardised grading form on various features of the optic cup and disc for each stereo image pair of both eyes at every visit. The graded features included quality of the stereo pair of images: disc shape (round, oval, other); shape of the cup (reader makes an assessment on whether the walls of the cup slope toward the centre (conical), abruptly drop vertically down (cylindrical) or are excavated (partial and complete beanpot) with the predominant shape chosen in instances where the configuration was mixed); cup depth (shallow, moderate, deep); stereoscopically identified disc tilt determined by the rim plane position (reader makes an assessment to determine if the rim was at the same level in its entirety and if it was not, records the area where it was depressed); presence of beta peripapillary atrophy at each clock hour surrounding the disc; sloping region adjacent to the outer rim of the disc (assessed as partial or complete circumferential dip of the peripapillary retina, adjacent to the disc margin, below the level of the retinal plane); presence and location of haemorrhages; visible pores in the lamina cribrosa; baring of circumlinear vessels; bayonetting; cilioretinal vessels; GCs and pallor of the neural rim. Discrepancies between the two graders were adjudicated by the Reading Center Director, who reviewed the stereoscopic images used by the graders and determined if one of the recorded values could be used or if a new value needed to be generated.

Grading of the GC

Identification of the GC was dependent on the observation of the following features: the crescent must be slate grey in colour; it must be located within the peripheral portion of the rim inner to the scleral ring or to the outer margin of the rim if a scleral ring was absent. Examples of GCs and features that mimic GC are shown in figure 1.

A sample of 50 eyes (25 eyes with GC and 25 eyes without GC, based on original adjudicated grading) was selected for regrading independently by two graders, with adjudication by the Director of the Reading Center

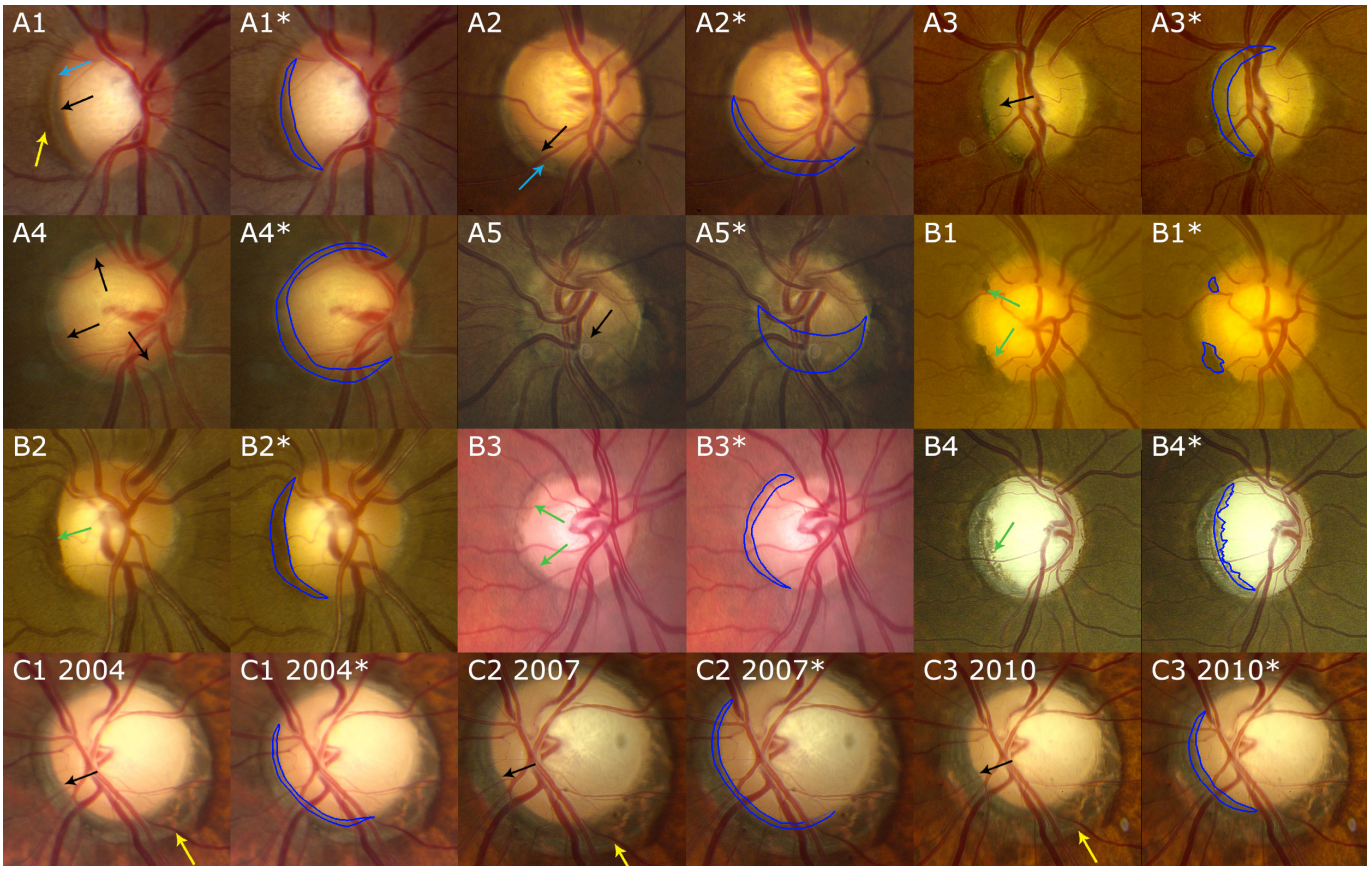

Figure 1 Colour images of the optic disc with examples of grey crescent (GC) and features that mimic GC. A1: right eye shows a temporal GC (black arrow). The GC is within the inner border of the scleral ring (blue arrow). An alpha peripapillary atrophy of a similar grey colour (yellow arrow) is observed outside of the scleral ring. Temporal location of GC is common. A2: right eye shows a temporal and inferior GC (black arrow) within the inner border of the scleral ring (blue arrow). The inferior quadrant is also a common location for GC. A3: left eye shows a nasal GC (black arrow) that is not common. A4: right eye shows a rare manifestation of a GC (black arrows) that extends into the temporal, inferior and superior quadrants. A5: a tilted optic disc that shows a thick inferior GC (black arrow). Tilted optic discs have 84% more odds of having GC. B1: right eye shows a temporally located conus pigmentosus. This was not considered a GC (green arrows). B2, B3: right eyes showing dark brown pigmented crescents (green arrows) not considered GC. They have been termed as type B GC in some reports. B4: right eye showing black pigmented granular crescent (green arrow) not considered as GC. C1, C2, C3: right eyes over time (2004–2010) with hardly any discernible changes to the GC (black arrows) but with an enlarging beta peripapillary atrophy (β-PPA) (yellow arrow). Eyes with β-PPA had more than twofold odds of having GC. A1*, A2*, A3*, A4*, A5*, B1*, B2*, B3*, B4*, C1 2004*, C2 2007* and C3 2010* are corresponding images with the outline of the GC.

for grading discrepancies. We assessed the agreement between the original adjudicated grading versus the adjudicated regrading for the presence of GC using per cent of agreement and the kappa statistic. The per cent agreement of GC grading was 78% with kappa of 0.56 (95% CI: 0.35 to 0.77). These results demonstrate the moderate reproducibility in the grading of GC.

Statistical analysis

Descriptive analyses were performed using mean, SD for continuous measures, and count and % for categorical measures. Comparison of demographic and ocular characteristics between eyes with versus without GC was performed using generalised linear models. Generalised estimated equations were applied to account for the intereye correlation among participants with both eyes eligible for the analysis. Risk factors associated with presence of GC were evaluated using univariable and multivariable logistic regression models, and the intereye correlation was accounted for by using generalised estimating equations. The multivariable model started with including all factors with $p<0.20$ in univariable analysis and went through stepwise variable selection by only keeping those factors with $p<0.05$ in the final multivariable model. All the statistical analyses were performed in SAS V.9.4 (SAS Institute), and two-sided $p<0.05$ was considered to be statistically significant.

RESULTS

GC was observed in 284 (9.9%) of 2866 eyes of glaucoma cases of the POAAGG cohort. Of these 1491 cases, 227 (15%) had GC, which was bilateral in 57 (3.8%) cases and unilateral in 170 (11.4%). For locations of GC on

Table 1 Univariable analyses for associations between demographic characteristics and grey crescent among glaucoma cases

	Grey crescent present (N=284 eyes)	Grey crescent absent (N=2582 eyes)	P value
Age (years)			<0.0001
Mean (SD)	66.2 (11.2)	70.1 (11.2)	
Median (IQR)	67.0 (58.0–73.5)	71.0 (62.0–78.0)	
Range	35.0–96.0	35.0–103.0	
Age groups, n (%)			0.001
33–60	90 (31.7)	555 (21.5)	
60–69	72 (25.4)	637 (24.7)	
69–79	88 (31.0)	827 (32.0)	
79–103	34 (12.0)	563 (21.8)	
Gender, n (%)			0.98
Male	114 (40.1)	1034 (40.0)	
Female	170 (59.9)	1548 (60.0)	
Diabetes, n (%)			0.03
No	150 (53.0)	1567 (60.9)	
Yes	133 (47.0)	1004 (39.1)	
Unknown	1	11	
Hypertension, n (%)			0.23
No	68 (23.9)	527 (20.5)	
Yes	216 (76.1)	2047 (79.5)	
Unknown	0	8	
Family history of glaucoma, n (%)			0.76
No	110 (40.9)	1015 (42.0)	
Yes	159 (59.1)	1401 (58.0)	
Unknown	15	166	
Tobacco use, n (%)			0.32
No	139 (49.5)	1167 (45.9)	
Yes	142 (50.5)	1377 (54.1)	
Unknown	3	38	
Alcohol use, n (%)			0.35
No	146 (52.1)	1411 (55.6)	
Yes	134 (47.9)	1129 (44.4)	
Unknown	4	42	
Ancestry (q0)			0.001
Missing	110	922	
N	174	1660	
Mean (SD)	0.22 (0.15)	0.27 (0.20)	
Median (IQR)	0.20 (0.10–0.31)	0.23 (0.13–0.36)	
Range	0.00–0.72	0.00–1.00	

the optic disc rim, it was most frequently observed in the temporal (44.4%) and inferior quadrants (44.7%), and less frequently in the nasal region (21.5%) and the superior quadrant (7.0%). GC was present in only one quadrant in 237 eyes (83.5%), while it overlapped two quadrants in 44 eyes (15.5%) and three quadrants in 3 eyes (1.1%).

Results from comparisons with demographic characteristics in glaucoma cases with versus without GC are provided in table 1. Compared with participants without GC, participants with GC were younger (mean age of 66 vs 70 years, p<0.001), more likely to have diabetes mellitus (47% vs 39%, p=0.03) and had lower mean value of the ancestral component q0 (0.22 vs 0.27, p=0.001), consistent with higher degree of African ancestry.[9]

Table 2 shows a comparison of optic disc features between eyes with versus without GC. Eyes with GC were more likely to have stereoscopically identified disc tilt (31.8% vs 16.0%, p<0.0001), sloping region adjacent to the outer disc margin (42.2% vs 25.2%, p<0.0001) and beta peripapillary atrophy (79.6% vs 67.6%, p=0.001) than eyes without GC. Results from multivariable analysis for associations with demographic and optic disc features are shown in table 3. Higher risk of GC was associated with younger age (adjusted OR (aOR) 1.3, 95% CI 1.1 to 1.4 for every 10 years younger in age, p=0.001), diabetes (aOR 1.5, 95% CI 1.1 to 2.0, p=0.01), optic disc tilt (aOR 1.8, 95% CI 1.4 to 2.5, p<0.0001), presence of a sloping retinal region adjacent to the outer disc margin (aOR 2.4, 95% CI 1.7 to 3.3, p<0.0001) and beta peripapillary atrophy (aOR 2.3, 95% CI 1.6 to 3.4, p<0.0001).

DISCUSSION

The prevalence of GCs in at least one eye of glaucoma cases of African ancestry is around 15%. In the earliest report on GCs, 12% of 100 consecutive African American participants referred for evaluation of possible glaucoma had GC.[1] The frequency of GC among consecutive African ancestry patients who presented to the Glaucoma Service of Yale University Eye Center as new or returning patients with glaucoma or glaucoma suspects during a 5-month period was 27%.[2] The few articles that have reported on the frequency of GCs among African ancestry glaucoma cases have had much smaller numbers than the POAAGG cohort. The only other large epidemiological study conducted on GCs was the Reykjavik Eye Study in Iceland, which found that 22% of 1012 right eyes from a random white population of people 50 years or older had GCs. In this study, the GC definition was not restricted to the originally described slate grey appearance of these crescents, but also included what the authors reported as pigmented crescents, most likely including conus pigmentosus or type B crescents (examples in figure 1).[4]

GCs were more commonly found to be bilateral than unilateral in earlier studies, but in our study, we observed more GCs presenting unilaterally.[1 2 4] The location and extent of the GCs in our study are similar to the findings in earlier reports, occurring more frequently in the temporal and inferior regions. In the Reykjavik Eye Study on a white population, however, inferior GCs were rare and in 16% of eyes, the GCs encircled the entire 360° of disc rim.[4] In our study, extension beyond two quadrants was rare. Although comparison between African ancestry glaucoma cases and a general white population above 50 years in Iceland is not ideal, it does raise the possibility that the location and extent of GCs are quite different in these two populations of varying skin pigmentation.

Table 2 Univariate analyses for association between optic disc characteristics and grey crescent among patients with glaucoma

	Grey crescent present (N=284 eyes)	Grey crescent absent (N=2582 eyes)	P value
Disc shape, n (%)			0.75
Round	125 (44.2)	1162 (45.3)	
Oval	158 (55.8)	1405 (54.7)	
Unknown	1	15	
Shape of cup, n (%)			0.17
Conical	119 (43.6)	934 (38.0)	
Cylindrical	122 (44.7)	1153 (46.9)	
Bean	32 (11.7)	372 (15.1)	
Unknown	11	123	
Stereoscopically identified disc tilt, n (%)			<0.0001
No	189 (68.2)	2080 (84.0)	
Yes	88 (31.8)	397 (16.0)	
Unknown	7	105	
Sloping region adjacent to the outer disc margin, n (%)			<0.0001
No	159 (57.8)	1855 (74.8)	
Yes	116 (42.2)	625 (25.2)	
Unknown	9	102	
Visible pores in lamina cribrosa, n (%)			0.42
No	79 (27.8)	772 (30.3)	
Yes	205 (72.2)	1776 (69.7)	
Unknown	0	34	
Vessel bayonetting, n (%)			0.71
No	104 (36.6)	976 (37.8)	
Yes	180 (63.4)	1606 (62.2)	
Cilioretinal vessels, n (%)			0.28
No	215 (75.7)	2018 (78.6)	
Yes	69 (24.3)	551 (21.4)	
Unknown	0	13	
Pallor of disc, n (%)			0.21
No	275 (97.2)	2463 (95.6)	
Yes	8 (2.8)	114 (4.4)	
Unknown	1	5	
Beta peripapillary atrophy, n (%)			0.0001
No	58 (20.4)	832 (32.4)	
Yes	226 (79.6)	1736 (67.6)	
Unknown	0	14	

The demographic associations of GCs appear to be varied among prior studies. We found that participants with glaucoma who had GC were younger than those who did not have GC, a finding that was also seen in a study that investigated GCs in patients with glaucoma.[2] However, the association of GC in a younger age group persisted even after adjusting for other factors in our study, while it was not significant even in the unadjusted results of the other study. It is not clear why a younger population with glaucoma should have more GCs. It raises the possibility that over time, GCs may disintegrate and disappear, but this did not appear to be the reason in our study population. When we reviewed images with GCs at baseline with available follow-up visit images after several years, we found that in the few instances where there was discordance, it was either because the grader missed identifying the presence of GC or the images were not of sufficient quality to identify their presence with certainty. Both studies did not find any association between the presence of GC and the sex of patients with glaucoma, although the Reykjavik Eye Study on a white population found GC to be more common among women than men.[5] One other finding that we did not anticipate or find in any of the earlier reports on GCs was its association with diabetes mellitus. Our study found 46% increased odds of having GC in African ancestry glaucoma cases with diabetes. The reason for this association remains unknown currently.

When the first few cases of GC were identified and reported in 1980, it was suggested that increased pigmentation of the skin would be associated with increased prevalence of GCs.[1] This was evident by the finding in several studies where black people were reported to have more GCs than white people. The African ancestry population of the POAAGG cohort is an admixed population, with varying proportions from African ancestry individuals. We hypothesised that higher African ancestry would be associated with the presence of GCs among glaucoma cases within this population. We had earlier shown that in the POAAGG Study population, a higher degree of African ancestry was associated with an increased POAG risk.[8] Applying a similar methodology, as described in our previous study, among POAAGG glaucoma cases with and without GCs, we found that the ancestral component q0 (shown to have a significant lower mean in participants with higher degree of African ancestry) was significantly associated with presence of GC. These results suggest that African ancestry is a risk factor for developing GC.

We identified several features on the optic disc head that were associated with GC. Eyes with stereoscopically identified optic disc tilt had 84% more likelihood of having GC. In a cross-sectional study of 136 patients with early-stage POAG, optic disc tilt (defined as discs having an ovality index >1.3) appeared to be associated with bihemispheric retinal nerve fibre layer (RNFL) defects in patients with early glaucoma, regardless of their refractive status.[10] The disc images of representative cases showing the relationship of the extent of disc tilt and bihemispheric RNFL defects showed the presence of GC.[11] On reviewing the optic disc photographs of these 136 patients, GC was found to be present in 23.5% of the eyes examined. The authors contended that because GCs tended to occur frequently in eyes with large, non-tilted optic discs that had large horizontal diameters of the optic disc, they would not alter the results of the association of the ovality index and the bihemispheric RNFL defect.[12] While this is likely true when ovality index is used as a measure of optic disc tilt, when stereoscopically

Table 3 Multivariable analysis for demographic and optic disc factors associated with grey crescent in glaucoma cases

			Adjusted analysis*	
	Total N of eyes	Grey crescent present n (%)	OR (95% CI)	P value
Age (per 10 years younger)	2729	273 (10.0)	1.27 (1.11 to 1.43)	0.001
Diabetes				0.01
No	1650	144 (8.7)	Ref	
Yes	1079	129 (12.0)	1.46 (1.09 to 1.96)	
Stereoscopically identified disc tilt				<0.0001
No	2250	187 (8.3)	Ref	
Yes	479	86 (18.0)	1.84 (1.36 to 2.48)	
Sloping retinal region adjacent to the outer disc margin				<0.0001
No	1995	159 (8.0)	Ref	
Yes	734	114 (15.5)	2.37 (1.74 to 3.22)	
Beta peripapillary atrophy				<0.0001
No	852	55 (6.5)	Ref	
Yes	1877	218 (11.6)	2.32 (1.60 to 3.37)	

*The multivariable logistic regression model only included all the factors listed in this table.

identified tilt is used, it might alter the results, as has been shown in a previous report.[13] This study was performed on Korean eyes where optic disc tilt has been associated with myopic glaucoma.[14] More investigation is required to understand the association of optic disc GC and stereoscopically identified tilt in an African ancestry population with glaucoma. The likelihood of having a sloping margin adjacent to the outer disc margin increased more than twofold in eyes that had GC. Imaging modalities such as SD-OCTs are beginning to describe the disc margins in glaucoma in more detail. This sloping margin feature perceived in stereoscopically visualised colour images needs to be investigated by more accurate imaging modalities to understand how this feature is related to GCs in participants with glaucoma.[15 16]

The presence of GC increased more than twofold in eyes that had beta peripapillary atrophy. However, though there has been no evidence of a link between GC and POAG to date, there has been an association shown between the presence and area of beta peripapillary atrophy and POAG.[17–20] The presence of the GC did not correlate with the presence or degree of beta peripapillary atrophy in the study that investigated GC among both black and white glaucoma cases.[2] In the Reykjavik Eye Study, the prevalence of GC was inversely related to the prevalence of peripapillary atrophy, which included both alpha and beta peripapillary atrophy.

Study limitations

There was considerable variability in glaucoma characteristics, severity and treatment history as can be expected in a cross-sectional study. We therefore confined our investigation for associations to demographic features and the qualitative optic disc features evaluated by the Reading Center. We acknowledge that there was only modest grade–regrade agreement which highlights the difficulty in grading features of the optic disc in general. Previous literature on the reliability of examining colour images to detect features on the optic disc has reported only moderate, slight-to-fair or poor intergrader agreements. Suboptimal reproducibility continues to be a problem in grading of optic disc features in glaucoma. This is not specific to GCs. Previous studies among patients with glaucoma do not report on intragrader or intergrader agreements on the identification of GCs.[21 22] The large initial Reykjavik Eye Study had only single grading. In contrast, our study included a relatively large number of glaucoma disc images compared with other studies and applied a double-grading method with adjudication.

The POAAGG Study excluded individuals with high myopia (≥–6.00 D) and there were no comprehensive data on axial lengths. Refractive error was extracted from data on phakic eyes. After adjusting for refractive errors with available data, we found no substantial changes in the results except for age losing its significance. This study does not have enough power to substantiate an association of GCs with myopia. The glaucoma cases in the POAAGG Study consisted solely of individuals with African ancestry that precluded comparison with a white population. Medical history taken at enrolment may have been subject to misclassification due to recall bias. We could not use the available data from POAAGG controls without glaucoma since imaging in controls was confined to only those who had a medical reason for retinal imaging. Finally, due to the continuing recruitment of additional POAAGG subjects long after the genetic sample procurement was completed, there were a substantial number of missing values in the ancestry analysis (table 1). For this reason, we could not include ancestry for the multivariate analysis and therefore cannot say with certainty that this association

is independent of other significant demographic associations.

In summary, 15% of POAG cases of African ancestry had a GC in the optic disc that was mostly unilateral. Younger patients and patients with diabetes mellitus had more GC. The presence of GC was associated with optic disc tilt, a sloping retinal region adjacent to the outer disc margin and the presence of beta peripapillary atrophy in this population with glaucoma. These associations should be taken into account when evaluating demographic and ocular characteristics in patients with POAG.

Contributors ED—substantial contributions to the conception or design of the work; acquisition, analysis and interpretation of data for the work; drafting and revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. JG—analysis and interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. MGM—substantial contributions to the design of the work; interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. G-sY—analysis and interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. HVG—interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. RS—interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. VA—interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. PSS—interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. RL—acquisition and Interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. EJS—acquisition and interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. JO'B—substantial contributions to the conception or design of the work; interpretation of data for the work; revising the work for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. ED, guaranter.

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