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The Genetics of Pigment Dispersion Syndrome and Pigmentary Glaucoma

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Abstract. We review the inheritance patterns and recent genetic advances in the study of pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG). Both conditions may result from combinations of mutations in more than one gene or from common variants in many genes, each contributing small effects. We discuss the currently known genetic loci that may be related with PDS/PG in humans, the role of animal models in expanding our understanding of the genetic basis of PDS, the genetic factors underlying the risk for conversion from PDS to PG and the relationship between genetic and environmental—as well as anatomical—risk factors. (**Surv Ophthalmol 58**:164–175, 2013. © 2013 Elsevier Inc. All rights reserved.)

Key words. pigment dispersion syndrome • pigmentary glaucoma • genetics

Pigment dispersion syndrome (PDS) is characterized by disruption of the iris pigment epithelium by iridozonular friction and deposition of the released pigment throughout the anterior segment, especially behind the lens at the insertion of the lens zonules into the posterior lens capsule, producing the Zentmayer ring or Scheie stripe.[117] The classic diagnostic triad consists of corneal endothelial pigmentation (Krukenberg spindle), radial mid-peripheral iris transillumination, and dense trabecular pigmentation.[44] Pigmentary glaucoma (PG) is encountered in PDS patients as a result of the accumulation of pigment in the trabecular meshwork, leading to increased resistance to aqueous outflow, although it is not currently known whether the raised intraocular pressure arises purely as a result of pigment load or whether there are additional susceptibility factors.

Historical Background

PDS PATHOPHYSIOLOGY

The spindle-shaped pigment deposition on the cornea was first described by Krukenberg in 1899.[77] He considered PDS to be a congenital anomaly caused by the approximation of the pupillary membrane to the cornea during early embryogenesis. Von Hippel, in 1901, believed that pigment obstructing the aqueous outflow system could lead to elevated intraocular pressure (IOP).[171] Levinsohn, in 1909, was the first to suggest that pigment in the anterior chamber angle of patients with glaucoma originated from the iris pigment epithelium,[85] a concept which was revisited in 1958 when Scheie described the iris transillumination defects in these patients.[138] Earlier, Sugar et al described two young, myopic men with

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Krukenberg spindles, trabecular hyperpigmentation, and open angles whose IOP increased with mydriasis and decreased with pilocarpine. They identified the disorder as a rare, distinct form of glaucoma, which they termed *pigmentary glaucoma*.[153] Sugar reported another 147 cases in 1966, mentioning several additional features, including bilaterality, frequent association with myopia, greater incidence in men than in women, and a relatively young age at onset.[154] Lichter et al postulated that congenital mesodermal dysgenesis was the cause of iris pigment loss and developmental drainage angle anomaly in PG,[86,87] whereas Kupfer thought that primary atrophy or degeneration of the iris pigment epithelium led to PDS/PG.[82] In 1979, Campbell proposed the pathogenesis to involve mechanical damage to the iris pigment epithelium resulting from rubbing of the posterior iris against the anterior zonular bundles during physiologic pupillary movement.[24] In 1983, Kaiser-Kupfer, Kupfer, and McCain challenged Campbell's theory, suggesting that other risk factors, possibly genetic, may play an important role.[71] They proposed that an underlying congenital or developmental defect in the pigmented epithelial cells of the iris, as well as the ciliary body, is the primary abnormality, making some groups of cells especially vulnerable to the contact with the zonules and the subsequent mechanical rubbing. More recently, the common embryological origin of the pigment epithelium of the iris and retinal pigment epithelium led researchers to evaluate the functional changes of the retinal pigment epithelium in PDS by electrooculography.[140] The idea that there is primary involvement of the retinal pigment epithelium in PDS and PG is supported by the significantly lower mean Arden ratios in PDS and PG patients compared with controls and patients with primary open-angle glaucoma and ocular hypertension.[51]

These concepts of the pathophysiology of PDS provide an indication as to the possible genetic background of the disorder, with structural abnormalities being characteristic of autosomal dominant disorders and consistent with a genetic origin. Other conditions in which pigment may be dispersed have also been described, including the overlap (combined exfoliation and pigment dispersion) syndrome[131] and the long anterior zonules syndrome.[109]

POSTERIOR IRIS BOWING AND LASER PERIPHERAL IRIDOTOMY

Following Campbell's proposal in 1979 that the posteriorly bowed iris led to frictional contact between packets of anterior zonular fibres and the posterior pigment epithelium, resulting in pigment dispersion,[24] Karickhoff introduced the concept of "reverse pupillary block."[73] He proposed that abnormal iridolenticular contact causes the iris to act like a flap valve, permitting unidirectional flow of aqueous from the posterior to the anterior chamber and maintaining the posterior bowing. He also suggested that laser peripheral iridotomy (LPI) may relieve the posterior bowing of the peripheral iris by equalizing the pressure between the anterior and posterior chambers, thus preventing further dispersion of pigment. Mid-peripheral iris concavity was confirmed by Potash et al in 9 out of 16 eyes with PDS using ultrasound biomicroscopy (UBM).[125] In another study comparing anterior segment parameters in 20 PDS and 4 PG eyes with age-, sex-, and refraction-matched controls, iris concavity was noted to be significantly different between the two groups.[108] The non-contact modality of optical coherence tomography reveals an increase in iris concavity with accommodation,[91] and Pavlin et al used UBM to confirm this in 11 of 13 patients with PDS/PG.[124] Interestingly, following LPI in six of these patients, the iris showed a planar configuration that remained unchanged on near fixation.[124] Resolution of iris concavity with LPI was verified in 17 out of 18 PDS patients in a subsequent UBM study.[26]

INHERITANCE PATTERNS

Prior to the 1980s, only occasional families with Krukenberg spindles were recognized.[100,135,150] Becker et al reported that PG was characterized by a significantly higher prevalence of combinations of HLA-B12 and B13 or HLA-B12 and Bw17 antigens—as compared with PDS without glaucoma, primary open-angle glaucoma (POAG), or the general population—and suggested that PG differs genetically from POAG and is a separate entity.[17] Reports in the 1980s described familial PDS, but were inconclusive regarding the mode of inheritance.[67] Several authors have reported an autosomal dominant inheritance of PDS,[21,71,120,135] and an autosomal recessive inheritance of PG was described in four generations of a family by Stankovic et al.[150] In 1983, Mandelkorn et al described four families with PDS and observed that this syndrome was transmitted in a direct linear manner from parent to sibling in three of the four, independent of refractive error, iris color, and sex.[98] McDermott et al examined relatives of 21 probands and found involvement in 36% of parents and 50% of siblings, but none in children under the age of 21 years.[101] This suggested a strong pattern of autosomal dominance, with phenotypic onset probably beginning in most persons in the mid 20s.[101] In 1996, Ritch attempted to tie together the disparate findings in PDS into a unifying, genetic hypothesis. He concluded that a gene affecting some aspect of the development of the middle third of the eye early in

the third trimester was the most likely cause,[130] which could also explain the association of PDS with lattice retinal degeneration[173] and retinal tears. Retinal detachment occurs in a frequency of 12% in PG.[136]

Epidemiology

PDS and PG typically affect young myopes[39,137,153] and are more common in white patients.[39,133,142,178] Unlike PDS, which is almost equally common in men and women,[130,137] with possibly a slight male predominance,[104] PG is much more prevalent in men (78–93% of PG patients).[146,154] The estimated incidence of PDS and PG in the United States is 4.8/100,000 and 1.4/100,000 population per year, respectively.[146] In the Western world PG accounts for 1–1.5% of glaucoma cases[178] and is the most common nontraumatic cause of glaucoma in young adults.[132] The prevalence of PDS, as estimated by Ritch et al following two population glaucoma screening studies that involved 934 individuals, was 2.45%.[132] Although the precise molecular basis of PDS is not established, it is most likely a genetically heterogeneous disorder resulting from the interaction of multiple genes and environmental factors. Also, the relatively low prevalence of familial PDS and PG suggests a multifactorial pattern of inheritance or a trait of variable penetrance and expressivity.[137]

Phenotype and Genetics

GEOMETRICAL–ANATOMICAL FACTORS

Despite a recent ultrasound biomicroscopy study that shows that PDS patients do not have larger than normal irides compared to controls,[160] as was widely believed,[125,130] genetically influenced geometrical–anatomical factors may play an important role in its development. Interestingly, two of the five candidate genes mapped to the long arm of chromosome 7 where the first genetic locus for PDS was identified[6]—the muscarinic acetylcholine receptor gene[19] and the human endothelial nitric oxide synthase gene *NOS3*[134]— affect the vascular tone and structure of the iris, thus supporting the mechanical theory of PG. Genes implicated in anterior segment developmental abnormalities, including iris hypoplasia and glaucoma, such as the forkhead transcription factor gene *FOXC1* (formerly *FKHL7*),[70,83,84,102,116] might be suitable candidates to explain the underlying congenital or developmental iris defects in PDS proposed by Kaiser-Kupfer et al in 1983.[71] Mutations in other transcription factor genes, including *PITX2*,[4,33,57,81,141] *PAX6*,[14,105,159] and *LMX1B*,[34,54,89,170] have also been found to be responsible for disorders of anterior segment development associated with glaucoma. Nevertheless, none of these genes has been linked to the pathogenesis of PDS/PG.

GENETIC RISK FOR CONVERSION FROM PDS TO PG

At present there is limited evidence to suggest that family history is a significant risk factor for conversion from PDS to PG.[40,104,129,146] Various, mainly retrospective, studies have identified male sex,[40,87,99,129] baseline IOP,[99,146] black race,[40] severe myopia,[18,40,99] active dispersion of pigment,[129] exercise,[35,56,139] blinking,[25,88] accommodation,[124] pupil dilation,[53,76] and Krukenberg spindles[40,80] as possible risk factors for conversion. Some of the these may themselves be genetically influenced, as for example the Krukenberg spindle, which has been found to be more common in PG than nonglaucomatous PDS, suggesting that the spindle may be predictive of PDS eyes that may develop PG. Three early reports of familial Krukenberg spindles suggest a possible genetic aetiology.[100,152,169] Interestingly, family history of glaucoma has been found to be present in 4–21% of PDS patients,[49,137,146] whereas a much higher percentage (26–48%) of PG patients have a positive family history,[40,146] suggesting an additional genetic predisposition. In the study by Siddiqui et al, however, where a positive family history for glaucoma was recorded in 48% of PG patients, none of the family members were known to have PDS or PG.[146] This would suggest an additional genetic susceptibility for glaucoma, where the development of glaucoma may or may not require the presence of PDS. In contrast, Gramer et al found a family history of glaucoma in 39% of 207 patients with PDS and PG. Family history of glaucoma in PG was no more frequent than in PDS, indicating that this is not a significant risk factor for conversion from PDS to PG.[50] Also, patients with and without a family history of glaucoma showed no significant differences in risk factors, such as maximum IOP, refraction, and cup–disk ratio, suggesting that these were not genetically determined.[50]

Reported Loci and Candidate Genes

7Q35-Q36

In 1997, Andersen et al described four 3-generation pedigrees with PDS and PG and showed that a gene responsible for this syndrome maps to the telomere of the long arm of human chromosome 7 (7q35-q36).[6] *GPDS1* (glaucoma-related pigment dispersion syndrome 1) (OMIM ID 600510) was the first genetic locus associated with PDS. The locus was identified in 28 of 54 patients from the four pedigrees, two of Irish and two of mixed western

European descent. Autosomal dominant inheritance of the trait was supported by the presence of affected individuals in each generation and equal numbers of affected men and women. The gene itself has not yet been discovered, and this linkage has not been replicated to date, but candidate genes mapped to this region of chromosome 7 include a homeobox gene involved in the development of the forebrain,[94] a muscarinic acetylcholine receptor gene,[19] the human endothelial nitric oxide synthase gene *NOS3*,[134] and a gene associated with human cyclops.[52] Also, the gene responsible for phenylthiocarbamide tasting has been mapped to the telomeric portion of the long arm of chromosome 7 and could serve as a genetic marker for this region.[30] Interestingly, there is a lower prevalence of phenylthiocarbamide tasters in patients with adult-onset open-angle glaucoma,[15] supporting the hypothesis proposed by Becker et al that PG may be a variant of POAG.[16] Since the initial identification of *GPDS1* by Andersen et al, microsatellite polymorphisms of the *GPDS1* locus have also been shown to be associated with normal tension glaucoma in the Japanese population.[113] The currently proposed loci for PDS/PG are summarized in Table 1. Note the variability in the genetic background of PDS/PG among different ethnic groups.

OTHER PROPOSED GENETIC LOCI

In 1998 another pedigree with pigment dispersion syndrome analyzed by Andersen et al showed significant linkage to markers at 18q11-q21.[5] Wagner et al conducted linkage studies on a further four families and also found significant linkage to the 18q21 region.[172] A maximum two–point LOD score of 7.8 was obtained for marker D18S1144 on18q21 using all pedigree members, both affected and unaffected, and a significant lod score of 4.2 was obtained for marker D18S1144 using only affected pedigree members. Haplotype analysis identified a 12-cM critical region extending from marker D18S1119 to D18S483. Two novel (not previously described in the Database of Genomic Variants[64]) deletions in 2q22.1 and 18q22 were then discovered in a 34-year-old Estonian man with PDS.[106] There is one known gene—the *LRP1B* (low density lipoprotein-related protein 1B)—in this region of chromosome 2. The low density lipoprotein receptor gene family is thought to play an important role in normal cell function and development through its interaction with multiple ligands,[90] and it is possible that mutations of this gene may lead to the dysembryogenesis of the eye (midperipheral iris concavity, elongated zonules, iridocorneal angle anomalies) resulting in the PDS.

MYOCILIN

PG has been associated in several studies with mutations in the myocilin (*MYOC*) gene.[2,41,168] *MYOC*, which is located on chromosome 1q25 at the *GLC1A* locus,[143] was the first gene to be associated with juvenile open-angle glaucoma (JOAG) and adult-onset POAG.[3,46,151] *MYOC* encodes a 504-amino-acid glycoprotein, which contains an olfactomedin domain (residues 246–501) where the majority (42/46 [91%]) of the mutations documented have been identified. In normal eyes, *MYOC* mRNA is expressed in the iris, ciliary body, and trabecular meshwork,[47] as well as in retinal photoreceptor cells[79] and optic nerve head.[118] Although the exact role of myocilin in the pathogenesis of glaucoma is not clear, it is thought to interact with the trabecular extracellular matrix affecting aqueous outflow.[42,156] In a recent study, a patient with the Thr293Lys *MYOC* mutation was found to have glaucoma associated with pigment-dispersion syndrome diagnosed at the age of 31 years.[168] The Ala445Val *MYOC* mutation was also found in a 40-year-old white patient with PG and no family history of glaucoma.[41] Finally, a study evaluating the prevalence of *MYOC* mutations in a large, consecutive, unselected series of 779 patients with a variety of open-angle glaucomas (including 66 with PG and 21 with PDS) reported two plausible disease-causing sequence variations in the *MYOC* gene (Arg470Cys in one patient with PG and Gln368Stop in one patient with PDS). The following coding sequence polymorphisms (non–disease-causing) were also present: Tyr347Tyr in four patients with PG and one with PDS, Lys398Arg in two patients with PG, and Gly122Gly in two patients with PG.[2] *MYOC* mutations have been firmly associated with JOAG and POAG, yet the rare observation of these mutations in patients with PDS might be a chance occurrence.

LYSYL OXIDASE-LIKE 1 (*LOXL1*)

Although a strong association between the *LOXL1* gene on chromosome 15 and both pseudoexfoliation syndrome and exfoliative glaucoma has been described in various populations,[10,27,36,45,55,59,110,121,123,127,158] there is no significant association with PDS or PG.[128,177] Interestingly, a recent study suggests that the nonsynonymous SNP rs1048661 in exon 1 of the *LOXL1* gene may act as a modulator of age at disease onset in PG.[177] *LOXL1* is essential for elastic fibre homeostasis[93,157] and is known to be expressed both in lamina cribrosa cells and optic nerve head astrocytes,[166] but its role in PG remains unclear.

TABLE 1

Genetic Loci Proposed to Be Related to PDS/PG in Humans

Chromosomal Location	Causal Gene	Type of Study	Ethnic Background	References
7q35-q36	Unknown Candidate genes: homeobox (Logan et al[94]), muscarinic acetylcholine receptor (Bonner et al[19]), *eNOS3* (Robinson et al[134]), cyclops (Gurrieri et al[52]), phenylthiocarbamide (Conneally et al[30])	Genome-wide linkage analysis (4 pedigrees)	Ireland - Western Europe (PDS)	Andersen et al (1997)[6]
18q11-q21	Unknown	Genome-wide linkage analysis (one and four pedigrees respectively)	Ireland - Western Europe (PDS)	Andersen et al (1998)[5] Wagner et al (2005)[172]
1q25	*MYOC* (Thr293Lys)	*MYOC* mutational analysis (single case report)	Toronto, Canada (PG)	Vincent et al (2002)[168]
1q25	*MYOC* (Ala445Val)	*MYOC* mutational analysis (single case report)	Quebec, Canada (PG)	Faucher et al (2004)[41]
1q25	*MYOC* (Arg470Cys, Gln368Stop, Tyr347Tyr, Lys398Arg, Gly122Gly)	*MYOC* mutational analysis (case series)	Iowa, USA (PDS/PG)	Alward et al (2002)[2]
2q22.1	Unknown Candidate gene: *LRP1B* (Liu et al[90])	Array CGH analysis (single case report)	Estonia (PDS)	Mikelsaar et al (2008)[106]
15q24	*LOXL1* (rs1048661)	*LOXL1* mutational analysis (case series)	Germany (PG)	Wolf et al (2010)[177]

Studies in Mice

DBA/2J MICE: GLYCOPROTEIN nmb (*Gpnmb*^{R150x}) AND TYROSINASE RELATED PROTEIN 1 (*Tyrp1*^{b}) GENES

Glycoprotein nmb (*Gpnmb*^{R150x}) Gene

Genetic studies in mice are proving to be a powerful means to understand human disease[122] and to explore the role of genes in the pathogenic mechanisms that cause disease and influence disease susceptibility.[148] DBA/2J mice are a model of PG that may allow further research to delineate its genetic and pathophysiological basis and provide a basis for the evaluation of therapeutic interventions.[68] In 2002, iris pigment dispersion (IPD) in DBA/2J mice was found to be caused by a premature stop codon mutation in the Glycoprotein nmb (*Gpnmb*^{R150x}) gene[9] localized to mouse chromosome 6 (position 25.5 cM).[28] IPD in these mice was characterized by a deterioration of the posterior iris pigment epithelium, transillumination defects, and pronounced pigment dispersion, thus resembling human PDS. *Gpnmb* is known to be expressed in pigmented cells[174] and the eye.[164] Similarity has been found between *Gpnmb* and *si*, the product of the mouse *silver* locus, which has been implicated as a structural component of the melanosomal matrix.[75] Moreover, the truncated protein encoded by *Gpnmb*^{R150x} has been shown to lack a carboxy-terminal dileucine melanosomal sorting motif.[167] These findings support Anderson et al's hypothesis that the isolated *Gpnmb* mutation alters melanosome function, allowing toxic intermediates of pigment production to leak out, causing iris disease and subsequent PG.[9] Importantly, *Gpnmb* is also expressed in some types of dendritic cells and immune dysfunction, including inability of the aqueous humor to inhibit T-cell activation and loss

of ocular immune privilege, and may contribute to the pathogenesis of pigment dispersion in DBA/2J mice.[107] Pigment-laden macrophages are present in the eyes of PDS/PG patients[44,72] and synergistic interactions between melanosomal defects and the immune system are proposed to explain the complex pattern of occurrence of PG in humans.[107]

Tyrosinase Related Protein 1 (*Tyrp1^{b}*) Gene

Iris stromal atrophy (ISA), another important feature of the DBA/2J mice, is caused by the recessive Tyrosinase related protein 1 (*Tyrp1^{b}*) *brown* mutant allele[9] localized to mouse chromosome 4 (position 34.4 cM).[28] ISA in these mice is associated with deterioration of the anterior iris stroma, resulting in loss of clinically detectable iris stromal complexity and accumulation of stromal pigment and cell debris in the ocular drainage structures. *Tyrp1*, the most abundant melanosomal glycoprotein,[66,155] influences melanosome structure[111] and is required for the stabilization of a membrane-bound melanogenic protein complex. Furthermore, *Tyrp1* is a member of a multiprotein complex required for the stabilization of tyrosinase, the enzyme that catalyzes the first committed step in pigment production.[74] Mice that are homozygous with respect to both the IPD-causing gene (*Gpnmb*) and the ISA-causing gene (*Tyrp1*) manifest earlier-onset, more severe iris disease and more severe glaucoma than those with either single mutation.[9] DBA/2J mice with *Gpnmb* and/or *Tyrp1* genes of normal function do not appear to develop elevated IOP or glaucoma with age.[63]

In summary, *Tyrp1^{b}* is an important mutant melanosomal protein gene that, together with *Gpnmb^{R150x}*, may contribute to PG, although neither of them are known to contribute to the disease in humans.[9,96] DBA/2J mice are known to have two different missense mutations (Cys110Tyr, Arg326His) in the *Tyrp1* gene,[144] whereas missense mutations have not been identified in the *Tyrp1* gene in humans.[22] Interestingly, although the extent of the pigment-dispersing iris disease in mice is determined by the *Gpnmb* and *Tyrp1* mutations, the susceptibility to develop high IOP and glaucoma appears to be influenced by other, yet unidentified genes,[8] thus further supporting the likely multi-genetic etiology of human PG. Recently, microarray analysis of iris gene expression in pigment dispersion-prone C57BL/6J mice with *Tyrp1* and *Gpnmb* mutations has revealed significant changes in crystallin-mediated stress responses compared with wild-type C57BL/6J mice, suggesting a potential role for stress-related pathways in the pathogenesis of human PDS.[161]

C57BL/6J AND LT/SvEiJ MICE: ADDITIONAL PIGMENT DISPERSION CAUSING GENES

In another study analyzing a diverse group of 11 mouse substrains with coat color variations or mutations that otherwise influence pigmentation, the *beige* substrain (*Lyst$^{bg\text{-}J}$* mutation; Lysosomal trafficking regulator gene) of the C57BL/6J mice demonstrated significant pigment dispersion.[7,162] No clear link between *beige* and dysfunction in melanin synthesis pathways is known, although it has been observed that *beige* melanosomes are substantially enlarged.[145] The altered surface to volume ratio of these melanosomes could influence the toxicity of intermediates of melanin synthesis by disturbing the balance between protective molecules found at the melanosomal membrane and the toxic intermediates.[7] Pigment dispersion occurs in mouse strains with genetic defects in pathways influencing *Tyrp1* and therefore melanin synthesis, such as the *light* substrain (*Tyrp1$^{B\text{-}lt}$* mutation; Tyrosinase related protein 1 gene) of the LT/SvEiJ mice and the *vitiligo* substrain (*Mitf$^{mi\text{-}vit}$* mutation; Microphthalmia-associated transcription factor gene) and the *nm2798* strain (*Dct$^{Slt\text{-}lt3J}$* mutation; Dopachrome tautomerase) of the C57BL/6J mice.[7] Inbred LT/SvEiJ mice are homozygous for the *Tyrp1* allele, *light*, that acts dominantly to influence melanocyte survival and coat color.[69,97] Thus iris disease may not only result from the *brown* allele (*Tyrp1^{b}*) described previously. With regards to the vitiligo substrain, the *Mitf* gene is known to encode a transcription factor that regulates expression of several genes important to ocular development and function, including *Tyrp1*[38,112,147] and possibly *Dct*[112] and *Gpnmb*.[1,164] This would provide an interesting link between the *vitiligo* phenotype and intermediates of melanin synthesis, as the *Tyrp1*, *Dct*, and *Gpnmb* alleles may influence the toxicity of these intermediates.[31,165] Regarding the *nm2798* strain, *Dct* (also referred to as *Tyrp2*) encodes a transmembrane melanosomal protein sharing significant homology with *Tyrp1*[23] and is thought to influence melanin synthesis and melanosome morphology.[60,149] The *nm2789* mutation has been mapped to mouse chromosome 14 and, as a result of the toxicity of the melanin intermediate dopachrome (the substrate for *Dct*), may lead to melanosomal mediated toxicity. In summary, these results indicate that the iris pigment dispersion phenotype in mice can be initiated by multiple, though not all, pigment-related genes and alleles. These additional pigment dispersion-causing genes identified in recent animal studies remain interesting candidates for

human PDS. The currently known mutations in mice are summarized in Table 2.

Gene-Environment Interactions

Although there has been some progress in the knowledge of the underlying genetics of PDS, the contribution of environmental factors is still poorly understood. The relationship between genetic and environmental glaucoma risk factors may be highly complicated, and extensive research is required to ascertain how any genotype may affect individual susceptibility to PDS. Factors such as accommodation,[124] exercise,[56] pupil dilation,[76] and blinking[25] increase the posterior iris concavity that is likely to induce pigment dispersion. Nevertheless, although accommodation would explain the young age of onset for PG compared with other types of glaucoma, the effect of accommodation on iris profile in PDS/PG is highly variable, with some irides increasing in concavity, others remaining unchanged, and some decreasing.[11] Also, although pharmacological pupillary dilation is widely believed to induce pigment showers and a rise in IOP, Epstein et al only found a significant IOP rise in 2 out of 10 patients with PG and none of nine patients with PDS, despite pigment liberation in both groups following instillation of 10% phenylephrine.[35] Another environmental factor, ultraviolet light, known to induce melanogenic pathways and to activate *Trp1* in vivo,[119] may acutely exacerbate iris pigment dispersion, although this hypothesis has not been clinically validated.

Discussion

The recent modest progress in our understanding of the genetic basis of PDS offers insight into the pathophysiology of pigment dispersion. The isolation and determination of the function of the candidate predisposing genes would be of great interest, enabling the cascade of events controlling PDS/PG to be unravelled. Immunomodulatory treatments have been advocated to prevent or delay PG[107] and whether pharmacologic manipulation of the expression of the predisposing genes could provide any benefit to these patients remains to be determined. Improved methods of diagnosis and treatment would reduce ocular morbidity in PG, a disorder that tends to affect young adults and is often undetected until at an advanced stage. The lack of identified mutations in *Gpnmb* and *Tyrp1* in humans[96] does not preclude their involvement, or that of genes of similar function, in other families or in more complex cases. It also remains to be seen whether any defects in the candidate genes mapped to the long arm of chromosome 7[19,52,94,134] will be found in patients with pigment dispersion, as this would suggest a developmental abnormality as a cause of the syndrome.

Newer methods attempt to identify complex diseases and common disorders that do not appear to follow the classical Mendelian inheritance pattern,[58,65,175] as in the case of PDS. The most useful methods at present are exome sequencing and genome wide association study (GWAS) using high density single nucleotide polymorphism (SNP) arrays.[61,95] The GWAS approach uses data sets from a large number of unrelated cases and controls to search for statistical associations between common genetic variations within the human genome and the disease.[20] This has led to the identification of common disease-associated genetic variants in chronic disorders,[43] such as Crohn disease,[13] coronary disease,[32] diabetes mellitus,[126] and several common cancers—including colorectal[62] and breast cancer.[163] In glaucoma, GWAS has been used recently in Japanese[48,114] and Barbadian[115] populations with POAG, in normal-tension glaucoma,[103] and in German[78] and Icelandic-Swedish[158] populations with pseudoexfoliation glaucoma, but no similar studies exist for PDS/PG.

TABLE 2

Genetic Mutations Causing Iris Disease and Pigment Dispersion in Mice

Mutation	Chromosome	Causal Gene	Mouse Strain	Condition	References
Gpnmb^{R150x}	6	Glycoprotein nmb	DBA/2J	Iris pigment dispersion (IPD)	Anderson et al 2002[9]
Tyrp1^{b}	4	Tyrosinase related protein 1	*Brown* DBA/2J substrain	Iris stromal atrophy (ISA)	Anderson et al 2002[9]
Lyst$^{bg\text{-}J}$	13	Lysosomal trafficking regulator	*beige* C57BL/6J substrain	Pigment dispersion Exfoliation syndrome	Anderson et al 2008[7] Trantow et al 2009[162]
Tyrp1$^{B\text{-}lt}$	4	Tyrosinase related protein 1	*light* LT/SvEiJ substrain	Pigment dispersion	Anderson et al 2008[7]
Mitf$^{mi\text{-}vit}$	6	Microphthalmia-associated transcription factor	*vitiligo* C57BL/6J substrain	Pigment dispersion	Anderson et al 2008[7]
Dct$^{Slt\text{-}lt3J}$	14	Dopachrome tautomerase	*nm2798* C57BL/6J strain	Pigment dispersion	Anderson et al 2008[7]

In the future, identification of PDS/PG genes and the advent of more cost- and time-efficient mutation screening strategies may enable a more generalized population-based screening to identify at-risk individuals. It would also allow genetic screening of individuals with a family history of PDS, allowing individuals that do not carry risk associated mutations or haplotypes to forego years of follow-up. Moreover, good clinical record-keeping in families with known PDS mutations will enable us to characterize the significance of each mutation in terms of risk of conversion to PG and response to treatment. Identifying family members who carry mutations that may convey a risk for PG may also lead to more vigilant surveillance and aggressive treatment of these at-risk individuals. The underlying genotype of a given PDS or PG patient may predict the rate of disease progression and the likely response to specific pharmacologic agents or laser treatment, and identify those who need early surgery. The effort to identify those SNPs that are associated with significant biological effects will be beneficial for pharmacogenomics, the emerging field of personalized medicine.[176] Finally, although gene therapy is not on the immediate horizon for PDS/PG,[37] the chronic nature of these conditions makes them a good target for long-term therapeutic strategies, such as viral vector-mediated gene therapies, that can target and correct relevant defective molecular pathways.[12,29,92]

In summary, it remains possible that many cases of PDS result from a combination of mutations in more than one gene and more specifically from common variants in many genes each contributing small effects. The observation by Andersen et al that one member of an affected pedigree did not seem to have the same genetic defect in the 7q35-q36 region as other members of his family supports this hypothesis.[6] Moreover, only 30% of the affected PDS members of the pedigrees linked to this region developed PG, suggesting that multiple factors, including other genetic factors, may be necessary for the development of increased IOP and eventual PG.[6] There may be genes predisposing to PDS and additional genes predisposing to PG. Interestingly, drawing an analogy to pseudoexfoliation glaucoma, although a gene responsible for pseudoexfoliation has been identified, this does not explain which patients develop pseudoexfoliation glaucoma, suggesting that there may be a gene necessary for PG, but not sufficient. The isolation of these genes will be necessary to enable systematic study of the way in which they interact with each other and with environmental factors to determine the eventual phenotype. We hope that future, more comprehensive studies will advance our understanding of the PDS genetics, thus ultimately allowing the development of targeted treatments.

Method of Literature Search

For this review we conducted a Medline and Pubmed search of the medical literature for the period between 1960 and February 2012 using the following key words as well as various combinations of them: *pigmentary glaucoma, pigment dispersion, genetics, IOP, genomics, gene therapy, mice, animal model, inheritance, conversion risk, genetic loci, candidate genes, myocilin, LOXL1, Gpnmb,* Tyrp1b, *posterior iris bowing, laser peripheral iridotomy, epidemiology, environment, genome wide association study.* Articles populated under 'Related citations' from these articles were reviewed. Additional articles and textbooks were selected from the bibliographies of the references.

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