The Heritability of Pigment Dispersion Syndrome and Pigmentary Glaucoma

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• PURPOSE: **Pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) are presumed to be inherited in an autosomal dominant manner. We examine relatives of patients with PDS and PG in order to determine the heritability of these diseases.**

• DESIGN: **This was a prospective, cross-sectional study.**

• METHODS: **One hundred and one patients with PDS were prospectively recruited over 11 months. Four of the patients had PDS without ocular hypertension or glaucoma, 6 had PDS and ocular hypertension, and 91 had PG. Criteria for PDS were 2 of 3 signs: Krukenberg spindle, midperipheral iris transillumination defects, and/or heavy trabecular meshwork pigmentation. Criteria for PG were PDS and 2 of 3 signs: intraocular pressure >21 mm Hg, glaucomatous optic nerve damage, and/or glaucomatous visual field loss. Ninety-nine first-degree relatives living within a 100-mile radius of Iowa City, Iowa were examined in the clinic to determine the probability of familial transmission.**

• RESULTS: **A total of 10 of 99 (10.10%) first-degree relatives were diagnosed with PDS (1 with PDS alone, 2 with PDS and ocular hypertension, and 7 with PG). Seven families with ≥2 affected members were identified. The majority of affected family members (8/10) showed moderate to heavy trabecular meshwork pigmentation and either Krukenberg spindle or transillumination defects.**

• CONCLUSIONS: **Most of the cases of PDS in our study were sporadic, and the risk to first-degree relatives is lower than previously reported. However, there are families with apparent autosomal dominant inheritance of PDS in which the risk to relatives may be high. (Am J Ophthalmol 2019;202:55–61. © 2019 Elsevier Inc. All rights reserved.)**

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WHEN SUGAR AND BARBOUR[1] FIRST DESCRIBED pigmentary glaucoma (PG) in 1949, they felt that it was a "rare clinical entity." It is now recognized that PG and the underlying pigment dispersion syndrome (PDS) are common disorders. PDS is characterized by an abnormal loss of iris pigment epithelium with dispersion throughout the anterior segment of the eye. This pigment is deposited along the corneal endothelium as a Krukenberg spindle, in the trabecular meshwork (TM) as a dark band, on the anterior surface of the iris, and at the junction of the posterior zonules and lens capsule, as a Scheie stripe or Zentmayer ring. The pigment originates when a back-bowed iris causes the iris pigment epithelium to abrade against packets of lens zonules, resulting in characteristic radial slit-like midperipheral transillumination defects (TIDs) in the iris.[2] A subset of patients with PDS develop elevated intraocular pressure (IOP) because of progressive trabecular dysfunction caused by the dense trabecular pigment. Some of these patients with elevated IOP will develop glaucomatous optic nerve head damage and are considered to have PG.[3]

In 1966, Sugar[4] reviewed 147 cases of PG and reported many additional characteristics, including bilaterality, a frequent association with myopia, a greater incidence in men than in women, and a relatively young age at onset. Bick,[5] in 1956, first proposed that concentric atrophy of the iris pigment epithelium is the primary lesion in PG. Later, many others, including Scheie and Fleischhauer,[6] Sugar,[4] and Kupfer and associates[7] advocated this concept. Kupfer and associates[7] studied the histopathology of iris tissue and TM from patients with PDS and described outer pigment epithelial cell loss with a marked thinning of the remaining outer layers of iris. Campbell[2] described mechanical rubbing between anterior zonular packets and iris pigment epithelium to be causative in the pathogenesis of PDS and PG.[2] The location and number of the TIDs correlated with the position and number of the underlying zonular bundles. He hypothesized that iridozonular friction during pupillary movement disrupts the iris pigment epithelium, releasing pigment into the posterior chamber.

Kaiser-Kupfer and associates[8] proposed a hereditary basis for pigment dispersion caused by abnormal pigment epithelium of the iris and the ciliary body, which increases the vulnerability to contact with zonules and subsequent mechanical rubbing. In 1996, Ritch[9] proposed a unification hypothesis of pigment dispersion, which postulated that a

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gene affecting some aspect of the development of the middle third of the eye early in the third trimester could be the cause. This hypothesis could explain the abnormally high incidence of lattice degeneration of the retina and retinal detachment in patients with PDS and the high susceptibility of iris pigment epithelium cells to disruption.

Other conditions can also lead to the release of iris pigment without all of the classic features of PDS. Iris trauma from iris cysts, injury, surgery, or abrasion from an artificial lens implant or a subluxed crystalline lens may cause release of iris pigment.[10–12] Pigment release from the iris has also been detected in patients with diseases that are frequently associated with lens dislocation and secondary glaucomas, such as exfoliation syndrome and Marfan syndrome.[13,14] A recent report of PG in a patient with Marfan syndrome without a subluxed lens suggested that mutations of fibrillin-1 or other genes associated with microfibrils might have a role in PDS/PG.[15]

Previous studies have suggested a hereditary basis for PDS and PG. A positive family history of glaucoma has been found in 4% to 26% of patients with PDS and/or PG.[16–18] The largest study to date was by Mandelkorn and associates,[19] who reported 23 patients in 4 families with PDS and observed this syndrome to be transmitted in an autosomal dominant pattern in 3 of the 4 families, independent of refractive error, iris color, or gender. A genetic basis for dispersion of iris pigment and glaucoma in mice also provides support for a genetic basis for PG in humans.[20]

The purpose of our prospective study was to examine the familial prevalence and type of inheritance in a large cohort of family members of patients with PDS and PG.

METHODS

IN THIS CROSS-SECTIONAL STUDY, PATIENTS WERE IDENTIfied in the Glaucoma Service, Department of Ophthalmology and Visual Sciences at University of Iowa Carver College of Medicine over an 11-month period. Consecutive patients with PDS and PG were evaluated after obtaining informed consent for participation in the study. Approval for this Health Insurance Portability and Accountability Act–compliant study was prospective and was obtained through the Institutional Review Board of University of Iowa, Iowa City, Iowa, and all research adhered to the tenets of the Declaration of Helsinki.

A total of 101 unrelated individuals with PDS and PG were prospectively enrolled. We excluded patients with pigment dispersion caused by other conditions, such as trauma, iris cysts, iritis, intraocular lens implant, and pseudoexfoliation of the lens capsule, etc. A complete ocular history was obtained, including a history of ocular hypertension (OHT) and glaucoma and family history of glaucoma. Patients were also asked if they had first-degree relatives >18 years of age who lived within a 100-mile radius of Iowa City, Iowa, and whether they would be willing to be evaluated for PDS.

A standardized ophthalmic examination was carried out, which included slit-lamp biomicroscopy looking for a Krukenberg spindle that was graded from 0 to 4 (0 = none, 1 = few flecks, 2 = subtle spindle, 3 = dense spindle, and 4 = diffuse pigment). IOP was measured with Goldmann applanation tonometer. Gonioscopy was performed with a Posner or Sussman 4-mirror lens. TM pigmentation was graded from 0 to 4 (0 = no pigment, 1 = light pigment, 2 = moderate pigment, 3 = heavy, nonconfluent pigment, and 4 = confluent, heavy pigment). The iris contour was also graded (back-bowed, flat, or convex). Infrared transillumination was performed to evaluate the iris for TIDs as has been described previously.[21] Refractive error was determined by autorefractometer (Topcon, Tokyo, Japan). Biometry (IOL Master; Carl Zeiss Meditec, Dublin, CA) determined anterior chamber depth, keratometry, and axial eye length. Optic nerve status was determined by evaluation with an indirect fundus lens and the vertical and horizontal cup-to-disc ratio was determined. Humphrey visual fields (Humphrey instruments; Carl Zeiss Meditec) and optical coherence tomography (Cirrus HD OCT; Carl Zeiss Meditec) were obtained to evaluate glaucoma severity. Ninety-nine first-degree relatives within a 100-mile radius also underwent standardized ophthalmic examination to determine the presence of PDS and/or PG. There is a potential for misclassification of PDS in very young people because the disease may not manifest until the 20s or 30s, and therefore we did not examine family members who were <18 years of age. The first-degree relatives ranged in age from 19 to 99 years (mean age 54.30 ± 18.76 years; median 53 years). All of the first-degree relatives underwent a complete ophthalmologic examination similar to the patients, including slit-lamp biomicroscopy, applanation tonometry, gonioscopy, and infrared videography to identify iris TIDs. In addition, their refractive status was evaluated with an autorefractometer and their axial eye length and anterior chamber depth were recorded. Relatives were asked whether they knew their highest previous IOP measurement and the higher of the historical or measured IOP was recorded.

Based on our examination, subjects were separated into 1 of 3 categories: 1) PDS—≥2 of 3 characteristics in at least 1 eye: Krukenberg spindle, midperipheral iris TIDs, or heavy TM pigmentation (grade 2 or higher); 2) PDS with OHT—PDS plus IOP >21 mm Hg; and 3) PG—PDS plus ≥2 of the 3 characteristics in at least 1 eye: IOP >21 mm Hg, glaucomatous optic nerve head damage (cup-to-disc ratio > 0.5 or cup-to-disc ratio asymmetry > 0.2) with neuroretinal rim loss, or glaucomatous visual field defect.

We described PDS/PG cases as familial if we were able to identify an affected family member on our examination. If we were not able to identify an affected relative, we called the patient sporadic, recognizing that there are possibly

TABLE 1. Features of Probands with Pigment Dispersion Syndrome and Pigmentary Glaucoma

Feature	Number of Patients/Number of Eyes	Percent
Krukenberg spindle	159/201	79.10
Iris TIDs	151/198	76.26
TM pigmentation		
≥Grade 2	195/202	96.53
Grade 2	62/202	30.69
Grade 3	72/202	35.64
Grade 4	61/202	30.20
Iris contour		
Flat	157/202	77.72
Concave	30/202	14.85
Convex	9/202	4.46
Eyes on pilocarpine	6/202	2.97

TID = transillumination defect; TM = trabecular meshwork

affected relatives that we did not have the chance to evaluate. It is also possible that some sporadic cases may represent disease caused by recessive genes that have not yet been discovered.

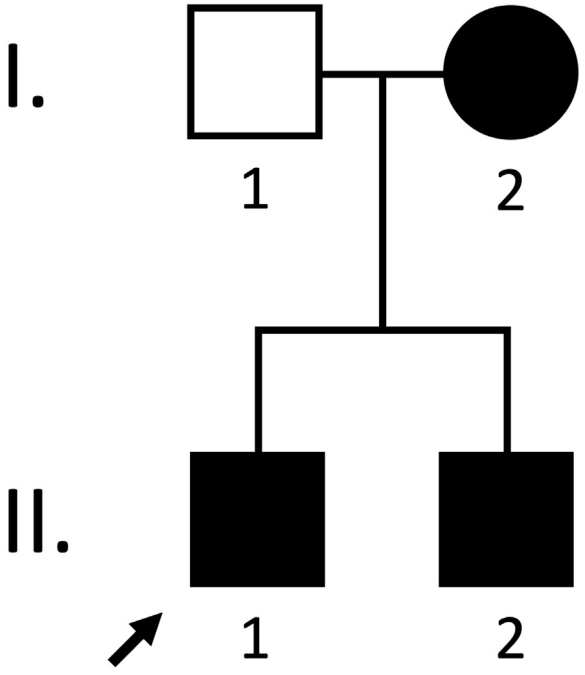

FIGURE 1. Pedigree of family 1, with 3 affected members (filled symbols). Arrow indicates proband.

RESULTS

OF THE 101 PROBANDS WITH PDS, 4 HAD PDS WITHOUT OHT or glaucoma, 6 had PDS with OHT, and 91 had PG. Because the patients were recruited from a tertiary glaucoma practice, the probands were skewed toward patients with glaucoma and cases of PDS without glaucoma were underrepresented.

• **FEATURES OF PROBANDS:** *Age of diagnosis and gender*. The age at diagnosis ranged from 12 to 75 years. The mean age at diagnosis was 42.49 ±13.10 years (41.52 ±13.87 years for men and 44.17 ±11.54 years for women). The median age at diagnosis was 43 years for men and 46 years for women. Sixty-four (63.37%) of the probands were men and 37 (36.63%) were women, with a male:female ratio of 1.73:1. The mean age at diagnosis of the probands who were found to have an affected family member (familial PDS) was 30.5 years, compared with 43.73 years for sporadic PDS.

Race. The patient population was predominantly white (93.07%), with only 2 patients being Latino (1.98%) and 1 patient each being of African-American, East Asian, South Asian, Mediterranean, and Native American origin. For comparison, the population of the state of Iowa in 2017 was 91.1% white, 6.0% Latino, 3.8% African-American, and 2.6% Asian (U.S. Census Bureau 2017 estimate).

Clinical features. Table 1 describes the clinical features of the probands with PDS. A Krukenberg spindle on slit-lamp biomicroscopy was found in 79.10% (159/201) of eyes. One eye could not be examined for Krukenberg spindle because because it had undergone corneal endothelial transplantion. Iris TIDs were seen in 76.26% (151/198) of eyes on infrared videography and asymmetric transillumination was observed in 13.13% (13/99) of patients. Four eyes of 2 patients could not be transilluminated because of dilation (2 eyes) or technical difficulties with the infrared camera (2 eyes). The majority, 60.10% (119/198) of eyes, demonstrated both corneal endothelial pigment and iris TIDs.

The anterior chamber angles of all eyes reported in this study were open. Gonioscopy revealed heavy TM pigmentation (grade 2 or higher) in 96.53% (195/202) of eyes. Asymmetric TM pigmentation was present in 11.88 % (12/101) of patients. The iris contour was found to be in a characteristic concave midperipheral configuration in only 14.85% (30/202) of eyes, while other patients had a more flat (77.72%) or a convex (2.97%) configuration. The contour of 6 eyes (2.97%) could not be evaluated because of pilocarpine usage.

Of the 126 phakic eyes, 113 (89.68%) were myopic, 10 (7.93%) were hyperopic, and 3 (2.38%) were emmetropic. The mean axial eye length was 25.39 ± 1.90 mm (range 20.67–35.9 mm), with the majority of eyes (87.56%) being longer than the published normal mean of 23.67 mm.[22]

• **FAMILY HISTORY OF GLAUCOMA AND INHERITANCE IN PDS:** A positive family history of glaucoma was elicited in 58.41% (59/101) of our patients, but only 6.93% (7/101) of the patients reported having a known relative with PDS or PG.

Ninety-nine first-degree relatives of 44 of the 101 probands were available for examination. Of these 44 probands, 7 (15.91%) had first-degree relatives with PDS. There were 7 families with ≥2 affected individuals. Five had only 2 affected individuals (3 with an affected father and son, 1 with an affected father and daughter, and 1 with 2 affected brothers). Two probands had >1 first-degree relative with PDS (Figures 1 and 2).

In total, 10 (10.10%) of 99 first-degree relatives were diagnosed with PDS (1 with PDS, 2 with PDS with OHT, and 7 with PG). All of the families were white. All of the family members were examined in the clinic by a single examiner (Dr. Tandon). However, during the study, a proband (family 2 in Figure 1) belonging to a large PDS family that had been previously examined by our group presented to the clinic, and we therefore included 5 of those first-degree relatives examined earlier for the purpose of this study.

In the affected family members, Krukenberg spindles were found in 14 of 20 eyes (70.00%). Midperipheral iris TIDs were detected in 13 of 20 eyes (65.00%). Moderate to heavy TM (≥2) pigmentation was present in 16 of 20 eyes (80.00%).

Table 2 compares the clinical features between affected and unaffected relatives. Eleven of 20 eyes (55%) from family members with PDS had myopia of −1 diopter (D) or worse. Only 1 patient had significant iris concavity. It is interesting that the unaffected relatives were, on average, more myopic than the affected relatives and had slightly longer axial eye lengths, although this was not statistically significant ($P = .08$).

Among the first-degree relatives there were 4 individuals with primary open angle glaucoma, 2 with OHT, and 1 with normal tension glaucoma.

DISCUSSION

SINCE THE INITIAL SUGGESTION OF A GENETIC ETIOLOGY underlying familial Krukenberg spindles[23,24] and reports of familial pedigrees with PDS/PG,[19,25–27] PG has been largely considered to be a disorder with autosomal dominant transmission.

Scheie and Cameron[16] studied 407 patients with PDS and/or PG and reported a positive family history of glaucoma in 4% of patients with PDS and 16% of the patients with PG. They concluded that the "low incidence suggests a multifactorial inheritance pattern or trait of variable penetrance and expressivity."[16]

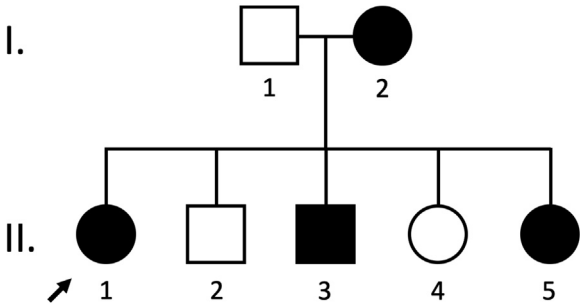

FIGURE 2. Pedigree of family 2, with 4 affected members (filled symbols). Arrow indicates proband.

Becker and associates[28] suggested an association between human leukocyte antigen-B13 and Bw17 and PDS, and an increased prevalence of human leukocyte antigen-B12 when PG is present, but these findings have not been replicated by others.[29,30] Krukenberg spindles have been described in 3 separate mother and daughter pairs[23,24,31] and in twins.[26] The inheritance pattern of PDS and PG has been explored in various studies.[32,33] Roth and associates[26] described 8 families with PDS, concluding that it was inherited in an autosomal dominant fashion. Mandelkorn and associates[19] described 4 families with PDS and observed this syndrome to be transmitted in an autosomal dominant pattern from parent to offspring in 3 of the 4 families, independent of refractive error, iris color, or gender. Several routes of inheritance (father-to-son, father-to-daughter, mother-to-son, and mother-to-daughter) were observed. Sugar[33] suggested that PG was inherited in an "autosomal dominant multifactorial" manner. Bovell and associates[34] identified and phenotypically characterized 6 North American families with autosomal dominant PDS. However, an autosomal recessive pattern of inheritance was suggested by Stankovic[27] in his study of 1 family with PG in 4 generations.

A genetic locus for PDS has been mapped to chromosome 7q35-q36 in white patients with autosomal dominant PDS and PG.[35] However, this linkage has not been replicated. In 2018, Lahola-Chomiak and associates[36] reported that nonsynonymous sequence variations in the premelanosome protein gene were found in 2 families with PDS/PG. Seven additional nonsynonymous variants were found in targeted screening of 394 patients with PDS/PG from 3 cohorts.

Linnér[37] suggested an association between PG and myopia. This association between PG and myopia was also explored by Bovell and associates,[34] Stankovic and associates,[27] and Campbell and associates.[38] Moreover, myopia was also prevalent in the affected subjects in the chromosome 7q families reported by Anderson and associates.[35]

We identified 7 pedigrees with PDS. In these pedigrees, transmission from parent to child was observed in 6 of

TABLE 2. Clinical Features of Relatives of Patients with Pigment Dispersion Syndrome and Pigmentary Glaucoma

Feature	Affected (n = 10)	Unaffected (n = 89)
Male:female ratio	1.5:1 (6:4)	0.4:1 (28:62)
Refraction (diopters)		
OD mean	−1.42 ± 1.55	−2.00 ± 3.05
OS mean	−1.11 ± 1.66	−2.35 ± 3.13
Intraocular pressure (mm Hg)		
OD mean	24.39 ± 7.64	19.83 ± 5.85
OS mean	24.0 ± 18.06	19.72 ± 5.52
Axial eye length (mm)		
OD mean	24.17 ± 0.90	24.70 ± 1.92
OS mean	24.09 ± 1.01	24.68 ± 1.64

OD = oculus dexter; OS = oculus sinister.

7 pedigrees. Specifically, transmission of PDS was noted from father-to-daughter (1 family), father-to-son (3 families), mother-to-son (2 families), and mother-to-daughters (1 family). These transmission patterns exclude X-linked and mitochondrial inheritance in at least some cases of familial PDS. Overall, the frequent vertical transmission of disease in these pedigrees suggests that some cases of PDS may have an autosomal dominant mode of inheritance. However, none of the pedigrees demonstrated transmission of PDS through 3 generations, which is typically required as strong evidence for autosomal dominant inheritance. Autosomal recessive or pseudodominance cannot be ruled out.

The risk of a first-degree family member developing glaucoma in our study was 10.10%. This risk for our predominantly white Iowa population may not be the same in all other populations. This may overestimate the risk because 1 of the probands was a member of a previously identified PDS/PG family. While this risk is lower than some previous reports,[19] it is still higher than the general population. A slit-lamp examination–based screening in a population undergoing glaucoma screening found the prevalence to be 2.45%.[39] We may have found a higher prevalence, not only because we were examining PDS/PG relatives instead of the general population but also because we used infrared videography to look for iris transillumination and gonioscopy to make the diagnosis.[21] If we relied on slit-lamp examination for Krukenberg spindles only, we would have found a prevalence of 7.07% in these relatives. Therefore, using only slit-lamp examination for Krukenberg spindles, these PDS/PG relatives were at only a 2.89 times higher risk of being diagnosed than what has been reported in the general population.[39]

It is possible that we missed some cases of PDS/PG because some relatives were too young to develop the disease. To decrease the likelihood of this, we limited our evaluation of first-degree relatives to individuals >18 years of age. The mean age of the examined relatives was 54.30 ± 18.76 years (median 53 years). It is also possible that some relatives were so old that they may have "burned-out" and lost signs of PDS. There were 4 relatives with primary open angle glaucoma, 2 with OHT, and 1 with normal tension glaucoma. The use of infrared iris transillumination and gonioscopy (looking for angle pigmentation and Scheie stripes) would make it unlikely, but not impossible, that subtle PDS would have been missed.

This is the largest study on PDS and PG subjects with a complete office-based ophthalmic examination including infrared videography. The gender predilection in our study reveals a 2:1 prevalence of males:females with PG, which correlates well with previous reports.[3,32,40]

In this study population, there was a predominance of myopic (89.68 %) eyes. These figures are consistent with others who found a strong correlation between myopia and PDS. Krukenberg had noted in his original report in 1899 that all 3 of the patients with PDS he described were myopic.[41] Since then, the association of myopia with PDS and PG has been explored in various studies that have found a prevalence of myopia ranging as low as 6.6% to as high as 78.2% among patients with PDS.[2,4,16,19,42,43] Mandelkorn and associates[19] found a predominance of myopia (16/23) in their PDS population. Stankovic[27] felt that myopia may be considered as a part of the PDS/PG disease spectrum and that polygenic inheritance could account for this spectrum. Myopic individuals have been shown to have a positive pressure response to topical steroids, even in the absence of any evidence of glaucoma.[44] This was substantiated by Farrar and associates,[18] who felt that refractive error has prognostic significance in patients with PDS and PG. They found that patients with PG had a more myopic mean refractive error (OD −3.53 D, OS −3.65 D) when compared with patients with PDS (OD −1.91 D, OS −1.88 D), thus concluding that myopia was one of the independent risk factors for PDS and PG. In our study, patients with PG were found to have longer axial eye lengths, figures consistent with earlier observations by Lord and associates,[45] who studied the keratometry and axial eye length in patients with PDS and PG and reported a mean of 25.98 ± 2.00 mm. The fact that most patients did not demonstrate iris concavity on gonioscopy was not surprising because many of these patients were older and 76 of 202 eyes were pseudophakic.

In conclusion, we found that most of our cases of PDS and PG are sporadic. The risk to most family members is lower than previously reported. However, there are a few families with an apparent autosomal dominant inheritance pattern.

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