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REVIEW ARTICLE

Pigment dispersion syndrome and pigmentary glaucoma: overview and racial disparities

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Abstract

Pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) are two stages within the same ophthalmic disease spectrum, which are known to be affected by race. The prevalence of PDS is underestimated, largely due to its minor clinical symptoms. Although the prevalence of PG is low, the visual impairment associated with PG is extremely severe. The prevalence of PDS-PG is four or more times higher in Caucasians than in Blacks or Asians, and the "classic" PDS in Caucasians has long been used as a benchmark diagnostic criterion. Following extensive research focused on African Americans and Asians, the standard for diagnosing PDS-PG was refined. At the same time, the pathogenesis of PDS is not the same in different races. Hence, the effectiveness of preventive treatment and the need for treatment may not be equivalent in different races. The rate of conversion of PDS to PG is nearly 1/3 in Caucasians and higher in blacks and Asians, requiring more aggressive treatment and monitoring. We systematically searched a PubMed database from inception to March 2022 to provide an overview of research progress in various aspects of PDS-PG. Specifically, this paper considers the effects of race on disease prevalence, clinical manifestation, diagnostic criteria, disease mechanism, hereditary traits, treatment, and prevention to provide an accurate and comprehensive guide for the diagnosis and treatment of PDS-PG in various races.

Keywords Pigment dispersion syndrome · Pigmentary glaucoma · Race · Ethnicity

Key messages

- Pigment dispersion syndrome and pigmentary glaucoma are two different stages within the same disease spectrum and is known to be affected by race.
- This paper summarizes the prevalence, diagnostic criteria, and pathogenesis of pigment dispersion syndrome and pigmentary glaucoma in different races to correct the previous pattern of disease diagnosis and analysis dominated by Caucasian population studies.
- Based on the genetic patterns and disease outcomes in different races, this paper discusses the treatment options for pigment dispersion syndrome and pigmentary glaucoma and different races, thereby increasing the awareness of individually tailored management and clarifying future research directions.

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Introduction

Pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) belong to the same spectrum of diseases of concern. PDS is a group of clinical syndromes caused by the release, dispersion, and deposition of iris pigment to various structures in the anterior segment. The glaucomatous optic neuropathy associated with PDS is known as PG [1]. PDS has an underestimated prevalence and minor clinical symptoms. In contrast, PG has a low prevalence but severe vision effects and is easily confused with other types of open-angle glaucoma [2].

Notably, PDS-PG is one of the ophthalmic diseases that is most affected by racial factors. "Classic" PDS and PG were identified in Caucasians in 1949 and were once thought to occur only in Caucasians [3, 4]. Subsequent studies have confirmed an atypical clinical presentation in blacks, resulting in the underestimation of PDS and PG prevalence in blacks [5, 6]. The atypical PDS-PG subtype is also present in Asians [7, 8]. Racial factors play important roles in the epidemiological features, clinical manifestations, pathogenesis, hereditary traits, and disease outcomes of PDS-PG. Thus, the use of uniform diagnostic criteria and treatment protocols for patients with PDS-PG across racial groups can result in missed diagnoses and incorrect treatment. Herein, we provide an overview of recent advances of PDS-PG and highlight the impact of racial factors in various aspects of the disease.

Methods

Literature in PubMed was systematically searched from inception to March 2022. The following combinations of terms were searched: "pigment dispersion syndrome," "pigmentary glaucoma," "race," "Caucasian," "blacks," and "Asian." Relevant articles and appropriate cross-references were considered for inclusion, including basic studies, clinical studies, genetic studies, case reports, and reviews.

Results

Epidemiology

Prevalence of PDS and associated racial differences

The prevalence of PDS is underestimated, partly due to the lack of self-reported symptoms in PDS without glaucoma or elevated intraocular pressure (IOP). On the other hand, atypical PDS and differences in the distribution of PDS among different races make it impossible to standardize the prevalence of PDS. Ritch et al. reported that the prevalence of PDS was 2.45% in Caucasians and 0.53% in African Americans in a US-based study [9]. However, that study was conducted on employees of investment firms with higher rates of myopia compared with the general population [9]; thus, the resulting prevalences are not representative of the real-world situation. The actual difference in PDS prevalence between blacks and Caucasians appears to be greater. Gaton et al. performed ocular screening on 374 Israelis and found excessive corneal endothelial pigmentation in 5.90% of the subjects [10]. Roberts et al. estimated the prevalence of PDS to be only 0.15% in blacks over seven years of age [6]. In a retrospective study in Minnesota (95% Caucasians), the annual incidence of PDS was estimated at 4.8 per 100,000; all PDS patients were Caucasians, and no incidence was seen in African Americans [11]. The prevalence of PDS in Asians, which has been overlooked, is similar to that in blacks and much lower than that in Caucasians. In a study in Japan, Yamamoto et al. found that none of the 3021 subjects had PDS [12]. The prevalence of PDS in a Chinese glaucoma clinic was only 1.10%, and the population prevalence in Asians is much lower than this [7]. The large difference in PDS prevalence between non-Caucasians and Caucasians may be related to the different iris structures and colors, which prevent non-Caucasian PDS patients from being easily diagnosed. However, even when comprehensive ocular examinations are given, the prevalence of PDS remains higher in Caucasians than in other races. Doane et al. found a much higher rate of PDS in patients seeking refractive surgery (26.46% in Caucasians and 16.67% in others) compared with the general population, and no PDS was detected in any of the six African Americans in the study [13].

Prevalence of PG and associated racial differences

The prevalence of PG is much lower than that of PDS. In Indian study involving multiple races, Paul et al. found a population prevalence of PG of only 0.04% [14]. Racial differences are also present in PG. In a clinical study of open-angle glaucoma involving 14 clinical centers in the USA, only 7.1% of the PG patients recruited were African Americans, in contrast to 41.5% of primary open-angle glaucoma (POAG) patients [15]. Studies in western countries with predominantly Caucasians suggest that PG accounts for 1%–1.5% of all glaucoma patients [16]. Scheie reported a PG rate of 1.13% in 9200 glaucoma patients, including five mixed-race subjects but no black participants [17]. This proportion of PG may be higher than that found in Caucasians alone. In studies on black and Asian patients in the Congo and China, Kaimbo Wa Kaimbo et al. and Qing et al. found that PG accounted for 0.6% and 0.92% of glaucoma patients,

respectively [7, 18]. Zhang et al. conducted a comprehensive survey of 111 hospitals in 67 cities in mainland China and found that PG accounts for only 0.30% of glaucoma patients [19]. In Japan, Yamamoto et al. did not report any patients with PG [12].

Discrepancies in the PG/PDS ratios reported in different studies may be related to race. Becker et al. reported that 55.56% of blacks with PDS had glaucoma at the time of diagnosis, compared to 33.3% of Caucasians [20]. Farrar et al. reviewed the PDS patients attending glaucoma clinics and found that all black patients had developed PG at the time of initial diagnosis, whereas 16.98% of Caucasians patients did not have combined glaucoma [21]. Roberts et al. found that 57.14% of African-American PDS patients had glaucoma or suspected glaucoma, and an additional 28.6% also had elevated IOP [6]. We found that 83.3% of Asian PDS patients attending the glaucoma clinic had glaucoma at their first visit [7]. The source of recruited subjects varied between studies, resulting in some variation in the PG/PDS ratio. Three studies on Caucasians indicated PG/PDS ratios ranging from 16.9%–33.3% [11, 17, 20], while three other studies reported ratios in the range of 61.82%–83.02% [21–23]. Previous studies were unable to obtain accurate conclusions regarding the differences in PDS/PG ratios between races; thus, further epidemiological investigations are needed.

Clinical Presentation and Diagnosis

PDS patients with normal IOP often lack subjective symptoms. Headaches, blurry vision, and contraction of the visual field may occur when the patient's IOP increases or develops into glaucoma [24]. Nilforushan et al. found that the temporal visual field is less involved in PG than in POAG; this was mainly seen in patients with early and mid-stage glaucoma and needed to be detected by automated visual field examination [25]. Subjective symptoms are not easily distinguished in PG and other types of open-angle glaucoma. However, unlike POAG, exercise or physical exertion can lead to increased symptoms in PDS-PG patients [26]. The glaucomatous optic neuropathy in PG is not significantly different from other types of glaucoma. Signs associated with pigment dispersion are therefore even more critical in the diagnosis of PDS-PG. The signs and diagnostic criteria for PDS in different races are shown in *Table 1*.

Clinical presentation and diagnosis of classic PDS

Classic PDS occurs in Caucasians [1]. Since Sugar et al. first proposed PG as a clinical entity in 1949, the clinical triad of PDS and other signs common to the disease in Caucasians have been used as diagnostic criteria and remain in use today [3, 4]. Iris transillumination defect (ITD), Krukenberg spindle (KS), and Trabecular meshwork (TM) pigmentation are collectively known as the clinical triad of PDS and are the most characteristic clinical signs in classic PDS [27]. The presence of two components of the clinical triad can be used as criteria for the diagnosis of PDS in Caucasians [11]. In 136 Caucasian PDS patients, the prevalence of ITD, KS, and TM pigmentation was 86%, 95%, and 86%, respectively, and 42% of patients presented with the complete clinical triad [11]. ITD is a manifestation of iris pigment loss. The iris pigment epithelium (IPE) in the mid-periphery of the iris rubs against the lens-zonule bundle complexes and causes loss of pigment. The iris in the area of pigment loss appears as radial mid-peripheral ITDs when exposed to light. KS results from the deposition of released pigment on the corneal endothelial surface [28]. The pigment is not merely deposited on the surface of the endothelium; it is phagocytosed by the endothelium and deposited in a vertical spindle-shaped island known as the KS, whose specific morphology is thought to be related to the aqueous convection currents

Table 1 Clinical Presentation and Diagnosis in Different Races

	White patients	Black patients	Asian patients
Typical Signs	TM pigmentation	TM pigmentation	TM pigmentation
	KS	Zonular/lenticular pigmentation	Zonular/lenticular pigmentation
	ITD		KS (small triangle)
Major Signs	Zonular/lenticular pigmentation	KS	Posterior iris bowing
	Anterior iris stromal pigment dusting		
	Posterior iris bowing		
Minor Signs	–	ITD	ITD
		Anterior iris stromal pigment dusting	Anterior iris stromal pigment dusting
		Posterior iris bowing	
Diagnostic Criteria	At least two typical signs	TM pigmentation and another typical/major sign	At least two typical signs

TM, trabecular meshwork; KS, Krukenberg spindle; ITD, iris transillumination defect

and the phagocytosis of pigment by the endothelium [4, 29]. The released iris pigment that reaches the anterior chamber angle can result in the homogenous pigmentation of the TM (Scheie grade II or higher). Occasionally, a pigmented line (Sampaolesi line) can be found in the chamber angle anterior to Schwalbe's ring, which is more common in the inferior anterior chamber angle [27].

In addition to the clinical triad of PDS, classic PDS is often accompanied by posterior iris bowing. Using a slit lamp, a thin concave slit beam is observed on the mid-peripheral iris surface. Ultrasound biomicroscope and anterior segment OCT can be used for the morphological identification of posterior iris bowing [30, 31]. Meanwhile, pigmentation on the anterior iris surface, anterior lens surface, zonules, and posterior capsule of the lens all cause associated signs [4–, 32–34]. Zonular and/or peripheral lenticular pigmentation and anterior iris stromal pigment dusting are also common in 'Classic' PDS [32]. While the above signs are not necessary for the diagnosis of classic PDS, they are important in the diagnosis of atypical PDS, as described in Sect. 2.2.

Atypical PDS and associated racial effects

Although PDS has similar pathogenesis and pathology in different races, the clinical signs differ significantly. PDS is not typical in blacks and Asians, and following the same diagnostic criteria can cause great confusion [5–, 6–8]. Signs such as KS, TM pigmentation, and zonular or peripheral lenticular pigmentation are diagnostic of atypical PDS (Fig.*1*).

The most common subtype of PDS in blacks is not associated with the typical triad of PDS manifestations, although the population characteristics are similar to those of Caucasian PDS. ITD is only present in 14.29% of African American PDS patients and presents as a small, isolated, slit-like transillumination defect. The incidence of KS in African Americans (57.14%) is also lower than that in Caucasians. In the 42.86% of African-American PDS patients without KS, only mild dusting pigmentation of the corneal endothelium is present [6]. TM pigmentation (100%) and zonular and peripheral lenticular pigmentation (85.71%) are common clinical features in African American PDS patients [6, 35]. TM pigmentation is considered more common in the black race and therefore should be used as a diagnostic criterion together with the zonular and peripheral lenticular pigmentation or KS. Zonular and peripheral lenticular pigmentation, which is present in patients with PDS of all races, is an important diagnostic criterion for black patients [36]. Zonular and peripheral lenticular pigmentation is caused by the deposition of released pigment on the peripheral surface of the lens and/or zonules. After pupil dilatation, a ring-shaped deposition of pigment granules, known as Scheie's stripe or Zentmayer's line, can be seen at the junction of the zonules and posterior capsule [37].

Semple et al. reported another subtype of PDS in blacks based on a group of 20 patients (95% women) with a mean age of 73 years and a hyperopia rate of 90% [5]. Although the clinical presentation of this subtype is similar to that of the common PDS subtype in blacks, the population characteristics of the subtype differ significantly from those of classic PDS. Additionally, there may be differences in the pathogenesis of the two black PDS subtypes, as described Sect. 3.

The Asian PDS phenotype is often overlooked. Similar to PDS in blacks, TM pigmentation and zonular and peripheral lenticular pigmentation are present in almost all Asian patients with PDS [7]. KS is observed in 61.1% of Asian patients with PDS; however, unlike the typical KS in Caucasians, the corneal endothelium pigmentation in Asians resembles a small triangle and requires special attention in clinical diagnosis. The presence of two of the above three signs is often used as a diagnostic criterion for PDS in Asians [7, 8, 38, 39]. ITD is rare in Asian PDS patients. Qing et al. reported that only two of 18 PDS patients (11.1%) had isolated short slit-like transillumination defects, and none exhibited typical spoke-like radial ITDs [7]. The most significant difference in the phenotype of PDS in Asians compared to the blacks is that varying degrees of posterior iris bowing are present in 94.4% of Asian PDS patients, while bowing rarely occurs in blacks [6, 7].

Anterior iris stromal pigment dusting is difficult to detect in atypical PDS due to the darker iris color; it is barely observed in blacks and observed in 16.7% of Asians [6, 7]. Although this sign is much less commonly found in Asians than in Caucasians, it is more easily observed by slit lamp compared to TM pigmentation or zonular and peripheral lenticular pigmentation; thus, it should not be overlooked in Asians.

Pathogenesis

PDS pathogenesis and associated racial factors

The theory of mechanical contact and rubbing is the classical pathogenesis of PDS. This theory was proposed by Campbell in 1979 and has been validated in numerous clinical and pathological studies in Caucasians, Asians, and some blacks [5, 7, 9]. The anterior zonules, which are arranged in packets, contact and rub against the posterior surface of the peripheral iris. Mechanical rubbing causes the IPE to rupture and release pigment granules, which are dispersed and deposited on the posterior surface of the lens, zonules, anterior surface of the iris, corneal endothelium, and TM with aqueous humor circulation. ITDs are important evidence of mechanical rubbing, and the location of the spoke defect area in the iris corresponds to the zonular packets [28]. Although the clinical observation of

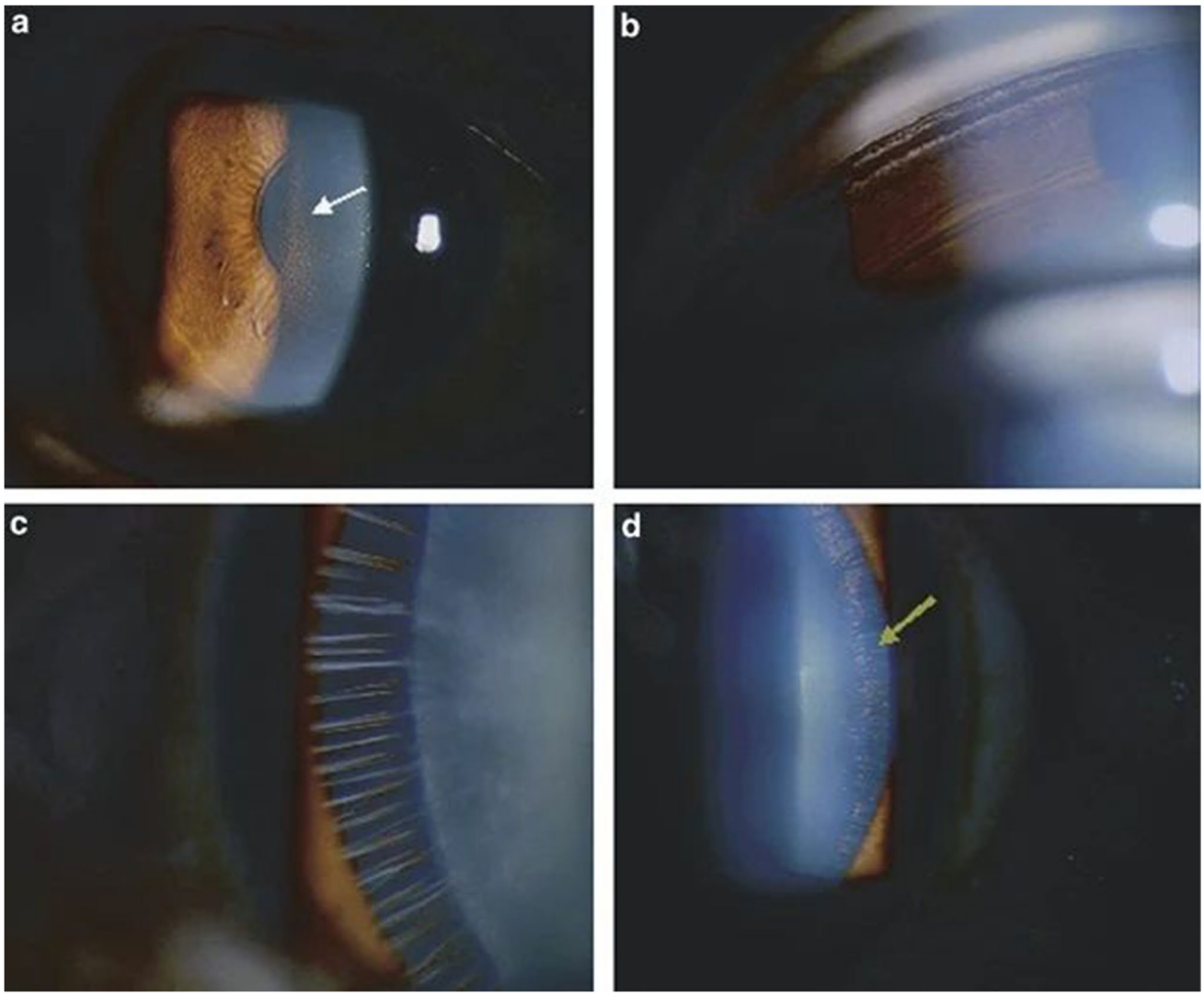

Fig. 1 Signs of "Atypical" Pigment Dispersion Syndrome (**a**) Krukenberg spindle (white arrow), (**b**) trabecular meshwork pigmentation, (**c**) zonular pigmentation, (**d**) lenticular pigmentation (green arrow). (Reprinted from Qing et al. [7] with permission of Eye.)

ITDs is common only in Caucasians, ITDs are also present in non-Caucasians but are not easily observed due to the iris characteristics. We conducted a histologic study of donated iris specimens from Asian and Caucasian PDS patients and found that the anterior surface endothelium of Asian iris specimens consisted of multiple layers of melanocytes filled with melanin granules. In contrast, Caucasians have only a small amount of pigment in the iris stroma and anterior surface endothelium. The IPE in Caucasians is also thinner than in Asians [40]. Moderate to heavy pigmentation masks the spoke-like defects in non-Caucasian PDS patients. In black PDS patients, Roberts et al. detected invisible ITDs by infrared imaging, confirming the presence of mechanical rubbing [41]. Mechanical rubbing is caused by a variety of factors and is closely linked to race. Reverse pupillary block [42, 43], insufficient fixation of the iris dilator muscle [44], abnormal iris insertion position [45, 46], and long anterior zonule (LAZ) contribute to the occurrence of mechanical rubbing in different races (Fig. *2*) [47].

The prevalence of posterior iris bowing in Caucasian and Asian PDS patients is the structural basis for mechanical rubbing [7, 28]. Reverse pupillary block is an important mechanism for the appearance of posterior iris bowing [43]. Liebmann et al. found that the iridolenticular contact area was more extensive in those with posterior iris bowing compared with patients without posterior iris bowing [42]. The iris, which contacts the lens, acts as a flap and does not allow aqueous fluid trapped in the anterior chamber to move into the posterior chamber. Posterior iris bowing occurs when the aqueous pressure in the anterior chamber is higher than that in the posterior chamber. In addition to reverse pupillary block, abnormalities in the position and function of the iris

dilator muscle can also cause posterior iris bowing [44, 48]. Flügel-Koch et al. dissected the eyes of three donors with PG and found that the insufficient fixation of the peripheral end of the iris dilator muscle may have contributed to the formation of posterior iris bowing [44]. In blacks, posterior iris bowing is not common in the initial iris configuration due to the thick iris [28]. This does not mean that blacks with PDS never exhibit posterior iris bowing. Accommodation and prevention of blinking can also alter the iris configuration, causing real-time iris bowing [42, 49]. Therefore, PDS is more prevalent in young, myopic patients. Real-time posterior iris bowing not only exacerbates mechanical rubbing in Caucasians and Asians, it may also cause iris–zonule contact and rubbing in black patients. This might explain the decline in visual accommodation and corresponding decrease in mechanical rubbing and pigment dispersion in patients with increasing age. In such patients, differentiation from normal-tension glaucoma is often required [49].

In PDS patients of all races who do not exhibit posterior iris bowing, other ocular anatomical abnormalities can contribute to the occurrence of mechanical rubbing. Sokol et al. found that the insertion of the iris into the ciliary body is more posterior in PDS patients compared with patients without PDS. This anatomical variation brings the iris closer to the zonules, increasing contact and rubbing [45]. On the other hand, Moroi et al. found LAZs on the surfaces of anterior lens capsules in patients with PDS. Central LAZs on the lens capsule may cause mechanical disruption of the pigment epithelium at the pupillary margin and central iris, leading to pigment dispersion [47, 50]. Notably, Newman et al. found that LAZs occurred more frequently in black women older than 50 years and were closely associated with the presence of KS and pigmented lens striae; moreover, they found that rubbing between the LAZ and IPE may be responsible for the appearance of these signs [51, 52]. LAZs have also been reported to be associated with hyperopia and high IOP [53, 54]. These findings appear to provide a novel explanation for the specific subtype of PDS found in black, elderly, hyperopic, and female patients [5].

In addition to the theory of mechanical rubbing, congenital abnormalities of mesodermal migration are also thought to be an important mechanism of PDS-PG [55]. Gillies et al. found hypoperfusion of iris in patients with PDS, which may be associated with progressive mesodermal dysplasia [56, 57]. PDS has been found to be associated with a variety of retinal and choroidal diseases, including retinal lattice degeneration and retinal detachment [58–60]. PDS may be associated with hypoplasia involving multiple parts of the eye, although iris hypoplasia is the only prominent manifestation. The retinal pigment epithelium is thought to have the same embryological origin as IPE. Based on electrooculography, Scuderi et al. found a decrease in the Arden ratio (the ratio of the light-peak

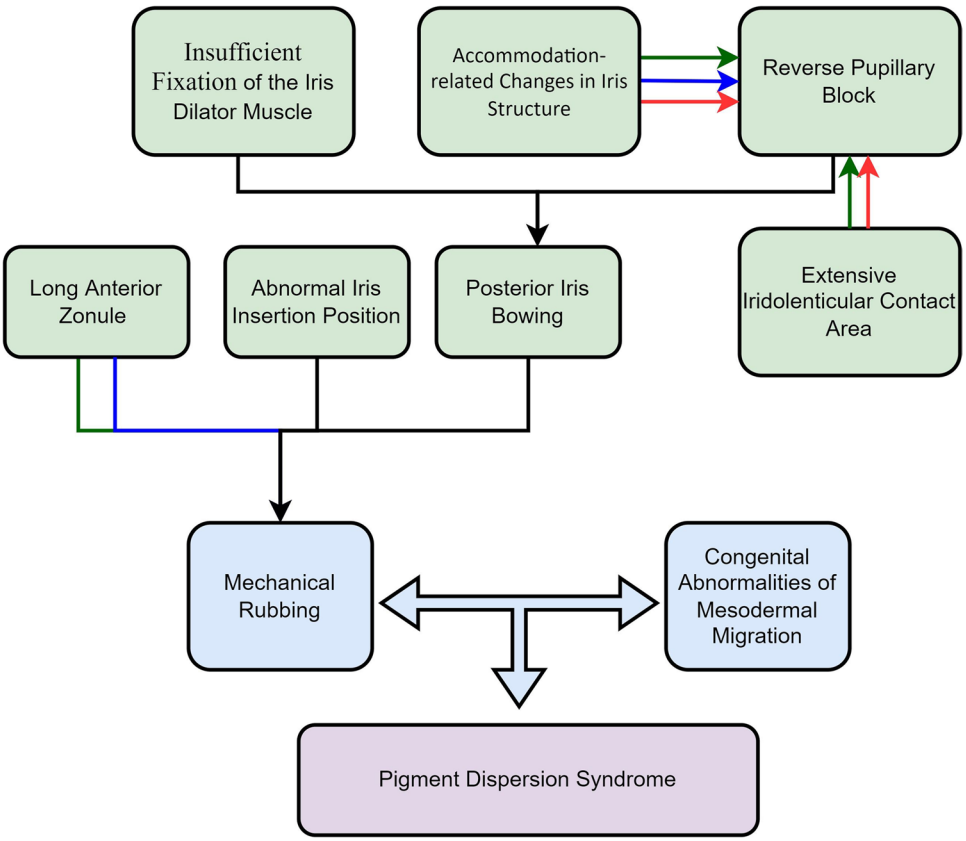

Fig. 2 Pathogenic Mechanism of Pigment Dispersion Syndrome. The green line indicates that the mechanism is common in Caucasian patients. The red line indicates that the mechanism is common in Asian patients. The blue line indicates that the mechanism is common in black patients. The black lines represent unreported race specificity.

amplitude to the dark-trough amplitude) in PDS-PG patients compared to POAG patients and normal subjects [61]. Subsequently, Greenstein et al. reported that the integrity of the retinal pigment epithelial/photoreceptor complex was affected in PDS-PG patients [62]. The hypothesis related to the congenital abnormalities of mesodermal migration requires further development; the next steps are searching for related genes and determining the genetic pattern.

PG pathogenesis and associated racial factors

The conversion of PDS to PG is thought to be associated with the pigment granules that reach the TM with aqueous humor circulation, affecting the function of trabecular cells and causing structural changes in the TM [63]. Microscopic observation of the TM structure in PG patients revealed that free pigment granules were not extensively deposited on trabeculae or intertrabecular spaces; however, they were found in large numbers within trabecular cells [63]. This rejects the hypothesis that pigment granules cause elevated IOP by means of prolonged physical obstruction. Structural abnormalities of the TM caused by pigment granules are thought to be the main cause of PG. Gottanka et al. suggested that the loss of trabecular cells, destruction and fusion of the trabecular lamellae, increase in extracellular material, and obliteration of the canal lead to increased IOP and the development of glaucoma [63]. Trabecular cell dysfunction precedes abnormalities in TM structures. Trabecular cells are responsible for the phagocytosis of pigment granules and the regulation of aqueous humor circulation [64]. Wang et al. found that pigment dispersion decreased phagocytosis and migration in trabecular cells, increased actin stress fiber formation, and increased cell contraction [65]. The long-term deposition of large amounts of pigment granules leads to trabecular cell overload, resulting in the previously observed structural abnormalities [64]. Dang et al. suggested that the small increase in IOP at the beginning of pigment dispersion preceded the dysfunction in trabecular cells and may be associated with the alteration of actin stress fibers [66].

The TM is thought to be more heavily pigmented in blacks than in Caucasians [6]. However, it is unclear whether this heavier pigmentation of the TM is associated with an increased probability of conversion to PG in black PDS patients. While the degree of TM pigmentation is not associated with the risk of developing PG, it is related to PG severity [24]. The roles of racial factors in the pathological changes of the TM and the conversion of PDS to PG require further study.

Genetics and Genes

Familial aggregations of PDS and PG are present in all races, and PDS-PG was initially thought to be inherited in an autosomal-dominant fashion [27, 67]. However, subsequent studies on the prevalence of first-degree relatives of PDS-PG patients found a large number of sporadic cases, which points to a more complex pattern of inheritance [5, 23]. Moreover, multiple genes and environmental factors are associated with PDS-PG [23, 68]. Tandon et al. reported that a family history of PDS or PG was present in only 6.9% of Caucasian PDS patients [23], while Siddiqui et al. found that no patients had a family history of PDS in a study on Caucasian PDS patients [11]. The proportions of PDS patients with a family history of PDS were reported as 18.2% and 22.2% among blacks and Asians, respectively [7, 36]. The prevalence of having first-degree relatives with PDS and PG does not differ significantly among races. Tandon et al. followed 99 first-degree relatives of Caucasian PDS patients and found that 10.1% had PDS-PG [23], while Roberts et al. reported a prevalence of 9.1% in black patients [5]. When only Caucasian PDS families with familial aggregation were considered, this proportion reached 42.4% [69]. Numerous patients with PDS-PG also have a family history of glaucoma (not limited to PG). The proportion of patients with a family history of glaucoma in PDS and PG patients is controversial. Among Caucasians, the proportion with a family history of glaucoma ranges from 7.4% to 58.4% [9, 11, 17, 21, 23]. Meanwhile the proportions of PDS patients with a family history of glaucoma are 14.3% among blacks, 16.7% for Asians, and 25% in Latin Americans, reflecting the complex genetic pattern of the disease [6, 7, 70].

Studies on the PDS-PG linkage chromosomal regions have generally focused on Caucasians. In Caucasian PDS families, 7q35-q36 was the first chromosomal location found to be linked to the disease [67]. However, to date, no potential candidate genes have been identified at this chromosomal location [67]. Wagner et al. identified four PDS pedigrees that were not linked to 7q35-q36, showing a significant linkage to 18q11-q211 [71]. Mikelsaar et al. identified two novel deletions of 2q22.1 and 18q22.1 in an Estonian PDS patient [72]. Unfortunately, none of the above findings have been verified in many pedigrees.

Regarding candidate genes, Lahola-Chomiak et al. reported the whole-exome sequencing of two Caucasian PDS families and found heterozygous non-synonymous variants of premelanosome protein (PMEL) that impair the ability of PMEL to form functional amyloid fibrils [73]; the detection rate of the PMEL variants in three white PDS-PG cohorts was 2.1%–3.5%. Although the LOXL1 variants associated with exfoliative syndrome and exfoliative glaucoma were previously thought to be unrelated to PDS and PG [74], Giardina et al. found haplotypes of LOXL1 in a Caucasian pedigree associated with PG-PDS independent of rs1048661, resulting in differential expression of transcripts [75]. Mutation of the LOXL1 gene may be associated with defects in stromal iris elastic fibers [75, 76]. Neither PMEL

nor LOXL1 is located in a known PDS-PG linkage chromosomal region. In addition, mutations in some candidate genes that may be associated with PDS-PG (e.g., TYRP1, GPNMB, LYST, DCT, and MITF) have been identified in animals [77–79]. Heide et al. performed whole-exome sequencing in a 97.55% Caucasian PDS cohort and did not find any difference in mutation frequency of the above candidate genes compared with the controls [80]. In a genome-wide association study, Simcoe et al. found that in Caucasians, PDS-PG shared a genetic basis with lighter iris color and myopia but not with POAG [81]. They subsequently reported that common SNPs associated with GSAP and GRM5/TYR genes were risk factors for PDS-PG and found a causal relationship between myopia and PDS-PG based on Mendelian randomization [82]. These factors help explain the higher prevalence of the disease in myopic populations. However, it remains difficult to explain the large number of patients with PDS who have a family history of glaucoma (not limited to PG). Furthermore, as described in Sect. 3.1, the occurrence of LAZ may be associated with atypical PDS pathogenesis in some patients. Ayyagari et al. identified a locus at 11q23 associated with LAZ and found that all individuals with LAZ and/or macular degeneration carried the same CTRP5 S163R mutation [83]. Although some patients with the mutation had elevated IOP, it is not clear whether the mutation is associated with a specific type of atypical PDS. Further investigation may provide a novel idea for finding genetic loci for atypical PDS.

In summary, much work remains to be done in terms of exploring the genetic pattern of PDS-PG and searching for related genetic loci and causative genes. The lack of genetic studies is relatively more pronounced in non-Caucasian populations; although a higher proportion of PDS-PG patients with a family history are found in non-Caucasians, no genetic loci associated with atypical PDS-PG in Asians or blacks have been reported to date. Notably, Roberts et al. found that among African Americans, patients with PDS had a higher frequency of Caucasian heritage than those who did not have the disease [84]. The role of genetic factors in non-Caucasian PDS patients and their relationships to skin color and ancestry are open questions that remain to be addressed in the field.

Outcomes and Management

Development and outcome of PDS and associated racial differences

The risk of conversion of PDS to glaucoma varies among races, which influences treatment options for asymptomatic PDS. In a retrospective community-based study of 113 patients with PDS, Siddiqui et al. determined that 10% of Caucasian PDS patients developed glaucoma within five years, while the 15-year conversion rate was only 15% [11]. In a prospective study on a predominantly Caucasian (98.2%) PDS group, Richter et al. found that 17.4% of patients developed glaucoma from PDS in an average of 2.3 years [22]. Migliazzo et al. conducted a retrospective study over an average of 17.2 years and observed conversion to glaucoma in 35% of PDS patients [85]. In summary, the proportion of patients in which PDS eventually progresses to glaucoma is close to one-third in Caucasians, and the rate of progression is relatively slow.

The rate of conversion of PDS to PG appears to be higher in non-white populations compared to in Caucasian populations. In a retrospective analysis of 111 racially diverse patients with PDS at the Duke Eye Center, Farrar et al. found that being black was a risk factor for the conversion of PDS to glaucoma [21]. In a Latin American study, Gomez Goyeneche et al. found that 37.5% of PDS patients developed glaucoma in an average of 4.2 years [70]. Estimates of the proportion of untreated Asian PDS patients who develop glaucoma are lacking; however, our observation of glaucoma clinic patients with PDS revealed that 90% of PDS patients had high IOP at the first visit and 83% had glaucomatous damage [7], again suggesting a higher rate of glaucoma conversion in non-Caucasian populations.

Non-Caucasian patients with PDS are more likely to develop PG than Caucasians with PDS, indicating that non-Caucasian patients should be followed-up more closely and receive more active treatment. The need for treatment in patients with PDS-PG is usually determined by the stage of their disease. Richter et al. divided PDS-PG patients into four groups based on IOP and pigment dispersion activity and suggested that the different groups should be treated differently [7]. For PDS-PG with high IOP, medication, laser treatment, or surgery are necessary to control IOP, regardless of the active dispersion status. In contrast, for those with normal IOP, the choice of preventive intervention should be based on the active dispersion status in combination with the patient's unique risk factors. In addition to the racial risk factor, being young or male, having a high initial IOP, and the presence of KS are also risk factors for the conversion PDS to glaucoma and should be considered together [11, 21].

Preventive PDS treatment and associated racial differences

Laser peripheral iridotomy (LPI) is thought to prevent the conversion of PDS to glaucoma. An iris hole balances the anterior and posterior chamber pressure, relieves reverse pupillary block, flattens the iris, and reduces mechanical rubbing between the iris and zonules. Although the structural changes to the iris and TM cannot be reversed, pigment deposition in the TM can be reduced; thus, LPI has the potential to control disease progression [43–, 86–88]. However, Michelessi et al. reviewed the Cochrane database

and found that the effect of LPI on PDS-PG progression is not straightforward [89]. Thus, the decision to perform LPI should account for racial factors.

In studies on predominantly Caucasian patients, the effectiveness of LPI is controversial. Küchle et al. found that LPI decreased the number of aqueous melanin granules in patients with PDS [90]. Gandolfi et al. treated 21 PDS patients with LPI in one eye, while the other eye received no intervention. The percentage of IOP elevation in the treated eyes over two years was lower than that in the non-treated eyes, and the effectiveness was more pronounced in patients up to 40 years of age [91]. In a subsequent 10-year observational study, LPI treatment reduced the risk of glaucoma development in the group at high risk of progression to the same level as the low-risk group [92]. However, in a randomized controlled study of 116 high-pressure PDS patients, Scott et al. found that LPI did not significantly change the time to visual field progression or commencement of topical therapy [93]. Based on the above studies, the assessment of age and other disease characteristics is critical for determining whether Caucasian patients with PDS need to be treated with LPI.

Compared to Caucasians, Asian patients with PDS have a more rapid and higher rate of progression to PG, often with posterior iris bowing. LPI is recommended for Asian PDS patients. We followed up with 19 Chinese patients treated with LPI and found that after treatment, all 19 eyes had a flattened posterior iris bowing, normal IOP, and reduced trabecular pigmentation, while none had deterioration or new visual field defects [38]. Qing et al. reported a 15-year follow-up study of 11 Chinese patients with PDS in which 10 eyes were treated with LPI; all were found to have satisfactory IOP control without visual field progression at follow-up [39]. A Japanese study also confirmed the benefits of LPI for IOP control [94]. The role of LPI in Asian patients with PDS needs to be validated with stronger evidence based on randomized controlled studies. Although the rate of PDS progression to PG is similar in black and Asian patients, it is not clear whether LPI is effective in black PDS patients because posterior iris bowing is uncommon in black populations. There is also a lack of PDS research specific to black populations.

In addition to LPI, pilocarpine and the restriction of physical activity are also thought to prevent the deterioration of PDS. Pilocarpine prevents pupillary dilation, flattens posterior iris bowing, prevents additional pigment granule loss, and widens the intertrabecular spaces to increase aqueous humor drainage. The use of pilocarpine causes visual impairment and ocular surface symptoms and increases the risk of retinal detachment. Pilocarpine can be used to control the progression of active PDS with elevated IOP but is not recommended for low-risk PDS patients [17]. Limiting physical activity can prevent changes in iris configuration, reduce rubbing between the iris and zonules, and control pigment dispersion and deposition [26].

Patients with PDS who are not treated prophylactically should be closely followed-up and observed, especially those with associated risk factors. The disease status and level of risk for PDS-PG changes as the disease progresses. A burnout phase can occur after approximately 10 years of disease. This burnout phase is associated with an increase in the anteroposterior diameter of the lens and an increase in the distance between the iris and the zonules as the patient ages [27]. Patients in this phase have reduced iris–zonule rubbing and pigment dispersion. Macrophages remove existing pigment granules and debris from the TM and control the IOP. Due to the thin IPE and small amount of pigment granules in Caucasians, years of irido-zonular rubbing can exhaust the pigment, causing the patient to enter the burnout phase [39]. Follow-up and treatment may be reduced for patients in the burnout phase.

IOP control in PDS-PG

When PDS-PG is associated with high IOP, as in open-angle glaucoma, IOP-lowering therapy should be administered. The first consideration is medical therapy, for which there are no reports of race specificity. In addition to pilocarpine, prostaglandin analogues, β-adrenergic antagonists, α-adrenergic agonists, and carbonic anhydrase inhibitors are used as IOP-lowering medications in PDS-PG patients with high IOP.

For patients with PDS-PG whose IOP cannot be effectively controlled with medications, laser therapy may be considered. Argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) are safer than surgical treatment and are widely used to treat POAG [95, 96]. Compared with POAG, the pigmented TM absorbs more energy during laser trabeculoplasty in PG. While this makes the treatment more effective in the short term, it may lead to secondary damage and scarring of the TM, post-SLT/ALT IOP elevation, and detrimental effects on aqueous outflow in the long term [1, 16, 97]. The effectiveness of laser treatment for PG remains controversial, and existing studies have focused primarily on Caucasian patients. For example, in the study of Ritch et al., 32 PG patients treated with ALT had a one- and six-year success rates of 80% and 45%, respectively, with younger patients having better results than older patients [98]. Ayala et al. report SLT success rates of up to 85% at one year but only 14% after four years, much lower than the success rates for other types of open-angle glaucoma [99]. Koucheki et al. reported that PG patients can develop a significant increase in IOP at six months after SLT, which was not observed for POAG or pseudo-exfoliation glaucoma [100]. Harasymowycz et al. reported three PG cases with elevated IOP within three months after SLT [97]. Lunde et al. reported 10 PG

patients with well-controlled IOP after receiving ALT but with elevated IOP after nine months [101]. Thus, the applicability of ALT or SLT for PG treatment requires further exploration.

Trabeculectomy is the first choice for PG patients whose IOP cannot be effectively controlled by medical or laser therapy [32]. Although trabeculectomy is widely used in PG therapy, few clinical studies have evaluated its therapeutic effects [101–104]. Two Chinese studies indicated that trabeculectomy has promising efficacy and safety, satisfactory long-term IOP control, and high survival rate of functional blebs in Asian PG patients [38, 39]. Qing et al. suggested that the higher long-term survival rate of functional blebs in PG patients compared to POAG patients may be associated with the unknown role of pigment granules in preventing tissue scarring around the operation site [38]. However, the available evidence is not sufficient to support this. Substantial evidence is needed in all races to determine whether there are differences in the long-term outcomes of trabeculectomy for PG compared with POAG.

Trabeculectomy disrupts the physiological structure of the eye, causing significant complications such as cataracts, choroidal detachment, malignant glaucoma, and endophthalmitis. A series of minimally invasive glaucoma surgeries (MIGS) that reduce complications have been used to treat open-angle glaucoma [105]. Several studies have described the effectiveness of various types of MIGS in the treatment of PG, including ab interno trabeculectomy [106, 107], trabecular micro-bypass stent implantation [108, 109], canaloplasty [110], EX-PRESS glaucoma shunt implantation [111], and trabecular aspiration [112]. In a study where the majority of POAG subjects were black, while the majority of PG subjects were Caucasian, Akil et al. found that ab interno trabeculectomy had similar outcomes in patients with POAG and PG [107]. The racial distribution of glaucoma subtypes in this study was consistent with the epidemiological distribution; however, whether race influenced the results of this study is unclear. The effectiveness of trabecular micro-bypass stent implantation for pigmentary glaucoma is controversial. Klammann et al. found that postoperative IOP control was worse in PG patients than in POAG or pseudo-exfoliation glaucoma patients [108]. In another retrospective study, Ferguson et al. reported that iStent implantation with cataract extraction in PG can control IOP below 18 mmHg at three years after surgery in 95% of cases [109]. The discrepant results might be explained by the different numbers of cases and devices. Canaloplasty also shows promise in PG patients based on the significant reduction in IOP and gradual absorption of TM pigment granules four years after surgery [110]. Jacobi et al. reported that trabecular aspiration in PG patients had a low success rate of 12% at one month after operation [112]. These existing studies of MIGS in PG patients, which primarily involved Caucasian patients, did not consider racial factors, which will be an important direction for future research. In POAG, Laroche et al. demonstrated differences in the effects of ab interno XEN implantation between different races [113]. Thus, racial factors are an important consideration when determining the patient's surgical modality.

Conclusions

PDS and PG are two different stages of the same disease spectrum. The prevalence of PDS-PG is much higher in Caucasians than in blacks and Asians. ITD, KS, and TM pigmentation are collectively known as the clinical triad of PDS signs. Having two of these three signs often serves as the clinical diagnostic criterion for "classic" PDS in Caucasians; however, it does not apply to the diagnosis of "atypical" PDS in blacks or Asians. Each race has unique clinical manifestations and diagnostic criteria. While mechanical iris–zonule rubbing is thought to be the dominant mechanism in the pathogenesis of PDS in various races, the main reasons for the occurrence of mechanical rubbing vary among races. Reverse pupillary block, LAZ, structural changes within the peripheral iris fixation, and abnormal iris insertion position can all lead to mechanical iris–zonule rubbing. PDS-PG has a complex pattern of inheritance influenced by both genetic and environmental factors. A family history of PDS-PG is present in a higher proportion of blacks and Asian PDS patients compared with Caucasian patients. The relevant loci and causative genes are still being explored. In the absence of intervention, non-Caucasian PDS patients are more likely develop glaucoma than Caucasian patients. LPI can be used to prevent the progression of PDS to glaucoma, and its effect is more pronounced in Asians than in Caucasians and blacks. PG patients can control their eye IOP with medication, laser treatment, or surgery. The use of SLT and ALT in PG patients of all races is controversial. While both trabeculectomy and multiple MIGS are effective for IOP control in PG, the effects of racial factors on the success rate of each type of surgery require further exploration.

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Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

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