Ophthalmologic Phenotype–Genotype Correlations in Patients With Oculocutaneous Albinism Followed in a Reference Center

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Purpose. Albinism is a group of genetic disorders that includes several conditions related to a defect in melanin production. There is a broad phenotypic and genotypic variability between the different forms. The aim of this study was to assess the ophthalmologic characteristics according to patients' genotypes in a cohort followed in the Reference Center for oculocutaneous albinism (OCA) of Bordeaux University Hospital, France.

Methods. A retrospective observational study was conducted in a cohort of patients with OCA seen in consultation in the ophthalmology department between 2017 and 2021 in whom a genetic analysis was performed.

Results. In total, 127 patients with OCA were included in this study and matched with the results of the genetic analysis. In the population aged over 6 years, there was no statistical difference in binocular visual acuity between the OCA1, OCA2, and OCA4 forms ($P = 0.27$). There was difference in ametropia between the three forms ($P = 0.003$). A two-by-two comparison using the Bonferroni correction showed a significant difference in ametropia between the OCA2 and OCA4 forms ($P = 0.007$) and between the OCA1 and OCA2 forms ($P = 0.0075$). Regardless of the form, most patients (75.4%) had grade 4 foveal hypoplasia. There was no association between the grade of foveal hypoplasia and the gene involved ($P = 0.87$).

Conclusions. We described a genotype–phenotype correlation for the three most represented forms of albinism in our cohort. This study allowed assessing the degree of visual deficiency in young children with OCA.

Keywords: albinism, OCT, foveal hypoplasia, choroid, genetic diseases

Albinism is a group of genetic anomalies due to a defect in the production of melanin. The worldwide prevalence is estimated at about 1 in 17,000.[1]

The ocular manifestations of albinism include an abnormal refraction, a decreased visual acuity (VA), photophobia, strabismus, nystagmus, iris transillumination, retinal hypopigmentation, foveal hypoplasia, and optic nerve head abnormalities.[2,3]

There are nonsyndromic forms of albinism, including an ocular form (OA1) and eight oculocutaneous forms (OCA1–8),[4,5] and syndromic forms, including Hermansky–Pudlak syndrome (11 forms, HPS1–11)[6] and Chediak–Higashi syndrome.[7] All forms are autosomal recessive except for OA1, which is X-linked.

Among all these forms of albinism, OCA1 is the most common form in Europe,[8] while OCA2 is the most common form in patients originating from Africa.[9]

Only a few published studies have investigated genotype–phenotype correlations in albinism.

The aim of this study was to assess the ophthalmologic characteristics (VA, degree of ametropia, astigmatism, iris atrophy, retinal hypopigmentation, and optical coherence tomography [OCT] findings: grade of foveal hypoplasia, retinal nerve fiber layer [RNFL] thickness, choroidal thickness)

according to the genotypes in 127 patients with a confirmed molecular diagnosis of albinism.

Materials and Methods

Molecular analyses were performed in the molecular genetics laboratory of Bordeaux University Hospital (Bordeaux, France).

Patients with oculocutaneous albinism (OCA) included in the study were seen in the ophthalmology department of Bordeaux University Hospital between 2017 and 2021.

Written consent was obtained from all patients or from parents if the patient was a minor prior to the genetic analysis.

Phenotypic Data

Data were collected from a standard questionnaire completed by an ophthalmologist during a specialized consultation. All patients underwent at least one medical examination.

Inclusion criteria were based on those described by Kruijt et al.[10]: an age greater than or equal to 6 years at the time of the first ophthalmologic examination and a contributing molecular genetic diagnosis with one major or two minor criteria. If the genetic diagnosis was negative or inconclusive, the presence of three major criteria or two major criteria associated with two minor criteria was investigated. Major criteria included grade ≥2 foveal hypoplasia, iris transillumination, or grade ≥2 retinal hypopigmentation. Minor criteria included skin hypopigmentation, grade ≥1 retinal hypopigmentation, or grade ≥1 foveal hypoplasia.

The phenotypic analysis included data collected on the day of the first consultation in the ophthalmology department such as the age at the time of consultation, the presence of nystagmus, strabismus, torticollis, the best-corrected visual acuity (BCVA) using the Monoyer scale, the degree of ametropia (hyperopia or myopia), the spherical equivalent, the degree and axis of astigmatism, the degree of iris atrophy, the degree of foveal hypoplasia (grades 0–4), the degree of retinal hypopigmentation (grades 1–4), the choroidal thickness (in micrometers), and the RNFL thickness.

Patients were divided into two distinct groups (Fig. 1): age less than 6 years and over 6 years due to the evolution of the VA at these ages. Patients <6 years were excluded from this

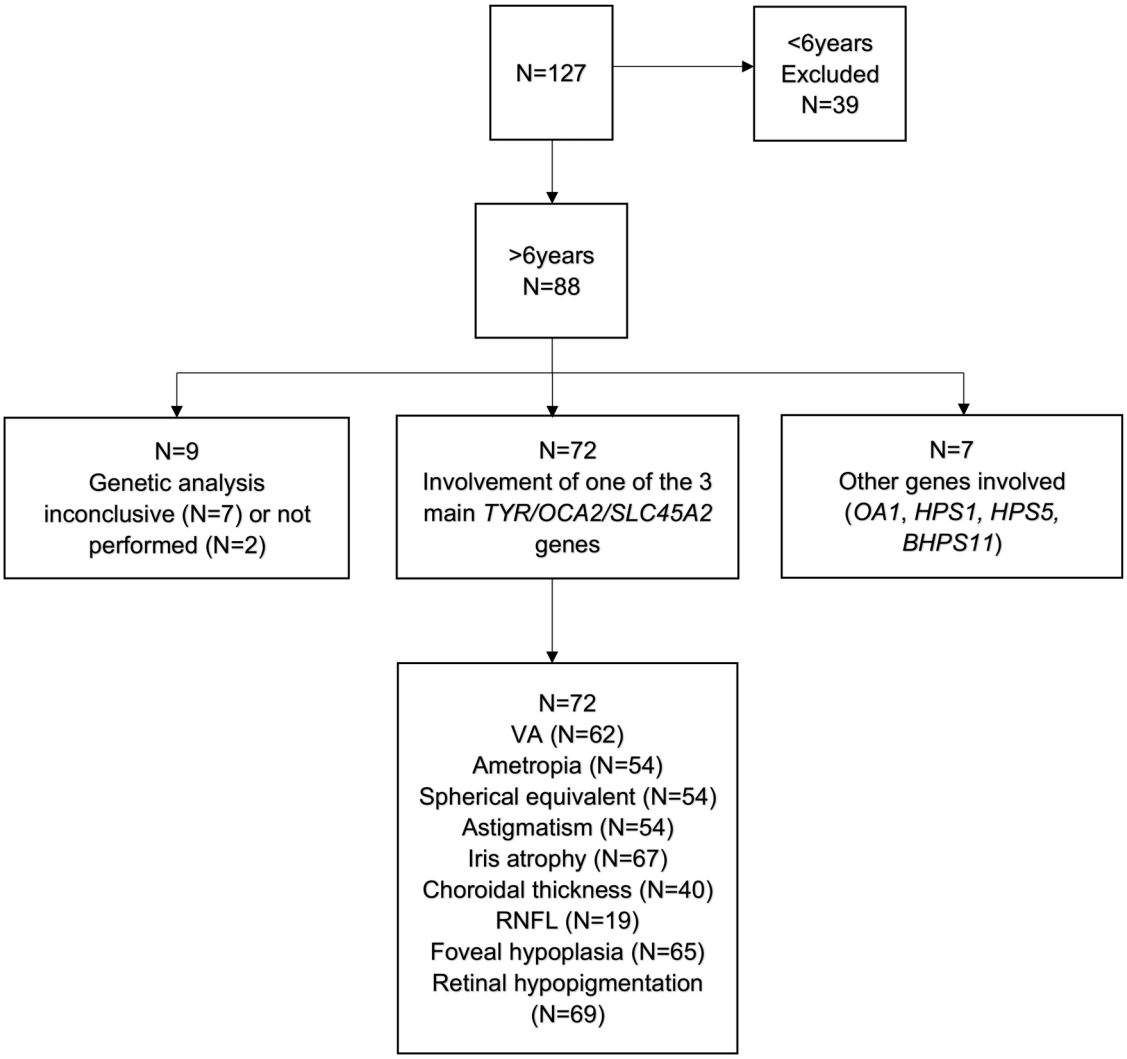

Figure 1. Study flowchart.

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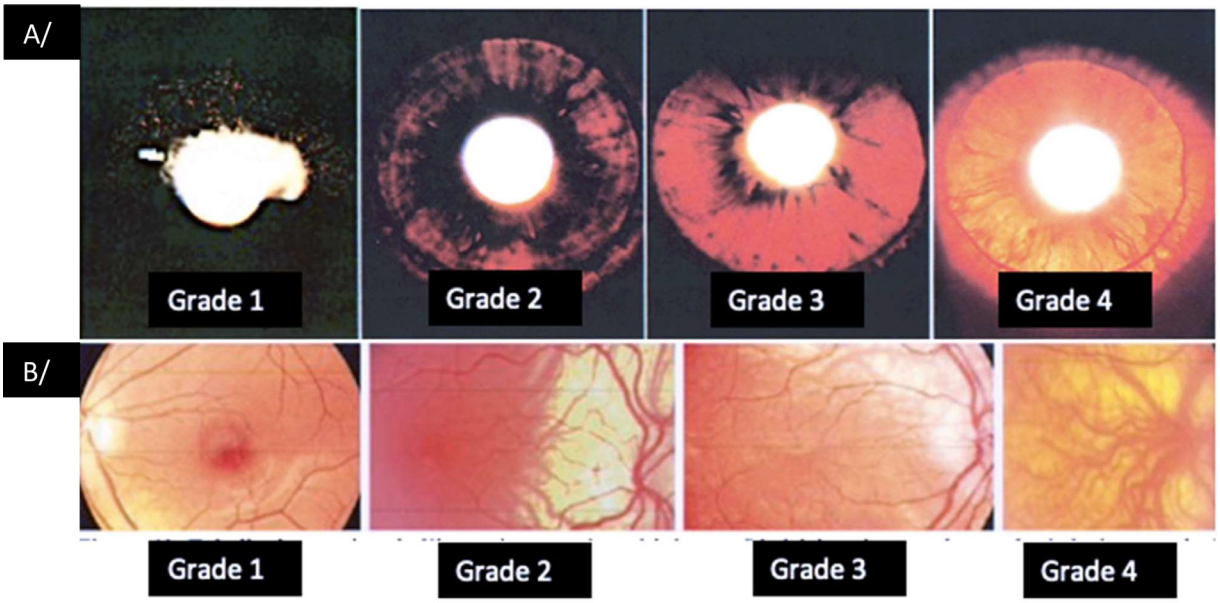

Figure 2. Grades of iris atrophy and retinal hypopigmentation. (**A**) According to the Summers et al.[11] classification: grade 1 = punctate peripheral transillumination, grade 2 = diffuse peripheral transillumination, grade 3 = diffuse transillumination with the lens equator visible, grade 4 = total transillumination including the pupillary rim. (**B**) According to the Käsmann-Kellner and Seitz[12] classification: grade 1 = peripheral hypopigmentation, beyondthe vascular arches; grade 2 = peripheral and central hypopigmentation sparing the macula; grade 3 = peripheral and central hypopigmentation with decreased macular pigment; grade 4 = diffuse hypopigmentation, absence of local increase in pigmentation at the macula.

study. For the VA, the binocular VA was used when available. If the binocular VA was missing, the monocular BCVA was used. The VA in decimal scale was converted into logMAR.

The degree of ametropia was assessed using a refractometer under cycloplegia.

Iris atrophy was graded according to the classification by Summers et al.[11] (Fig. 2A). Grading was performed by an experienced ophthalmologist using slit-lamp or indirect ophthalmoscopy if a seated examination was not possible.

Retinal hypopigmentation was graded by the ophthalmologist during the consultation according to the modified four-stage classification by Käsmann-Kellner and Seitz[12] (Fig. 2B).

Macular OCT images and RNFL measurements were obtained by spectral-domain optical coherence tomography (SD-OCT) (Cirrus HD-OCT; Carl Zeiss Meditec, Jena, Thüringen, Germany). Foveal hypoplasia was graded by the ophthalmologist during the consultation based on the albinism chart and then verified by a second ophthalmologist using the Leicester classification.[13] Only reliable RNFL thicknesses were used in this analysis (verification of correct signal and segmentation).

The choroidal thickness was measured subfoveally by locating manually the inner (retinal pigment epithelium) and outer (sclera–choroid interface) boundaries. When it was not possible to define them precisely, the data were excluded from the analysis.

For all OCT analyses, the infrared image was also used to ensure that the image was centered on the area of interest.

Genetic Analysis

The DNA was extracted from peripheral blood leukocytes using an automated procedure (Tecan EVO-ReliaPrep; Promega, Madison, WI, USA) or manually (Wizard Genomic DNA Purification Kit; Promega). The genotypic diagnosis was made using a next-generation sequencing (NGS) panel of exons of 19 genes, including *TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *SLC24A5*, *C10ORF11*, *GPR143*, *HPS1-10*, *LYST*, and *SLC38A8*. The variant pathogenicity was assessed using Alissa Interpret (Agilent Technologies, Santa Clara, California, USA) and Alamut Visual (Sophia Genetics, Lausanne, Switzerland) software.

NGS was performed using the Ion Torrent technology on a S5XL instrument (Life Technologies, Thermo Fisher Scientific, Waltham, Massachusetts, USA). The variants were confirmed by Sanger sequencing.

Statistical Analyses

Only the data from patients >6 years old were collected and included in the analyses. Patients <6 years old were excluded due to difficulties in collecting reliable VA values or in performing reproducible complementary tests. As the data were collected for both eyes, for the VA measurement, the binocular VA was used or, if missing, the VA of the best eye. In other cases, the value of the right eye was arbitrarily used. An ANOVA was performed to analyze the correlation between the genotype and the binocular VA, the degree of ametropia, the spherical equivalent, the degree of astigmatism, the choroidal thickness, and the RNFL thickness. A Fisher's test was performed to analyze the correlation between the genotype and the degree of foveal hypoplasia, retinal hypopigmentation, and iris atrophy.

Only the three most represented forms of albinism were used in the primary statistical analysis: OCA1, OCA2, and OCA4. The other rarer forms of OCA were reported for descriptive purposes only.

All statistical analyses were considered significant when the P value was ≤ 0.05.

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Results

General Data

This study was conducted in a cohort of 127 patients, but 39 patients were younger than 6 and excluded. Thus, 88 patients older than 6 years attended the first visit (Fig. 1 and Table 1). Most patients were Caucasians.

Of the 88 patients >6 years old, the genetic analysis was conclusive in 79 patients (2 without molecular analysis and 7 without conclusive molecular diagnosis). Finally, 72 patients carrying three main genes involved in OCA (*TYR*/OCA1, $n = 34$; *OCA2*/OCA2, $n = 22$; *SLC45A2*/OCA4, $n = 16$) were included in the statistical analysis.

Binocular Visual Acuity

Data were available for 62 patients in whom a genetic analysis was performed. The mean VA in our cohort ($n = 62$) was 0.27 in decimal scale (0.57 logMAR). The mean VA was 0.29 (0.1–0.7) in decimal scale (0.54 logMAR, 1–0.16 logMAR), 0.30 (0.1–1) in decimal scale (0.52 logMAR, 1–0 logMAR), and 0.20 (0.1–0.3) in decimal scale (0.7 logMAR, 1–0.5 logMAR) in the OCA1, OCA2, and OCA4 groups, respectively.

There was no significant difference in mean BCVA between the three groups ($P = 0.27$).

Spherical Ametropia

Data were available for 54 patients with a conclusive genetic analysis. The mean ametropia in our cohort ($n = 54$) was +2.5 diopters (D) (95% confidence interval [CI], −11 to +13.5). The mean ametropia was +3.4 D (95% CI, −10.25 to +13.5), −1.4 D (95% CI, −11 to +5), and +4.6 D (95% CI, +0.75 to +9) in the OCA1, OCA2, and OCA4 groups, respectively.

An ANOVA was performed with the null hypothesis of equality of means between the three groups. There was a statistically significant difference in mean ametropia between the three groups ($P = 0.003$). When comparing the means two by two with the Bonferroni correction with a 5% risk, there was a difference in mean ametropia between the OCA2 and OCA4 groups ($P = 0.007$) and between the OCA1 and OCA2 groups ($P = 0.0075$). The degree of myopic ametropia appeared to be higher in the OCA2 group.

Spherical Equivalent

The data were available for 54 patients with a conclusive genetic analysis. The mean spherical equivalent in our cohort ($n = 54$) was 0.93 D (95% CI, −13.1 to +12.8). The mean spherical equivalent was 1.9 D (95% CI, −13 to +12.75), −2.3 D (95% CI, −12 to +3.3), and 2.6 D (95% CI, −1 to +7.8) in the OCA1, OCA2, and OCA4 groups, respectively.

There was a statistically significant difference in mean spherical equivalent between the three groups ($P = 0.008$). However, when comparing the means two by two with the Bonferroni correction, there was a difference in mean spherical equivalent between the OCA2 and OCA4 groups ($P = 0.025$) and between the OCA1 and OCA2 groups ($P = 0.015$).

Astigmatism

The data were available for 54 patients with a conclusive genetic analysis. The mean astigmatism in our cohort ($n = 54$) was −2.8 D (95% CI, −6 to 0). The median astigmatism was −2.7 D with a maximum value of −6 D, −3.4 D with a maximum value of −5.5 D, and −3.4 D with a maximum value of −4.5 D in the OCA1, OCA2, and OCA4 groups, respectively. The astigmatism values were high in our cohort, but there was no significant difference between the three groups ($P = 0.36$) (Fig. 3A).

Choroidal Thickness

The data were available for 40 patients with a conclusive genetic analysis. The mean choroidal thickness in our cohort ($n = 40$) was 286 µm (95% CI, 86−460). The median choroidal thickness was 311 µm (95% CI, 86−460), 240 µm (95% CI, 128−322), and 291 µm (95% CI, 216−460) in the OCA1, OCA2, and OCA4 groups, respectively (Fig. 3B).

There was a trend toward a greater choroidal thickness in the OCA1 group compared to the OCA2 group. However, there was no significant difference ($P = 0.08$) between the three groups.

RNFL Thickness

The data were available for only 19 patients with a conclusive genetic analysis. The mean RNFL thickness was 92 µm (95% CI, 62−142). There was no significant difference between the three groups ($P = 0.51$).

Table 1. Presentation of the Main Results According to the Genotype

	TYR	OCA2	SLC45A2	*P* Value
Total (male/female), *n*	34 (18/16)	22 (10/12)	16 (6/10)	0.19
Binocular VA, decimal scale ($n = 62$)	0.29 (0.1; 0.7) ($n = 31$)	0.3 (0.1; 1) ($n = 18$)	0.20 (0.1; 0.3) ($n = 13$)	0.27
Spherical ametropia, D ($n = 54$)	3.4 (−10.25; 13.5) ($n = 30$)	−1.4 (−11; 5) ($n = 13$)	4.6 (0.8; 9) ($n = 11$)	0.003
Spherical equivalent, D ($n = 54$)	1.9 (−13; 12.75) ($n = 30$)	−2.25 (−12; 3.3) ($n = 13$)	2.63 (−1; 7.8) ($n = 11$)	0.008
Astigmatism, D ($n = 54$)	−2.7 (0; −6) ($n = 30$)	−3.4 (−0.5; −5.5) ($n = 13$)	−3.4 (−2; −4.5) ($n = 11$)	0.36
Choroidal thickness, µm ($n = 40$)	311 (86; 460) ($n = 21$)	240 (128; 322) ($n = 12$)	291 (216; 460) ($n = 7$)	0.08
RNFL, µm ($n = 19$)	96 (62; 142) ($n = 12$)	83 (81; 85) ($n = 2$)	82.5 (70; 104) ($n = 5$)	0.51

Values are presented as mean (minimum; maximum) unless otherwise indicated.

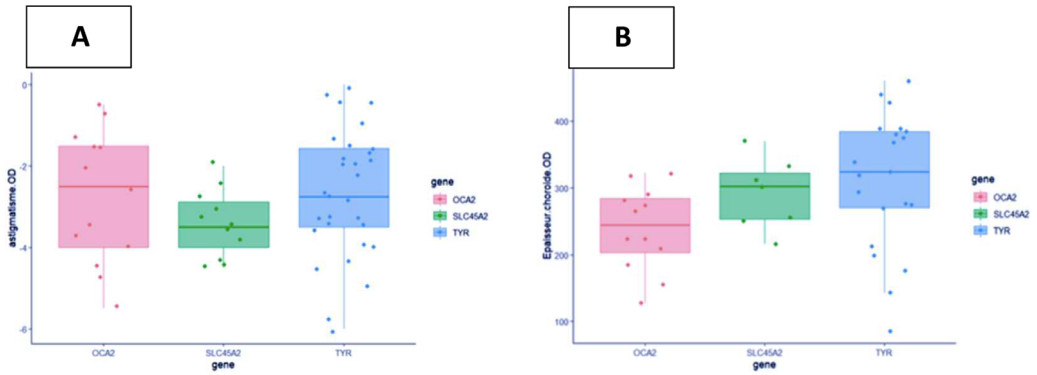

Figure 3. (**A**) Distribution of astigmatism for the three main forms ($n = 54$). (**B**) Choroidal thickness (micrometers) for the three main forms ($n = 40$).

Table 2. Grade of Foveal Hypoplasia According to the Genotype

Grade of Foveal Hypoplasia	*TYR* ($n = 34$)	*OCA2* ($n = 16$)	*SLC45A2* ($n = 15$)	Total ($N = 65$)
1 ($n = 1$)	1	0	0	1
% column	2.94	0	0	
2 ($n = 3$)	2	1	0	3
% column	5.88	6.25	0	
3 ($n = 12$)	8	2	2	12
% column	23.53	12.50	13.33	
4 ($n = 49$)	23	13	13	49
% column	67.65	81.25	86.67	
Total	34	16	15	65
% column	100	100	100	

Degree of Foveal Hypoplasia

The data were available for 65 patients with a conclusive genetic analysis: 49 out of the 65 patients (75.4%) had a grade 4. In addition, almost half of the patients with grade 4 foveal hypoplasia had OCA1. The Fisher's test showed that the grade of foveal hypoplasia did not depend on the gene involved ($P = 0.85$) (Table 2).

Retinal Hypopigmentation

The data were available for 69 patients with a conclusive genetic analysis. There was an overrepresentation of grades 3 and 4. The presence of a retinal hypopigmentation was gene independent ($P = 0.6$).

Degree of Iris Atrophy

The data were available for 69 patients with a conclusive genetic analysis. In the OCA1 group, 39% of patients had grade 4 iris atrophy. Most patients with OCA4 had grade 3 to 4 iris atrophy (13 of the 16 patients with OCA4).

Discussion

This study provided a descriptive ophthalmologic analysis of patients with albinism followed in Bordeaux University Hospital. The data were collected using a questionnaire completed during an ophthalmologic consultation between 2017 and 2021.

One of the strengths of this study was that a confirmed molecular diagnostic was obtained for most of the patients included: 72 of the 82 patients (i.e., 87%). The distribution of the different types of OCA in our study seemed to correlate with that described in the literature[14,15] for OCA1, OCA2, and OCA4.

The presence of ametropia was common in our cohort. Astigmatism and hyperopia were more common than myopia,[16] except in the OCA2 group. These data are in line with the result of previous studies where there is a high representation of patients with high with-the-rule astigmatism.[17–19] However, it should be noted that corneal topography was not performed in our study. Therefore, irregular astigmatism could not be ruled out. However, the presence of a poor ocular fixation and nystagmus may be challenging to obtain reliable corneal topography findings. A previous study has shown changes in astigmatism with age in a population of patients with albinism.[20] This could be due to ocular rubbing and to the stimulation of an often low visual acuity. This hypothesis reinforces the suggestion that using cycloplegic eye drops could be beneficial to achieve the most optimal visual development possible in patients with OCA.[21] Corneal topography could be performed to investigate the presence of keratoconus in patients with OCA.

The analysis was performed only on the data of patients older than 6 years at their first ophthalmologic visit. Indeed, it seemed useful to us to separate patients with a VA that can evolve and a foveal morphology that can change in the first years of life. Previous studies tend to show that the maturation of the visual system continues until the age of 5 to 8 years.[22–24] Furthermore, the morphology of the fovea continues to evolve after birth.[25–27] The deepening of the foveal funnel continues postnatally and is associated with an increase in macular cone density and elongation of the photoreceptor outer segments. It is interesting to note that the grades of foveal hypoplasia correspond to the key elements of foveal maturation that are the basis of the Leicester classification.[13]

The VA analysis did not find any significant difference between the three groups. However, there was a large disparity between the extremes of the values with a maximum of 7/10th (0.1 logMAR) for one patient with OCA1 (c.1205G>A/p.Arg402Gln variant) compared to 3/10th (0.5 logMAR) for one patient with OCA4. This could be explained by the frequency of the c.1205G>A/p.Arg402Gln variant already described by Monfermé et al.[28] Mean VAs of 0.6 logMAR in an OCA1 group and of 0.48 logMAR in an

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OCA2 group have been described in Israeli patients with albinism.[16] The mean VA of 0.57 logMAR found in our whole cohort is consistent with other studies.[29]

However, some limits can be noticed. VA was not obtained by the same person, and some information was unavailable: head free or fixed, luminosity of the room, adopting head postures, periodic alternating nystagmus, any and interventions performed. These could be sources of variability also unaccounted for as part of limitations of a retrospective study design.

Optic nerve hypoplasia is usually characterized by a nonprogressive alteration of the RNFL and ganglion cells. The signs include a small neuroretinal ring, an abnormal shape, and optic nerve pallor associated with a double ring sign. The appearance of optic nerve hypoplasia was studied as early as 1986.[30] More recently, a case-control study has shown that the mean optic disc diameter was smaller in patients with albinism. However, no relationship was found between the VA and the described optic nerve abnormalities.[31] In our series, the RNFL analysis was limited to the mean RNFL thickness. The RNFL thickness in the OCA population has very rarely been described in the literature.[32] This could be related to the difficulty in obtaining a reliable value, partly due to the presence of nystagmus in most patients. Indeed, the abnormal ocular development in patients with OCA does not seem to be limited only to the retina.

Table 3. Ophthalmologic Characteristics of Patients With a Nonconclusive Genetic Analysis

	Patient						
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Nystagmus	No	Yes	Yes	Yes	Yes	Yes	Yes
Strabismus	Yes	Yes	Yes	No	No	Yes	No
VA (decimal)	0.5	0.2	0.2	0.5	0.7	0.4	0.5
Iris atrophy	0	2	0	0	0	0	0
Retinal hypopigmentation	1	2	1	1	1	2	3
Foveal hypoplasia	1	1	4	2	4	3	4

Only one study, by Karabas et al.,[33] has assessed the choroidal thickness in OCA in 20 eyes of 10 patients and found a mean subfoveal choroidal thickness of 349 µm. In our study, the mean subfoveal choroidal thickness was 286 µm in 40 patients. This difference could be explained by the exclusion of all OCT images not allowing the accurate determination of the scleral border. Indeed, there was a probable underestimation of thick choroids. Many studies have described the variability of the choroidal thickness according to the time or topography.[34–38] In our study, most of the measurements were performed during the day (9 AM to 5 PM). The originality of our study relied on the comparison of the subfoveal choroidal thickness according to the

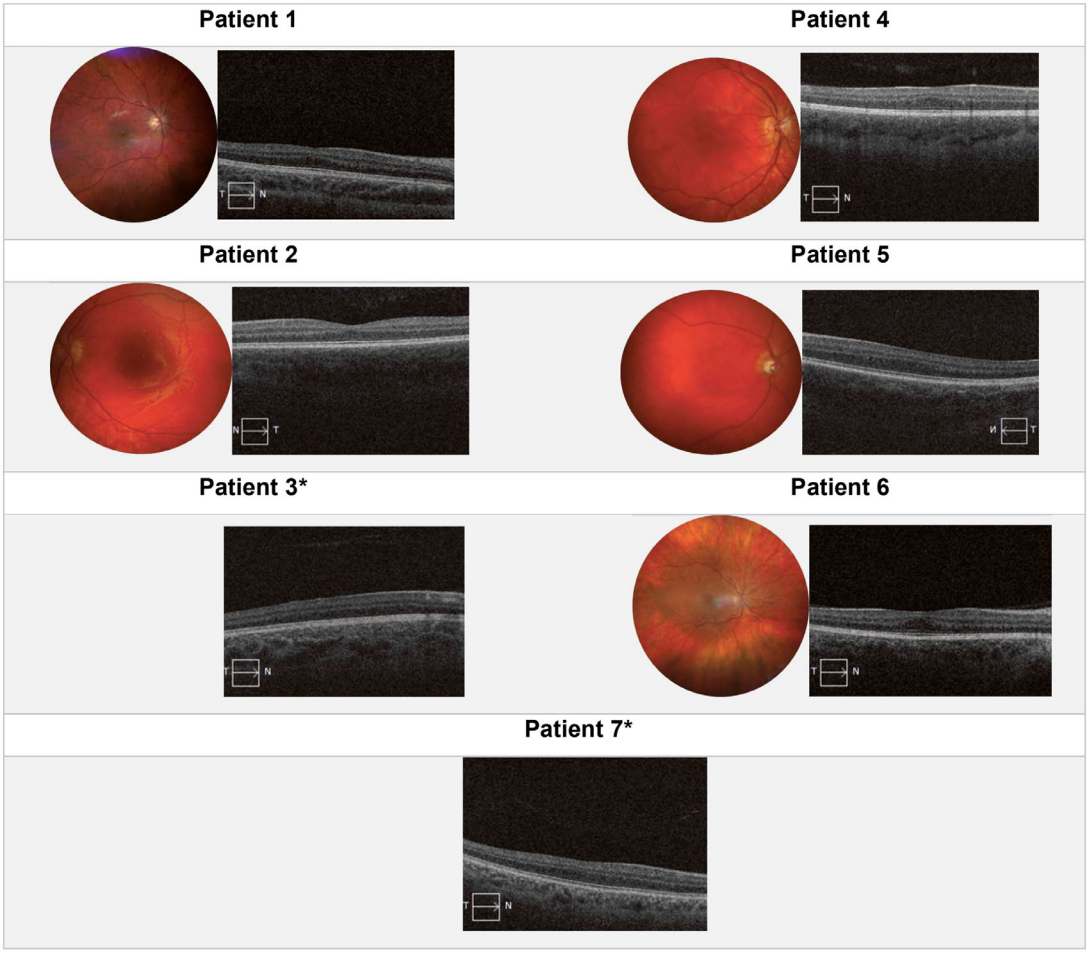

Figure 4. Retinophotography and OCT images of the seven patients with a nonconclusive genetic analysis. *An NGS analysis was performed in all seven patients. Retinophotography data were missing for patients 3 and 7. All seven patients carried a single heterozygous variant that did not allow confirming molecularly the diagnosis of albinism.

genotype. The choroidal thickness appeared to be greater in the OCA1 > OCA4 > OCA2 groups but without reaching significance. This finding needs to be confirmed in further studies.

Foveal hypoplasia was identified by OCT in the 2000s.[39,40] The value of the OCT exploration in patients with suspected albinism has been widely described.[41,42] In addition, the SD-OCT analysis of foveal hypoplasia is useful for the prognosis. Studies have described a correlation between the degree of foveal hypoplasia and the VA.[13,43,44]

Despite many questions, there is no complete answer to the different mechanisms leading to foveal hypoplasia.[45] In addition to foveal hypoplasia, there is a reduced or absent retinal avascular zone (RAZ). It would be interesting to investigate whether the RAZ is absent in all foveal hypoplasia etiologies, particularly in the different types of OCA.

Table 3 and Figure 4 describe the seven patients in the cohort for whom molecular testing was performed without significant results. It is interesting to note that for patients 3 and 5, grade 4 foveal hypoplasia was observed while retinal hypopigmentation was moderate (grade 1). This suggests that the abnormalities are not related to a melanin deficiency, as observed in foveal hypoplasia, optic nerve decussation defect, and anterior segment abnormalities.[10] These data are important to understand the pathophysiology and the relationship between a melanin deficiency and foveal hypoplasia. A better understanding could help to guide research aiming at developing new treatments.[46]

One of the main limitations of this study is its retrospective design resulting in missing data. In order to minimize missing data, a double search in paper and electronic records was performed. In addition, complementary examinations such as OCT could sometimes not be performed due to a poor VA, nystagmus, and a lack of cooperation from very young patients.

The binocular VA seems to be the most relevant parameter for assessing vision. However, it was sometimes missing, and the best monocular VA was therefore considered the best alternative.

Due to the presence of foveal hypoplasia, it was sometimes difficult to reproducibly measure the subfoveal choroidal thickness and RNFL despite the use of the eye tracker whenever possible.

The understanding of the ophthalmologic deficiency according to the genotype could allow using new therapies that could act directly to compensate for the observed deficiency. Numerous strategies have already been proposed, such as strabismus surgery and wearing an optical correction adapted to the different degrees of ametropia. Research projects are ongoing, including L-DOPA supplementation, which could help improve retinal development in the postnatal period,[47] and gene therapy approaches with subretinal injection of an adenovirus vector in a mouse model to increase retinal pigmentation.[48]

The results of our study should provide better prognostication and guidance, particularly with respect to VA. This could help the parents of children with albinism to receive early information according to their genotype.

In conclusion, we described a phenotype–genotype correlation for the three most represented forms of albinism in our cohort. When albinism is diagnosed, the family members often have many questions. This study allowed determining the predictable level of VA for a young child. Depending on the disability, school support and possibly early vocational guidance could be offered.

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