

# Red and/or blonde hair association with pigmentary glaucoma in Israel

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## Abstract

**Purpose** To assess the prevalence of red and/or blonde hair in a defined pigmentary glaucoma (PG) population and to compare their clinical findings with those of PG patients with black or brown hair.

**Methods** Hair color was studied in 35 consecutive PG patients and 35 consecutive primary open angle glaucoma (POAG) patients who served as controls. Patients were classified into red and/or blonde hair group or into black or brown hair group. Clinical characteristics were contrasted between PG patients of red and/or blonde hair with PG patients of black or brown hair.

**Results** Of the 35 PG patients, 19 (54.3%) had red and/or blonde hair and 16 (45.7%) had black or brown hair. Of the 35 POAG patients, two (5.8%) had red and/or blonde hair and 33 (94.2%) had black or brown hair. This difference in prevalence of hair color is highly significant ( $P < 0.001$ ;  $\chi^2$ ). Clinical characteristics of the PG patients (age at initial diagnosis, gender, positive family history for glaucoma, initial IOP, refraction, severity of optic nerve damage and prevalence of retinal detachment) were similar in the red and/or blonde hair and the black or brown hair groups.

**Conclusions** A very high prevalence of red and/or blonde hair was found among PG patients in Israel. Should supportive evidence for this association accumulate subsequent to this report, screening of people with these hair colors for PG may be justified.

*Eye* (2002) 16, 2–6. DOI: 10.1038/sj/EYE/6700007

**Keywords:** pigmentary glaucoma; pigment dispersion syndrome; primary open angle glaucoma; red hair; blonde hair

## Introduction

Pigmentary glaucoma (PG) is a bilateral disorder which typically affects young, Caucasian lineage patients with mild to moderate myopia. It is one of the most common forms of secondary open-angle glaucoma.<sup>1,2</sup> The classic manifestations of PG include heavy pigmentation of the trabecular meshwork, Krukenberg spindle on the corneal endothelium and radial midperipheral iris pigment epithelial defects.<sup>3</sup>

PG results from abnormal release of iris pigment epithelial melanin that obstructs and damages the outflow channels of the trabecular meshwork. Mechanical rubbing of the iris pigment epithelium due to posterior bowing of the peripheral iris with irido-zonular packets contact, irido-ciliary process contact or both, may be the causative mechanism of the pigment release.<sup>2,4,5</sup> However, this feasibly is not the only culpable factor as it can not account for why posterior bowing of the iris without pigment dispersion frequently occurs in myopic eyes<sup>2,6,7</sup> and why certain patients with pigment dispersion syndrome (PDS) do not exhibit posterior bowing of the iris, nor irido-zonular or irido-ciliary contact when studied by ultrasound biomicroscopy.<sup>4</sup> Therefore, it appears that posterior bowing of the iris is most likely only a pathogenetic cofactor in PDS or PG.

Histopathological observations of the iris in some eyes with the PDS or PG have revealed changes in the iris pigment epithelium, which embody focal atrophy and hypopigmentation, an apparent delay in melanogenesis and a hyperplasia of the dilator muscle.<sup>2</sup> The association of lattice degeneration with pigment dispersion syndrome suggests that an abnormality common to the anterior and posterior pigment epithelium may be at the root of these syndromes.<sup>8</sup> These observations have led researchers to speculate that a

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Received: 1 June 2001  
Accepted: 1 November 2001

developmental abnormality of the iris pigment epithelium is a fundamental defect responsible for pigment dispersion.

The most significant risk factors for the development of PG are young age, male gender, myopia, Caucasian lineage and a positive family history.<sup>2,3</sup> In the past five decades, no additional risk factors have been recognized aside from the above well-known, classic factors.<sup>1-3</sup>

It has been our clinical impression that the prevalence of red and/or blonde hair among our PG patients by far surpasses its prevalence in the general population of Israel, which is between 3% and 5.4%.<sup>9,10</sup> To confirm this perception, we undertook a prospective survey in our glaucoma clinic to determine the prevalence of red and/or blonde hair among PG patients and to compare it with that of primary open angle glaucoma (POAG) patients. We also studied the clinical findings of PG patients with different hair color.

## Methods

This was a prospective, controlled, prevalence study. The prevalence of red and/or blonde hair in PG patients was compared with that of a group of POAG patients.

Thirty-five consecutive, not related (not 1st or 2nd degree relatives) PG patients, examined by one of the authors (YG) within a period of 18 months in both governmental and private glaucoma referral centers, were included in this study. About 75% of the patients were referred to these clinics from the central part of Israel whereas the remaining 25% were referred from other parts of the country. Patients with a history of uveitis, trauma or any evidence of exfoliation, were excluded. For the purpose of PG diagnosis, patients had to have a bilateral heavily pigmented trabecular meshwork, typical Krukenberg spindle, and, in at least one eye, an untreated intraocular pressure of 24 mmHg or higher with glaucomatous optic nerve cupping or characteristic visual field defects or both. Slit-like midperipheral iris transillumination defects were not required as an inclusion criterion. However, most PG patients (33/35) had iris transillumination defects. A consecutive 35 POAG patients seen by the same author within a 1-week period were similarly examined and served as controls. POAG patients had to have in at least one eye, an untreated intraocular pressure of 24 mmHg or higher with glaucomatous optic nerve cupping or characteristic visual field defects or both. Patients with a history of uveitis, trauma or any evidence of exfoliation or pigment dispersion, were excluded.

Hair color (dye-free natural color of the head hair) was classified as black, brown; red-brown, red-blonde, red (fire) and blonde according to a hair color scale.<sup>11</sup> This was done by one of the authors (YG) who was unmasked to the patient's diagnosis. In instances of gray hair, the color of the eyebrows and beard (when present) were used for purposes of classification.<sup>12</sup> Patients with dyed or gray hair ( $n = 11$  and  $n = 29$ , in the PG and the POAG groups, respectively) were requested to report their dye-free natural hair color at the age of 20–30 years. Patients with red-brown, red-blonde, red (fire) or blonde hair were classified into a red and/or blonde hair group. Patients with black or brown hair were classified into a black or brown hair group.

Detailed histories were obtained from all patients and their clinical records were reviewed. They also underwent a complete ophthalmologic examination. In the PG patients, data were collected on age at initial diagnosis, disease duration, gender, manifest refraction, intraocular pressure at diagnosis, positive family history of PG (among first and second-degree relatives), positive history for retinal detachment, severity of glaucomatous optic nerve damage (vertical cup to disc ratio) and visual field changes (mean deviation measured by the computer-assisted static perimetry 30–2 program, Humphrey, Zeiss, Dublin, CA, USA). The data of PG patients with red and/or blonde hair were contrasted with those with black or brown hair.

Data were analyzed utilizing the SPSS WIN statistical software (SAS Institute, Cary, NC, USA). All calculations were made using the Chi-square test and the two-tailed, unpaired Student's *t*-test. Statistical significance was considered at  $P < 0.05$ . All data are reported as the mean (standard deviation).

## Results

Thirty-five PG patients (25 males and 10 females) were recorded in this study. The mean age was 50.9 (12) years (range, 18–77 years). Sixteen patients (45.7%) had black or brown hair and 19 patients (54.3%) had red and/or blonde hair. Thirty-five POAG patients (17 males and 18 females) were recorded in this study. The mean age was 69.9 (15) years (range, 30–90 years). Thirty-three patients (94.2%) had black or brown hair and two patients (5.8%) had red and/or blonde hair (Table 1). This nine-fold greater prevalence of red and/or blonde hair among PG patients is highly significant ( $P < 0.001$ ;  $\chi^2$ ).

The mean age and mean disease duration in PG patients with red and/or blonde hair were not significantly different from those in PG patients with black or brown hair. Similarly, no significant difference was observed in the male to female ratio, manifest

**Table 1** Prevalence (%) of hair colors among pigmentary glaucoma (PG) patients ( $n = 35$ ) and primary open angle glaucoma (POAG) patients ( $n = 35$ ). The nine-fold greater prevalence of red and/or blonde hair among PG patients is highly significant ( $P < 0.001$ ;  $\chi^2$ )

Hair color	PG	POAG
	No. (%)	No. (%)
Black or brown hair group		
Black	14 (40)	28 (80)
Brown	2 (5.7)	5 (14.2)
Total	16 (45.7)	33 (94.2)
Red and/or blonde hair group		
Red-brown	4 (11.4)	
Red-blonde	11 (31.4)	
Red (fire)	3 (8.6)	1 (2.9)
Blonde	1 (2.9)	1 (2.9)
Total	19 (54.3)	2 (5.8)

refraction, intraocular pressure at the time of diagnosis, prevalence of positive family history and the prevalence of retinal detachment (Table 2).

The features of pigment dispersion were similar in both hair color groups. Grossly, we were unable to identify difference in the color of the Krukenberg spindle, the trabecular pigmentary band or the extent of iris transillumination between the two groups.

Glaucomatous optic nerve and visual field changes estimated by cup to disc ratio and the mean deviation of visual field were similar in PG patients with red and/or blonde hair and PG patients with black or brown hair (Table 3).

**Table 2** Clinical data of pigmentary glaucoma (PG) patients with red and/or blonde hair and those with black or brown hair. No significant difference was observed between the two groups

	Red and/or blonde hair group ( $n = 19$ )	Black or brown hair group ( $n = 16$ )
Age (years)	50 (11.8)	51.9 (12.2)
Age at diagnosis (years)	43.4 (11.8)	43.2 (8.9)
Duration of disease (years)	6.6 (3.7)	8.7 (5.6)
Male ratio (%)	15/19 (79)	10/16 (62.5)
Manifest refraction (D)	-3.1 (2.7)	-3.7 (2.2)
Intraocular pressure of right eye at diagnosis (mmHg)	32 (12)	28 (5.6)
Intraocular pressure of left eye at diagnosis (mmHg)	28.5 (12.7)	25.7 (6.5)
Prevalence of positive family history (%)	8/19 (42.1)	7/16 (43.8)
Prevalence of retinal detachment (%)	2/19 (10.6)	3/16 (18.8)

## Discussion

This study revealed that the prevalence of red and/or blonde hair among PG patients far exceeds its prevalence in POAG patients, which in percentiles translated to 54.3% vs 5.8% respectively ( $P < 0.001$ ;  $\chi^2$ , Table 1). The prevalence of red and/or blonde hair among POAG patients was similar to its prevalence in the general young population of Israel, which is between 3% and 5.4%.<sup>9,10</sup> By itself, this finding suggests that red and/or blonde hair may be associated with PG besides male gender, myopia and Caucasian lineage.

The high prevalence of red and/or blonde hair among PG patients may be due to a genetic association, in which different genes are located in close proximity to each other on the same chromosome. Relatively little is known about the inheritance of hair color in humans.<sup>11</sup> In one study the major locus for red hair color was assigned to chromosome 4.<sup>13</sup> In another research, variants of the melanocyte-stimulating hormone receptor gene were associated with red hair and fair skin in humans.<sup>14</sup> In humans, this receptor maps to chromosome 16(q24).<sup>15</sup> A gene responsible for pigment dispersion syndrome was located on chromosome 7, but it is likely that other, yet unidentified, genes can induce this disorder.<sup>16</sup> Hence, it seems that the genetic association between red and/or blonde hair and PG cannot be ruled out at present. All the patients in our study were of Jewish descent. Accordingly, this case series represents a specific ethnic group, a fact that should be accounted for when evaluating possible genetic association between hair color and PG.

Two types of melanin pigments coexist in variable ratio mixtures in human cells and determine their color. They are eumelanin, which appears brown or black and is typically prevalent in people with brown or black hair and pheomelanin which appears red or yellow and is typically prevalent in people with red or blonde hair.<sup>11,17-19</sup> Both melanins are derived from

**Table 3** Cup to disc ratio and mean deviation (dB) of pigmentary glaucoma patients with red and/or blonde hair compared with those with black or brown hair. No significant difference was observed between the two groups

	Red and/or blonde hair group ( $n = 19$ )	Black or brown hair group ( $n = 16$ )
Cup to disc ratio (right eye)	0.7 (0.2)	0.66 (0.17)
Cup to disc ratio (left eye)	0.66 (0.26)	0.67 (0.19)
Mean deviation (dB) (right eye)	-7.7 (10.4)	-3.2 (5.1)
Mean deviation (dB) (left eye)	-6.3 (10.1)	-4.8 (7.5)

tyrosine with tyrosinase being the essential, rate-limiting enzyme. Pheomelanin is synthesized through a shunt in the eumelanin pathway and is distinguishable by its relative high content of sulfur. Melanosomes, which contain eumelanin, have an ellipsoidal shape while those with pheomelanin possess a spherical shape.<sup>11</sup> The constitution of melanines in the human iris was only recently discovered. Prota *et al* recently reported that melanin from the normal iris pigment epithelium (IPE) is essentially eumelanin, while the pigment in the stroma and the anterior iris pigment epithelium proved to be both eumelanin and pheomelanin.<sup>19</sup> Data on the eumelanin to pheomelanin ratio and the shape of melanosomes in the iris or the IPE in patients with red and/or blonde hair or PG are not available. One could speculate that pheomelanin, which is more abundant in humans with red and/or blonde hair, may also appear in a higher ratio in the IPE melanosomes of these PG patients, and may be released more freely by the mechanical rubbing of the iris against the zonular insertions, or may have a greater deleterious effect on the trabecular meshwork in comparison to eumelanin or eumelanin-containing melanosomes.

Only PG patients were included in this study. We have no comprehensive data on hair color among PDS patients because generally these patients are not referred to our glaucoma clinic. We have limited data on six PDS patients, of whom three had red hair. Obviously, conclusions cannot be drawn from such a small group. It would be of interest to perform a similar study on a large group of PDS patients to verify whether red and/or blonde hair is also associated with PDS. Indeed, an unpublished observation of an exceptionally high prevalence of red hair among PDS subjects was recently reported to us by a coordinator of a large health-screening program in Israel.

The average age at diagnosis of PG in our patients (Table 2) was somewhat higher than reported in other series.<sup>3</sup> This may be explained by the fact that most people in Israel are not involved in health-screening programs and indeed many of our patients presented to an ophthalmologist only when their PG became symptomatic.

This is the first report of an association between PG and hair color. Should supportive evidence accumulate following this account, screening for PG of red and/or blonde hair myopic young individuals might be advocated. In addition, an attempt should be made to determine and elucidate the grounds for this association. Data on melanin type in the iris, especially in IPE, of PG patients with red and/or

blonde hair should be obtained by analysis of peripheral iridectomy specimens. The effect of pheomelanin on the trabecular meshwork may be studied in an *in vivo* model in comparison to eumelanin. Finally, the probability of a genetic association between red and/or blonde hair and PG should be evaluated.

## References

- 1 Sugar HS. Pigmentary glaucoma: a 25-year review. *Am J Ophthalmol* 1966; **62**: 499–507.
- 2 Farrar SM, Shields MB. Current concepts in pigmentary glaucoma. *Surv Ophthalmol* 1993; **37**: 233–252.
- 3 Campbell DG, Schertzer RM. Pigmentary glaucoma. In: Ritch R, Shields MB, Krupin T (eds). *The Glaucomas*, 2nd edn. CV Mosby: St Louis, Missouri, 1996, pp 975–991.
- 4 Potash SD, Tello C, Liebmann J, Ritch R. Ultrasound biomicroscopy in pigment dispersion syndrome. *Ophthalmology* 1994; **101**: 332–339.
- 5 Lichter PR. Pigmentary glaucoma current concepts. *Trans Am Acad Ophthalmol Otolaryngol* 1974; **78**: 309–313.
- 6 Lagreze WD, Mathieu M, Funk J. The role of YAG-laser iridotomy in pigment dispersion syndrome. *Ger J Ophthalmol* 1996; **5**: 435–438.
- 7 Carassa RG, Bettin P, Fiori M, Brancato R. Nd:YAG laser iridotomy in pigment dispersion syndrome an ultrasound biomicroscopic study. *Br J Ophthalmol* 1998; **82**: 150–153.
- 8 Weseley P, Libermann J, Walsh JB, Ritch R. Lattice degeneration of the retina and the pigment dispersion syndrome. *Am J Ophthalmol* 1992; **114**: 539–543.
- 9 Pavlotsky F, Azizi E, Gurvich R *et al*. Prevalence of melanocytic nevi and freckles in young Israeli males. Correlation with melanoma incidence in Jewish migrants: demographic and host factors. *Am J Epidemiol* 1997; **146**: 78–86.
- 10 Mumcuoglu KY, Miller J, Gofin R *et al*. Epidemiological studies on head lice infestation in Israel. I. Parasitological examination of children. *Int J Dermatol* 1990; **29**: 502–506.
- 11 Jimbow K, Quevedo WC Jr, Fitzpatrick TB, Szabo G. Biology of melanocytes. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Husten KF (eds). *Dermatology in General Medicine*, 4th edn. McGraw-Hill: New York, 1993, pp 261–289.
- 12 Dawber RPR, de Berker D, Wojnarowska F. Disorders of hair. In: Champion RH, Burton JL, Burns DA, Breathnach SM (eds). *Rook/Wilkinson/Ebling Textbook of Dermatology*, 6th edn. Blackwell Science: 1998, pp 2869–2973.
- 13 Eiberg H, Mohr J. Major locus for red hair color linked to MNS blood groups on chromosome 4. *Clin Genet* 1987; **32**: 125–128.
- 14 Valverde P, Healy E, Jackson I, Rees JL, Thody AJ. Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nat Genet* 1995; **11**: 328–330.
- 15 Magenis RE, Smith L, Nadeau JH, Johnson KR, Mountjoy KG, Cone RD. Mapping of ACTH, MSH, and neural (MC3 and MC4) melanocortin receptors in the mouse and human. *Manm Genome* 1994; **5**: 503–508.
- 16 Andersen JS, Pralea AM, DelBono EA *et al*. A gene responsible for the pigment dispersion syndrome maps to chromosome 7q35–q36. *Arch Ophthalmol* 1997; **115**: 384–388.

- 17 Imesch PD, Wallow IHL, Albert DM. The color of the human eye: a review of morphologic correlates and of some conditions that affect iridial pigmentation. *Surv Ophthalmol* 1997; **41** (Suppl 2): S117–S123.
- 18 Menon IA, Basu PK, Persad S, Avaria M, Felix CC, Kalyanaraman B. Is there any difference in the photobiological properties of melanins isolated from human blue and brown eyes? *Br J Ophthalmol* 1987; **71**: 549–552.
- 19 Prota G, Hu DN, Vincensi MR, McCormick SA, Napolitano A. Characterization of melanins in human irides and cultured uveal melanocytes from eyes of different colors. *Exp Eye Res* 1998; **67**: 293–299.