Published in final edited form as:

Ophthalmic Genet. 2016 March ; 37(1): 89–94. doi:10.3109/13816810.2014.907920.

Ocular findings in patients with the Hermansky-Pudlak syndrome (types 1 and 3)

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Abstract

Purpose—To describe and compare ocular findings in patients with Hermansky-Pudlak syndrome (HPS) type 1 and 3.

Methods—This is a retrospective case series of 64 patients with HPS from 1999 to 2009 evaluated at an outpatient private ophthalmologic clinic. Patients underwent genetic analysis of selected albinism (Tyrosine and P gene) and HPS genes (HPS-1 and HPS-3) by screening for common mutations and exon sequencing with DNA screening. Descriptive and a non-parametric statistical analysis were done.

Results—Nearly 70% of the patients were homozygous for common Puerto Rican mutations leading to the HPS1 gene (16-BP DUP, 53.6%), while 30% had the 3904-BP DEL HPS3 gene mutation.

BCVA was poorer in patients with type 1 HPS than in patients with type 3 HPS ($p<0.001$), esotropia was more common among type 1 HPS ($p<0.018$), while exotropia was more common among patients with type 3 HPS. Total iris transillumination was more common in patients with type 1 HPS and minimal iris transillumination in patients with type 3 HPS ($p<0.001$). The maculae

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Declaration of interest

The authors have no conflicts of interest to report. The authors alone are responsible for the content and writing of the paper.

were translucent in patients with type 1 HPS, while patients with type 3 HPS had opaque maculae ($p<0.001$).

Conclusions—Patients with type 1 HPS had poorer BCVA, increase incidence of esotropia, lighter iris and macular appearance. In contrast, patients with type 3 HPS 3 had more exotropia. In addition, to our knowledge this is the largest series type 3 HPS ever reported.

Introduction

Oculocutaneous albinism (OCA) is a group of autosomal recessive disorders that affect skin, hair, and ocular pigmentations. Patients with OCA have visual manifestations such as reduced visual acuity, nystagmus, and photophobia. There are several types of OCA, designated as type 1 (OCA1) through type 4 (OCA4).[1–4] In addition, X-linked ocular albinism (OA) have nystagmus, impaired visual acuity, iris hypopigmentation with translucency, albinotic fundus, macular hypoplasia, and normally pigmented skin and hair. It has been demonstrated to be caused by *OA1* or *GPR143* gene mutations in contrast to autosomal recessive OA that may be a variant of either OCA1 or OCA2.[5]

The Hermansky-Pudlak syndrome (HPS) [MIM #203300] is a phenotypically and genetically heterogeneous autosomal recessive disorder. Nine different genotypes have been described. Patients with the HPS have bleeding diathesis; progressive pulmonary fibrosis, and granulomatous colitis in adition to albinotic findings. [6–7] HPS is thought to be the most common single-gene disorder in Puerto Rico (PR) where it has been reported to occur 1:1,800.[6,8] Type 1 HPS is the more prevalent in the above mentioned island and have been found to be more common in the northwestern part of it, in contrast to the type 3 HPS which is more common in the central area.

The first gene responsible for HPS in both the PR and Swiss patients was mapped to chromosome 10q2,[9–10] and cloned.[11] Puerto Rican patients with the syndrome were reported to have a 16 base pair (bp) duplication and frameshift mutation in exon 15 of the *HPS1* gene (*16-BP DUP*). The other genotype in Puerto Rico was reported by Anikster and co-workers[12] who mapped and characterized the third HPS gene, which also was found to be responsible for 6 families with 13 individuals affected with the HPS from Central Puerto Rico. A recombination event between two Alu sequences in the 5′ end of the *HPS3* gene was proposed to have caused the deletion of a 3,904 bp fragment (3904-BP DEL) which was most frequently carried in central PR newborns (1:32; 3.1%).[7,13]

Previous studies have reported on the ocular findings in patients with the Hermasnky-Pudlak syndrome.[14–20] To our knowledge our study is the largest series of HPS patients ever reported. In this study we will compare previous findings in addition to report new ophthalmic findings.

Patients and Methods

We conducted a retrospective case series of 64 patients referred by primary physicians to an outpatient private ophthalmological clinic with a diagnosis of albinism from 1999 to December 2009. Clinical diagnosis was based on a combination of phenotypic

characteristics such as fair skin and/or hair, nystagmus, impaired visual acuity, iris hypopigmentation, albinotic fundus, macular hypoplasia, bleeding diathesis, and in some cases pulmonary fibrosis or granulomatous colitis. Patients underwent a comprehensive ophthalmologic examination by at least one of the authors (NJI which is a specialist in genetical ophthalmic diseases) including: a best corrected visual acuity test using a contralateral +5.00 spherical lens; an external and slit lamp examination; indirect ophthalmoscopy with grading of macular transparency according to the Summers classification[18] as opaque (choroidal vessels not visible in macular area), translucent (choroidal vessels visible but indistinct), or transparent (choroidal vessels easily visible in macular area); and HRR color vision test.

Genetic analysis was done to determine the patient's mutations leading to the clinical findings associated to the syndrome. An informed consent was obtained from all participating patients. Peripheral blood samples were drawn for DNA analysis. Since previous studies determined that the most frequent mutation in Puerto Rican OCA patients was the *HPS1* gene 16-BP DUP, followed by the *HPS3* gene 3094-BP DEL, *TYR* and *OCA2(P)* gene mutations, we screened patients for mutations in that order, testing for the founder Puerto Rican mutations in each gene first, and performing exon screening by SSCP combined with automated DNA sequencing for these candidate genes in patients that did not have the founder mutations and/or no evidence of a bleeding diathesis. For the *HPS1* gene, DNA analysis for the 16 base pair (bp) duplication founder exon 15 of the *HPS1* gene was done by PCR amplification of the *HPS1* gene exon 15, using the primer sets described by Oh et al.[11] The expected sizes of the PCR products are 269 bp for the normal allele and 285 bp for the HPS-1 PR allele. The PCR products were run on a 3.5% agarose gels together with positive and negative control DNAs from known alleles for this region. To test for the *HPS3* gene 3904-BP DEL mutation, PCR analysis was carried out using the primer sets described for detecting this founder mutation[12] and amplification products evaluated on 1.6% agarose gels. The expected products were a 397 bp band for the normal allele; a 650 bp band for the 3904-BP DEL allele, as described.[13] Mutation screening for the tyrosinase (*TYR*) genes was done by exon screening using automated cycle sequencing by dideoxyterminator chemistry (Applied Biosystems)[2,21–22] in an ABI 377 automated sequencer. Screening for the *OCA2* gene 2.7-KB DEL, EX7DEL deletion was done as described by Durham-Pierre and co-workers.[23] Table 1 includes information on the PCR primer sets and reaction conditions used in this study.

Statistical analysis

A non-parametric Wilcoxon median sum test statistical analysis was done to compare continuous ophthalmic findings and diagnosis. Additionally, Shapiro Wilk normality test was done to evaluate the distribution of continuous ocular findings. Ocular findings were not normally distributed as demonstrated by the non-parametric tests. Finally, a Chi-square test was used to compare categorical ocular findings.

Results

Based on the results of genetic analysis, 45 out of the 64 patients (70.31%) had type 1 HPS based on the presence of the *HPS1* gene 16BP DUP mutation; 19 out of the 64 patients (29.69%) had the 3904BP DEL *HPS3* gene mutation and hence type 3 HPS. There was a majority of female patients (n=37; 57.81%) and the mean age was 24 years (±17).

Table 2 summarizes ocular findings in our case series. When analyzing multiple medians of visual acuities among the two genetic groups, a statistical significance difference was found: ($p<0.001$) and ($p<0.001$) in the right and left eye respectively.

Refractive errors were calculated in spherical equivalents (n=43). Marginal statistical significance was found when refractive errors of the two groups were compared: for the right eye ($p<0.058$) and the left eye ($p<0.054$).

Astigmatic axis median in patients with type 1 HPS was 90 degrees in both eyes (ranging from 70 to 120 degrees and from 60 to 103 degrees in the right and left eye respectively). Astigmatic axis median in patients with type 3 HPS was also 90 degrees in both eyes (ranging from 80 to 120 degrees and from 75 to 100 degrees in the right and left eye respectively).

Patients with type 1 HPS had several types of nystagmus. Most patients (97.6%) had periodic alternating nystagmus (PAN) with fast frequencies (81.3%); while slow and moderate frequencies were found in a smaller proportion of patients (12.4% vs 6.3%, respectively). Amplitudes ranged from small (88.2%) to large (11.8%) and a few patients (2.4%) had rotatory nystagmus. In contrast, all patients with type 3 HPS had PAN with frequencies ranging from slow (41.7%); moderate (16.6%); to fast (41.7%); and amplitudes ranging from small (69.2%) to large (30.8%).

Forty percent of patients (n=18) patients with type 1 HPS were orthophoric and 60% of patients (n=27) had strabismus. Of these, 59% of patients (n=16) had esotropia with a median of 30 prism diopters (range from 12 to 55 prism diopters) and nine patients (33.3%) had exotropia with a median of 25 prism diopters (range from 14 to 50 prism diopters). One patient (3.7%) had hypertropia; another patient (3.7%) had exophoria; and one of the patients with esotropia underwent strabismus surgery.

Of the 19 patients with type 3 HPS, nine patients (47.4%) were orthophoric and 10 patients (52.6%) had strabismus. Of these, eight patients (88.9%) had exotropia with a median of 35 prims diopters (ranging from 10 to 50 prism diopters); one patient had esotropia (11.1%) of 12 prism diopters; and another patient had strabismus surgery prior to our evaluation.

A statistical comparison between the two groups of albinism's exotropia and esotropia findings showed statistical significance ($p<0.007$). Esotropia was found more frequently in patients with type 1 HPS while exotropia was more frequent among patients with type 3 HPS.

A prominent Schwalbe's line was found in 9 patients with type 1 HPS. One patient had bilateral keratoconus. The latter underwent a penetrating keratoplasty. Two patients with type 3 HPS had prominent Schwalbe line and one patient had keratoconus. Three patients had bilateral corectopia: two patients with type 1 HPS; and one patient with type 3 HPS. The latter was aphakic.

Results of iris transillumination evaluation are shown in Table 2. A statistical comparison of iris findings showed a statistically significant difference ($p<0.001$).

All patients had foveal hypoplasia. For the purpose of the study, macula was graded using Summer's classification[18] as transparent, translucent, and opaque as summarized in Table 2. A statistical comparison showed a statistically significant difference ($p<0.001$).

HRR color vision test done in patients with type 1 HPS showed thirteen patients with color deficiencies males (n=4); seven patients had mild red-green deficiency; five patients had red-green defect; and one patient had blue-yellow deficiency. In patients with type 3 HPS, only 1 female patient showed color deficiencies and was mild red-green deficiency.

Discussion

Type 1 HPS occurs with a frequency of one in 1,800 in northwest Puerto Rico due to a founder effect[12] and it has a carrier frequency of 1:21[8]. Torres and co-workers[24] found that type 3 HPS has an average carrier frequency of 1:85 among Puerto Rican newborns. Our study demonstrated a higher frequency of patients harboring the clinical findings associated to the *HPS1* had poorer BCVA, higher incidence of esotropia, total iris transillumination, translucent maculae, and several color deficiencies. Due to subtle clinical findings in some of the patients with the type 3 HPS variety and the life threatening complications of HPS, screening has been suggested for every newborn presenting with albinism and nystagmus in P.R.

Previous studies [18,25] have reported that patients with the syndrome have reduced visual acuities. Tsilou E. T. and co-workers [20] compared visual acuities in patients with the various types of HPS. They found that patients with type 3 HPS have better visual acuity and less severe ophthalmic manifestations than patients with type 1 HPS. In our study when comparing patients with the type 1 HPS and type 3, patients with the type 1 had statistically significant poorer vision than patients with the type 3 HPS. These findings correlate with previous studies.

Earlier studies[25] have reported refractive errors in patients with HPS. We found that there were small statistically significant differences when spherical equivalents were compared. We found that patients with type 1 HPS were more myopic. This finding may be associated to poorer visual acuity seen among this group.

Sampath and co-workers[26] reported that patients with albinism have with the rule astigmatism. In our study, all patients had with the rule astigmatism. We suggest that this could be due to eyelid squeezing as part of the photophobia.

Several studies[18–19,27] mention that patients with OCA show congenital nystagmus. Gradstein[19] suggest that periodic alternating nystagmus (PAN) remains the most common type of nystagmus among patients with OCA. In our study, most (97.6%) patients had PAN, with a fast frequency and small amplitude in all two groups.

Strabismus has been described in patients with the syndrome. [15,19,25,28] In our study, statistical significance between the type of diagnosis and the type of strabismus was found. More patients with type 1 HPS had esotropia when compared to the other group. Exotropia was more frequent among patients with type 3 HPS. These findings suggest that different type of strabismus may correlate to the various types of albinism.

Previous studies have evaluated iris pigmentation in patients with OCA.[19–20,25,29] However, Tsilou and co-workers[20] reported that patients with type 3 HPS had less iris transillumination when compared to patients with type 1 HPS. In our study, a statistically significant difference was found. The iris transillumination of patients with type 1 HPS frequently had total transillumination; while type 3 HPS patients frequently had minimal transillumination. Our results correlate with previous comparisons between the type 1 HPS and type 3.

Previous studies[16,18–19,25,28] have reported that patients with OCA have foveal hypoplasia. Summers and co-workers in 1988[18] first described a systematic clinical description of macular appearance including: opaque; translucent; and transparent. Studies done by Tsilou and coworkers[20] demonstrated that patients with type 3 HPS have less macular transparency than patients with type 1 HPS. In our study, we found statistical significance when comparing macular findings among the two groups. Patients with the type 1 HPS patients had more translucent maculae when compared to those patients with type 3 HPS. On the other hand, more patients with the type 3 HPS had more opaque macula.

Rodríguez and co-workers[17] have reported that patients with HPS have color deficiencies. In our study, mild red-green deficiency was the most frequent color deficiency in patients with type 1 HPS and type 3. These findings correlate with previous studies. However, color deficiencies were found more common in female patients within the type 1 HPS.

Limitations in this study include: the small number of patients due to the low prevalence of autosomal recessive eye diseases; that patients in this study are not representative of the general population; not all the mutations for the genes were tested only the most prevalent and that several other variables were not analyzed.

In conclusion, the Hermansky-Pudlak Syndrome is a multi-system disorder characterized by oculocutaneous albinism, bleeding diathesis and, in some cases pulmonary fibrosis or granulomatous colitis. It has been shown that melanosomes and other lysosome-related organelles are affected causing the different phenotypes. In some cases, a clinical diagnosis based on a phenotypical presentation remains a challenge. Furthermore, the founder mutation leading patients to type 1 has more severe ocular phenotype as compared to patients with type 3. This study provides a description of the most common ocular manifestation to help ophthalmologist co-manage and lead primary physicians to proper

diagnosis. On the other hand, ophthalmologists may refer patients with the syndrome for systemic evaluation.

To our knowledge, this is the largest study that evaluates ocular findings in patients with the type 3 HPS founder mutation. Further studies will compare ocular phenotypes in patients with other genotypes leading patients to the Hermansky-Pudlak syndrome.

Acknowledgments

Funded in part by RCMI grant number G12RR03051/ and SCORE S06GM008224 from the National Institutes of Health.

References

1. Tomita Y, Takeda A, Okinaga S, Tagami H, Shibahara S. Human oculocutaneous albinism caused by single base insertion in the tyrosinase gene. Biochem Biophys Res Commun. 1989; 164:990–996. [PubMed: 2511845]
2. Lee S-T, Nicholls RD, Jong MTC, Fukai K, Spritz RA. Organization and sequence of the human P gene and identification of a new family of transport proteins. Genomics. 1995; 26:354–363. [PubMed: 7601462]
3. Boissy RE, Zhao H, Oetting WS, Austin LM, Wildenberg SC, Boissy YL, Zhao Y, Sturm RA, Hearing VJ, King RA, Nordlund JJ. Mutation in and lack of expression of tyrosinase-related protein-1 (TRP-1) in melanocytes from an individual with brown oculocutaneous albinism: a new subtype of albinism classified as 'OCA3.'. Am J Hum Genet. 1996; 58:1145–1156. [PubMed: 8651291]
4. Newton JM, Cohen-Barak O, Hagiwara N, Gardner JM, Davisson MT, King RA, Brilliant MH. Mutations in the human orthologue of the mouse underwhite gene (uw) underlie a new form of oculocutaneous albinism, OCA4. Am J Hum Genet. 2001; 69:981–988. [PubMed: 11574907]
5. Hutton SM, Spritz RA. A comprehensive genetic study of autosomal recessive ocular albinism in Caucasian patients. Invest Ophthalmol Vis Sci. 2008; 49:868–872. [PubMed: 18326704]
6. Witkop CJ, Nuñez Babcock M, Rao GH, Gaudier F, Summers CG, Shanahan F, Harmon KR, Townsend D, Sedano HO, King RA, et al. Albinism and Hermansky-Pudlak syndrome in Puerto Rico. Bol Asoc Med P R. 1990; 82(8):333–9. [PubMed: 2261023]
7. Spritz RA. Multiorganellar disorders of pigmentation: tied up in traffic. Clin Genet. 1999; 55:309–317. [PubMed: 10422800]
8. Santiago Borrero PJ, Rodriguez-Perez Y, Renta JY, et al. Genetic testing for oculocutaneous albinism type 1 and 2 and Hermansky-Pudlak syndrome type 1 and 3 mutations in Puerto Rico. J Invest Dermatol. 2006; 126:85–90. [PubMed: 16417222]
9. Wildenberg SC, Oetting WS, Almodovar C, Krumwiede M, White JG, King RA. A gene causing Hermansky-Pudlak syndrome in a Puerto Rican population maps to chromosome 10q2. Am J Hum Genet. 1995; 57:755–765. [PubMed: 7573033]
10. Fukai K, Oh J, Frenk E, Almodovar C, Spritz RA. Linkage disequilibrium mapping of the gene for Hermansky-Pudlak syndrome to chromosome 10q23.1-q23.3. Hum Molec Genet. 1995; 4:1665–1669. [PubMed: 8541858]
11. Oh J, Bailin T, Fukai K, Feng GH, Ho L, Mao J, Frenk E, Tamura N, Spritz RA. Positional cloning of a gene for Hermansky-Pudlak syndrome, a disorder of cytoplasmic organelles. Nature Genet. 1996; 14:300–306. [PubMed: 8896559]
12. Anikster Y, Huizing M, White J, Shevchenko YO, Fitzpatrick DL, Touchman JW, Compton JG, Bale SJ, Swank RT, Gahl WA, Toro JR. Mutation of a new gene causes a unique form of Hermansky-Pudlak syndrome in a genetic isolate of central Puerto Rico. Nature Genet. 2001; 28:376–380. [PubMed: 11455388]
13. Suzuki T, Li W, Zhang Q, Karim A, Novak EK, Sviderskaya EV, Hill SP, Bennett DC, Levin AV, Nieuwenhuis HK, Fong C-T, Castellan C, Miterski B, Swank RT, Spritz RA. Hermansky-Pudlak

syndrome is caused by mutations in HPS4, the human homolog of the mouse light-ear gene. Nature Genet. 2002; 30:321–324. [PubMed: 11836498]

14. Iwata F, Reed GF, Caruso RC, et al. Correlation of visual acuity and ocular pigmentation with the 16-bp duplication in the TYPE 1 HPS gene of Hermansky-Pudlak syndrome, a form of albinism. Ophthalmology. 2000; 107(4):783–9. [PubMed: 10768343]
15. Izquierdo NJ, Townsend W, Hussels IE. Ocular findings in the Hermansky-Pudlak syndrome. Trans Am Ophthalmol Soc. 1995; 93:191–200. discussion 200–2. [PubMed: 8719678]
16. Izquierdo NJ, Emanuelli A, Izquierdo JC, et al. Foveal thickness and macular volume in patients with oculocutaneous albinism. Retina. 2007; 27(9):1227–30. [PubMed: 18046229]
17. Rodríguez JA, Blasini M 2nd, Blasini M, et al. Color vision in patients with the Hermansky-Pudlak syndrome. Bol Asoc Med P R. 2004; 96(2):84–90. [PubMed: 15580910]
18. Summers CG, Knobloch WH, Witkop CJ Jr, et al. Hermansky-Pudlak syndrome. Ophthalmic findings. Ophthalmology. 1988; 95(4):545–54. [PubMed: 3174014]
19. Gradstein L, FitzGibbon EJ, Tsilou ET, et al. Eye movement abnormalities in hermansky-pudlak syndrome. J AAPOS. 2005; 9(4):369–78. [PubMed: 16102489]
20. Tsilou ET, Rubin BI, Reed GF, et al. Milder ocular findings in Hermansky-Pudlak syndrome type 3 compared with Hermansky-Pudlak syndrome type 1. Ophthalmology. 2004; 111(8):1599–603. [PubMed: 15288994]
21. Giebel LB, Strunk KM, Spritz RA. Organization and nucleotide sequences of the human tyrosinase gene and a truncated tyrosinase-related segment. Genomics. 1991; 9:435–445. [PubMed: 1903356]
22. Bailin T, Oh J, Feng GH, Fukai K, Spritz RA. Organization and nucleotide sequence of the human Hermansky–Pudlak Syndrome (HPS) gene. J Invest Dermatol. 1997; 108:923–927. [PubMed: 9182823]
23. Durham-Pierre D, King RA, Naber JM, Laken S, Brilliant MH. Estimation of the carrier frequency of a 2.7 kb deletion allele of the P gene associated with OCA2 in African Americans. Hum Mutat. 1996; 7:370–373. [PubMed: 8723691]
24. Torres-Serrant M, Ramirez SI, Cadilla CL, Ramos-Valencia G, Santiago-Borrero PJ. Newborn screening for hermansky-pudlak syndrome type 3 in Puerto Rico. J Pediatr Hematol Oncol. 2010; 32(6):448–53. [PubMed: 20562649]
25. Grønskov K, Ek J, Brondum-Nielsen K. Oculocutaneous albinism. Orphanet J Rare Dis. 2007; 2(2):43. [PubMed: 17980020]
26. Sampath V, Bedell HE. Distribution of refractive errors in albinos and persons with idiopathic congenital nystagmus. Optom Vis Sci. 2002; 79(5):292–9. [PubMed: 12035986]
27. Sen T, Mullerpattan J, Agarwal D, et al. Hermansky-Pudlak syndrome. J Assoc Physicians India. 2009; 57:660–2. [PubMed: 20214008]
28. Lacour JP, Ortonne JP. Oculocutaneous albinism. Ann Pediatr (Paris). 1992; 39(7):409–1. [PubMed: 1416662]
29. Gahl, WA. Hermansky-Pudlak Syndrome. GeneReviews [Internet]. Pagon, RA.; Bird, TC.; Dolan, CR.; Stephens, K., editors. Seattle (WA): University of Washington, Seattle; 1993-2000.

Table 1

PCR primers, regions analyzed and reaction conditions used in this study

Gene	Region amplified	Forward primer	Reverse primer	Size of amplicon expected	PCR Conditions
HPS1[*]	Exon 15	5′GATGGTCCACAAAGGACGAG-3′	5′-GCGTGAAGGAAGTACGGGCC-3′	269 bp for normal allele 285 bp for 16BP DUP allele	50–100 ng of genomic DNA, 95°C 4 minutes 35 cycles of 95°C 1 min, 1 min at 58°C, 1 min at 72°C, followed by 15 min at 72°C
HPS3[**]	5′flanking F1	5′GGTGTTGTTTAGAGATGCAGA-3′		650 bp in 3904BP DEL allele	20–50 ng of genomic DNA, standard PCR conditions with an annealing temperature of 58°C
	Intron 1 R3		5′GCATAGCCACCAGCTTTTGCAACG-3′		
	5′flanking F2	5′CGTGAACTCCACGTTGAGATGTCA-3′		397 bp in normal allele	
	5′flanking R2		5′CGTTCTGACAATTCATCATCTATC-3′		
OCA2 (P)[***]	MHP 72	5′-GCGGTGGCTGTCATGGC-3′		240 bp for normal allele 420 bp for 2.7KB DEL allele	20–50 ng of genomic DNA, 95°C 4 minutes, 35 cycles of 95°C 1 min, 1 min at 60°C, 1 min at 72°C, followed by 15 min at 72°C
	MHB107	5′CATAGTCTTGGTTTTTGTAGTCCT-3′			
	MHB 71		5′-GGAGGGTGCATTCATTCTTCAG-3′		
TYR[****]	Exon 1	5′ATGCTCCTGGCTGTTTTGTA-3′	5′-CTGCCAAGAGGAGAAGAATG-3′	820 bp	20–50 ng of genomic DNA, standard PCR conditions with annealing temperature of 50°C

[*] as described by Oh et al[11] Other regions of the *HPS1* gene examined with primer sets described in Bailin et al.[22]

[**] as described by Anikster et al.[12]

[***] as described by Durham-Pierre et al.[23]. Other regions of the *OCA2* gene examined with primer sets described in Lee et al.[2]

[****] as described by Giebel et al.[21] Other regions of the *TYR* gene examined with primer sets in this paper

Table 2

Ocular findings in the various types of albinism (n=84)

	HPS 1(n=45)	HPS 3(n=19)	p values
Sex	Male=16 (35.56%)	Male=11 (57.89%)	0.098
Age:			0.934
Median	15	19	
(Min,Max)	(6,58)	(7,66)	
BCVA:Right Eye			<0.001
Median	20/400	20/200	
Min-Max	20/80–20/1,300	20/30–20/400	
BCVA:Left Eye			<0.001
Median	20/400	20/200	
Min-Max	20/40–20/1000	20/25–20/400	
Sph Equivalent OD			<0.058
Median	+0.50 sph	+1.75 sph	
Min-Max	−10.00 to +4.25	−3.00 to +4.25	
Sph Equivalent OS			<0.054
Median	+0.50 sph	+1.75 sph	
Min-Max	−8.50 to +8.75	−3.00 to +5.50	
Iris minimal transillumination	10 (22.22%)	15 (78.95%)	<0.001
Iris scattered transillumination	10 (22.22%)	1 (5.26%)	
Iris total transillumination	25 (55.56%)	3 (15.79%)	
Macula transparent	10 (22.22%)	1 (5.26%)	<0.001
Macula translucent	32 (71.11%)	8 (42.11%)	
Macula opaque	3 (6.67%)	10 (52.63%)	