Chiasmal Decussation in Oculo-Cutaneous Albinism Type 8

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Purpose. Albinism is a genetic disorder characterized by a defect in melanin biosynthesis. Ophthalmological and dermatological impairments vary according to the patient genotype and are highly heterogenous. Recently, variants in the *DCT* gene were showed to be responsible for a new type of oculocutaneous albinism (OCA) named OCA8. We report the ophthalmological, electrophysiological, and dermatological characteristics of three patients with genetically confirmed OCA8.

Methods. This is a retrospective study of three patients with OCA8. Complete dermatological, ophthalmological, and orthoptic examinations were performed with clinical exploration and multimodal imaging. Visual evoked potentials (VEPs) were performed to characterize chiasmal decussation in two of the three patients.

Results. The dermatological phenotype was mild, whereas all three patients exhibited infantile nystagmus syndrome with reduced visual acuity, foveal hypoplasia (grade 3), macular hypopigmentation (graded from 2 to 1), and iris transillumination (grade 3). Patients who could undergo a VEP examination exhibited signs of strong chiasmal misrouting.

Conclusions. Recently, pathogenic variants in the *DCT* gene were proven to cause OCA. Whereas patients with OCA8 exhibit a milder dermatological phenotype than others, their vision was initially described as impaired. The present report confirms previous findings and suggests that chiasmal misrouting is present in OCA8. This, together with recent findings in the murine model, supports the hypothesis that DCT regulates levels of L-Dopa and downstream signaling in the developing retina. These results convey critical future therapeutic implications.

Keywords: oculocutaneous albinism (OCA), OCA 8, visual evoked potential (VEP), chiasmal misrouting

Albinism is a rare worldwide heterogeneous genetic disorder that affects melanin production or melanin transport in the skin, hair, and eyes. The global prevalence is hard to estimate due to variations according to the geographic distribution, ethnical origins, and albinism subtype. It is close to 1 in 12,000 in Europe.[1,2] It is clinically characterized by a lack of pigmentation of the skin and hair, and by ophthalmological abnormalities. Albinism can be divided in three main categories: oculocutaneous albinism (OCA), ocular albinism (OA1), and syndromic forms – Chediak-Higashi syndrome (CHS) and Hermansky-Pudlak syndrome (HPS). All but OA1 (X-linked) are inherited in an autosomal recessive manner. To note, mild forms of OCA can also result from a tri-allelic genotype involving two common hypomorphic variants in trans, with one pathogenic variant, in the *TYR* gene.[3,4]

Ophthalmological findings associated with albinism are: infantile nystagmus syndrome (INS), variable low vision, iris transillumination, foveal hypoplasia, and macular hypopigmentation,[5–7] the last three signs being quantifiable in a highly reproducible fashion. Clinically, the presence of a foveal hypoplasia is suspected by the observation of an abnormal foveal reflex on fundus examination; it is classically quantified using optical coherence tomography (OCT)

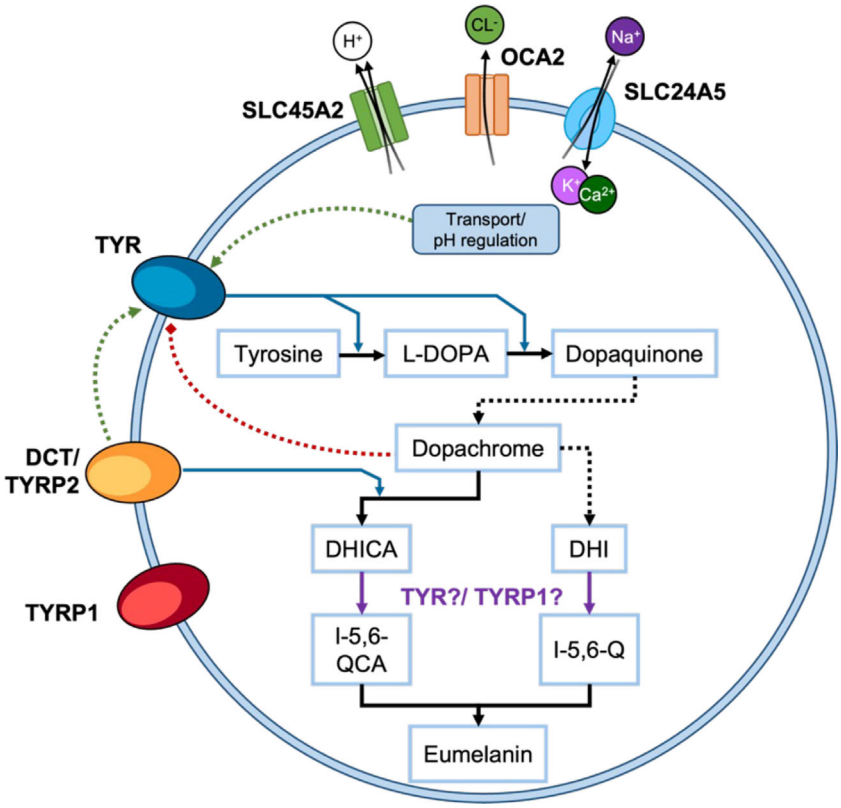

Figure 1. Model of eumelanin biosynthesis pathway in melanosomes of the human RPE (adapted from Tingaud-Sequeira, 2022[25]). *Green/Red dashed line*: Positive/negative functional interactions. The absence of DCT in OCA8 RPE may impact tyrosinase activity and/or L-Dopa stability resulting in insufficient L-Dopa for correct routing of retinal ganglion cell fibers.

and it correlates with visual acuity.[8] In addition, strabismus and high refractive errors are frequently encountered in the albinism spectrum.[9]

Albinism is also characterized by abnormalities in the visual pathway –chiasmal misrouting–: an excessive percentage of crossing ganglion cell fibers is present in the optic chiasm (>55% of crossing fibers), compared with healthy subjects.[10] This can be quantified by using specific visual evoked potentials (VEPs). In the retina, it results in a temporal shift of the fovea, located horizontally on the division line separating crossing and uncrossing ganglion cells, the latter being located in the temporal retina. This shift is likely the cause of another clinical sign of albinism – highly positive angle lambda (often mislabeled kappa) (>5 degrees), characterized by a nasal location of the corneal reflex.[11–14]

Currently, 8 genes have been identified in non-syndromic albinism, and 12 in syndromic albinism.[15] These genes play an important role in the synthesis/homeostasis of melanin (Fig. 1). The last gene identified is *DCT*, which encodes the dopachrome tautomerase (DCT), an enzyme also known as tyrosine-related protein 2 (TYRP2).[16,17] It was recently shown that genetic variants resulting in loss-of-function of *DCT* are responsible for an oculocutaneous form of albinism, named OCA type 8 (OCA8).[18,19] Patients with OCA8 reportedly exhibit subnormal to normal pigmentation of the skin and hair, whereas their ophthalmological phenotype has not been described in detail.[19]

In this study, we report the complete phenotype of three patients who had been investigated for INS and low vision, leading to the diagnosis of OCA8, through the identification of pathogenic variants in *DCT*.

Methods

This is a retrospective study of three patients diagnosed with OCA8. Written consent had been previously obtained for the use of data from the medical files. The genotypes of two patients (patient 1 and patient 2) were previously reported by Pennamen et al.[18] The following investigations had been performed according to the patients ages, as part of the systematic evaluation of albinisms in our reference centers for rare diseases.

Orthoptic and Ophthalmological Assessment

The orthoptic assessment included best corrected visual acuity (BCVA) measurement for far and near vision, assessment of the ocular motility, and the convergence reflex. The prism cover test (PCT) in far and near fixation and the quantification of stereoacuity (using Lang and TNO tests) were realized when possible. A clinical assessment of the nystagmus was performed, composed by the quantification of the abnormal head posture (AHP), when present, using a goniometer, the study of the convergence damping and the drawing of a Kestenbaum-Klainguti diagram. Monocular photographs using Nikon D5300 with ring flash were performed to quantify digitally the value of the angle lambda.[20]

The first part of the ophthalmological examination consisted of a slit-lamp examination and the classification of the iris transillumination according using Sjödell grade. Fundus examination was performed using ultra-wide field retinophotography (Optos, Dunfermline, UK). The score of the macular hypopigmentation, according to Summer's classification, and the identification of the presence of concentric macular ring were realized. Then, OCT (Spectralis, Heidelberg Engineering, Germany) was performed and the classification of the foveal hypoplasia was realized using Thomas et al. classification.

Electrophysiological Recordings

Multichannel VEPs were realized according to the last International Society for Clinical Electrophysiology of Vision (ISCEV) recommendations.[21] After a skin preparation, three copper-cup occipital electrodes were placed. The active electrode Oz was placed 2 cm above the inion and the both others – respectively O1 and O2 – 3 cm apart. The reference electrode was placed at the cranial vertex. Common ground was placed in the forehead using cutaneous electrode. The ON-OFF stimulations were: ON = 42 ms and OFF = 400 ms using 60' check size stimuli. Each eye was recorded separately after patching of the contralateral eye. VEP sequences were performed using an OLED TV screen at 1 m distance. Signals were recorded by using Metrovision MonPackOne system (Metrovision, Perenchies, France).

Chiasmal coefficient was calculated according to Jansonius method.[22] As indicated, a high-pass filter was previously applied by subtracting the signal average of the first 60 ms to the signal. The chiasmal coefficient was finally calculated using R version 4.3.1 software in a window of 60 to 300 ms, according to Jansonius recommendations, following the following formula:

$$\textit{Chiasmal coefficient} = \frac{\int_{t1}^{t2}\left[V_{RH,RE}(t)-V_{LH,RE}(t)\right]\cdot\left[V_{RH,LE}(t)-V_{LH,LE}(t)\right]dt}{\int_{t1}^{t2}\left|\left[V_{RH,RE}(t)-V_{LH,RE}(t)\right]\cdot\left[V_{RH,LE}(t)-V_{LH,LE}(t)\right]dt\right|}$$

Dermatological Assessment

Dermatological manifestations, that is, skin and hair color, and presence or absence of naevus, were collected from the patient files. Skin phototype characterization is based on the Fitzpatrick classification.[23]

Table. Phenotype of the Patients

	Patient 1	Patient 2	Patient 3
Sex – Age	F – 15 y	F – 41 y	F – 1 y 10 mo
Genetic background	Europe	North Africa	Europe
OCA8 variants (NM_001922.5)	c.118T>A; p.(Cys40Ser) c.1406_1419del; p.(Phe469*)	c.138C>G; p.(Cys61Trp) c.138C>G; p.(Cys61Trp)	c.125C>T; p.(Pro42Leu) c.217G>T; p.(Gly73Cys)
Hair/eyebrows, eyelashes	Venetian blond hair, brown eyelashes and eyebrows	Hair color light brown, as both eyelashes and eyebrows	Hair color light brown, as both eyelashes and eyebrows
Naevi	No	NA	Some pigmented naevi
Fitzpatrick phototype	Type I	Type I to II	Type I
Visual acuity in far vision (near vision) RE/LE	0.1 LogMAR (Parinaud 2)/ 0.2 LogMAR (Parinaud 3)	0.4 LogMAR (Parinaud 4)/ 0.4 LogMAR (Parinaud 4)	NA
Refraction RE/LE	+0.75 (+4.00 70 degrees)/+0.75 (+4.00 120 degrees)	Negligible since a refractive surgery for high myopia	+4.00 (+1.25 75 degrees)/+5.25 (+0.75 105 degrees)
Infantile nystagmus syndrome	Present – with extended null-zone in primary position	Present – with inverting position of the null-zone	Present – with centered null-zone
Abnormal head posture (AHP) and convergence damping (CD)	AHP present (5 degrees to the left for both far and near fixations) and CD present	Alternating AHP. CD was minimal and a head nodding was noticed	No AHP and no CD
Strabismus	Right eye fixating exotropia (18Δ in far and 20Δ in near vision) Right eye fixating History of two strabismus surgery during childhood	No strabismus (but no stereopsis was found)	Alternating esotropia (30Δ in near vision)
Angle lambda (RE/LE)	+9.2 degrees/+13.5 degrees	+4.6 degrees/−1.71 degrees	+12.47 degrees/+15.95 degrees
Foveal hypoplasia grade (Thomas et al.)	3	3	3
Macular hypopigmentation grade (Summers)	2	2	1
Iris color	Blue	Grey	Blue
Iris transillumination grade (Sjödell et al.)	3	3	3
Chiasma coefficient (Jansonius et al.)	−0.97	−0.90	NA

NA, non-applicable because of the young age of the patient.

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Molecular Analysis

DNA was extracted from blood using standard procedures. The 20 known albinism genes were analyzed (*TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *SLC24A5*, *LRMDA*, *TYRP2/DCT*, *GPR143*, *HPS1-11*, and *CHS1*), as well as the Foveal hypoplasia-optic nerve decussation defect-anterior segment dysgenesis syndrome (FHONDA) gene *SLC38A8*. This included for all genes the exons and intron-exon junctions. The introns and flanking sequences were also analyzed for *TYR* (OCA1), *OCA2* (OCA2), *SLC45A2* (OCA4), *GPR143* (OA1), and *BLOC3S1* (HPS1). Coordinates of all sequences included are available upon request.

Library preparation, capture, enrichment, and elution were performed according to the manufacturer's protocol (SureSelect XT HS Custom; Agilent Technologies). Each sample was sequenced in 75 bp paired-end reads on an Illumina NextSeq550Dx sequencer (Thermo Fisher Scientific). Alignment on the reference sequence (GRCh38) and variant calling (single nucleotide variants and copy number variants) were performed with Alissa Reporter (Agilent Technologies). Annotation and filtering of the variants were carried out with Alissa Interpret (Agilent Technologies). The sequence of the selected variants was visualized using Alamut Visual Plus (Sophia Genetics). A sample quality data check was performed. Details concerning the analytical method, bioinformatics analysis, and versions of the tools and database used are available on request. Segregation analysis of the variants in the parents was performed by Sanger sequencing (BDT version 3.1 on ABI3500xL Dx, Thermo Fisher Scientific). Pathogenicity prediction algorithms were implemented for each variant, including CADD, MPA score, MaxEntScan, SPiP, and SpliceAI-visual, integrated in MobiDetails (https://mobidetails.iurc.montp.inserm.fr/MD), Alamut visual Plus (Sophia Genetics), and RNA-Splicer (https://rddc.tsinghua-gd.org/). The minor allele frequency (MAF) was defined using the Genome Aggregation Database (gnomAD version 3.1.2; https://gnomad.broadinstitute.org/) with a threshold ≤ 0.001.

Results

Three unrelated patients with OCA8 were included in this study. The phenotypes – ophthalmological and dermatological – and genotypes of the patients are reported in the Table. Neither the BCVA evaluation nor electrophysiological

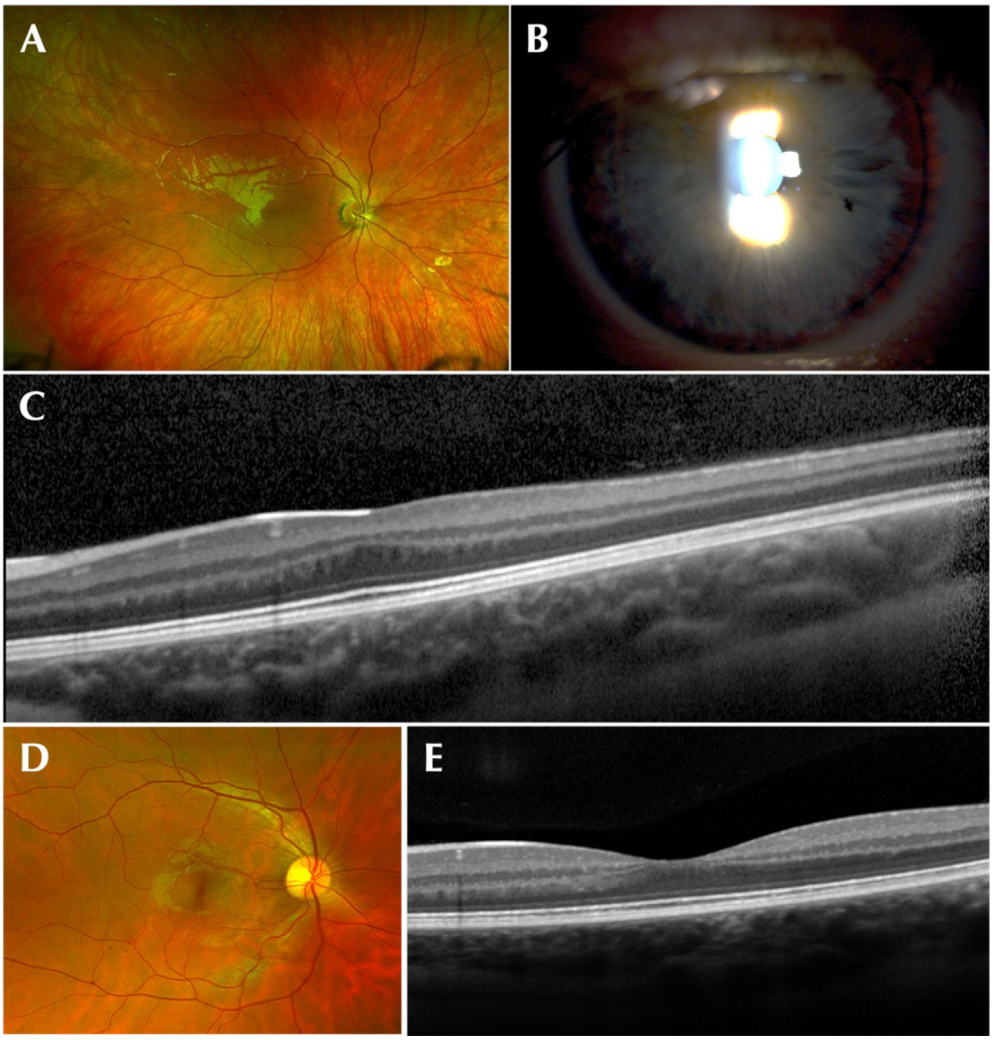

Figure 2. Multimodal imaging of the patient 1. (**A**) Fundus hypopigmentation associated with concentric macular rings; (**B**) grade 3 iris transillumination; (**C**) grade 3 foveal hypoplasia; (**D**) normally pigmented macula; and (**E**) normal fovea.

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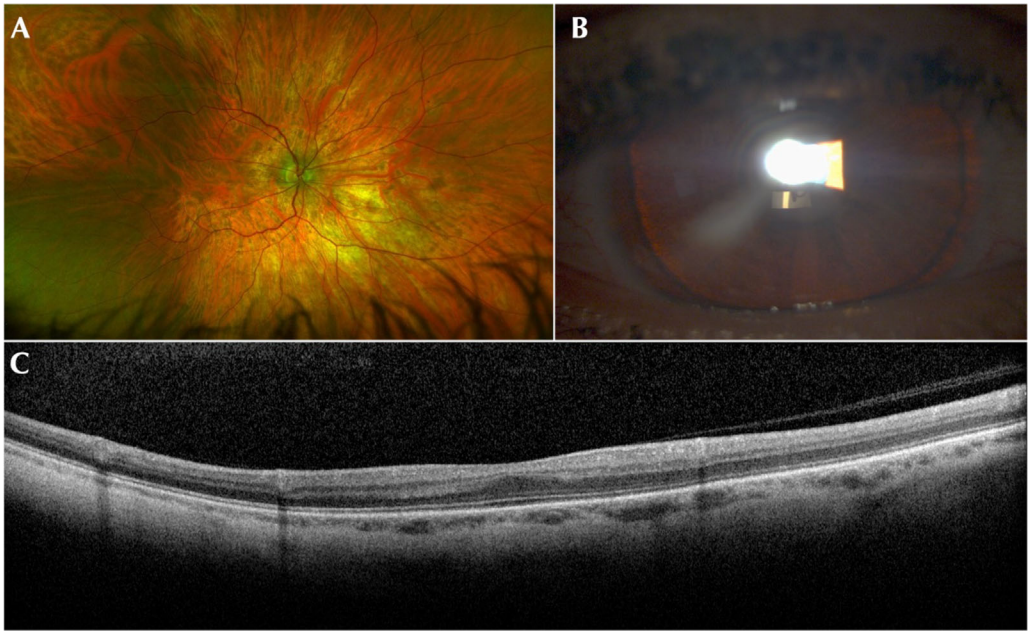

Figure 3. Multimodal imaging of the patient 2. (**A**) Fundus hypopigmentation associated with myopic choroidosis; (**B**) grade 3 iris transillumination; and (**C**) grade 3 foveal hypoplasia.

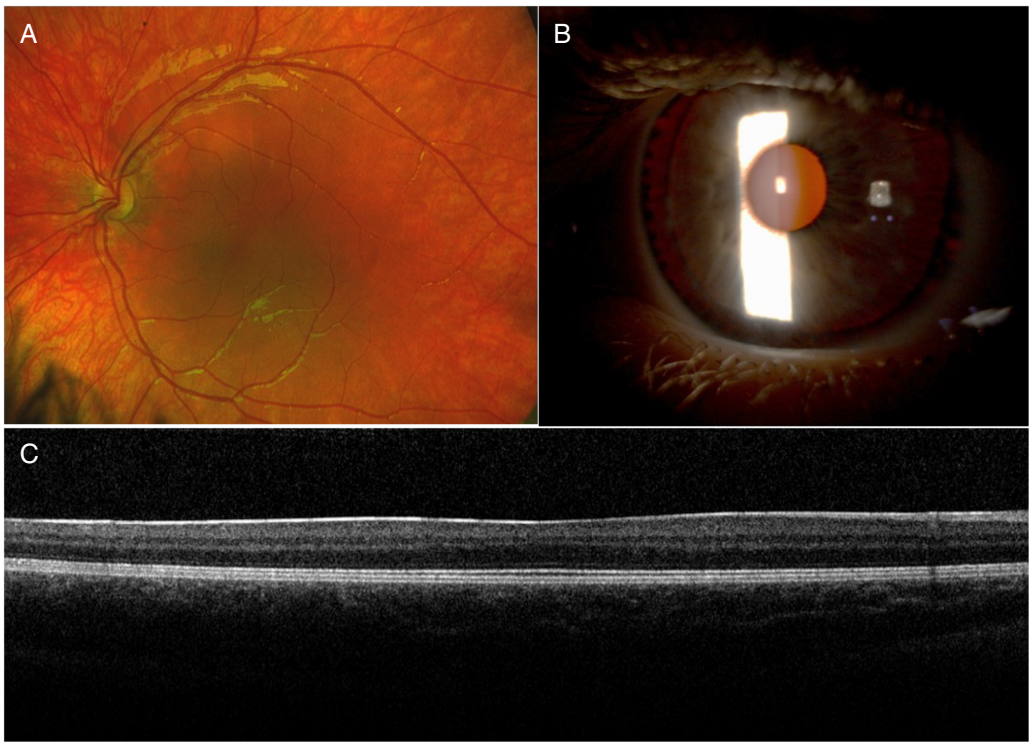

Figure 4. Multimodal imaging of the patient 3. (**A**) Fundus hypopigmentation associated with concentric macular rings; (**B**) grade 3 iris transillumination; and (**C**) grade 3 foveal hypoplasia.

assessment could be performed in the youngest patient (patient 3). For all patients, multimodal imaging is presented in Figures 2 to 4 and VEP responses of the two first patients are displayed in Figure 5.

All of the 3 patients are female patients aged 15, 41, and 1 year, respectively. Regarding the dermatological phenotype, patient 1 exhibited venetian blond hair, and had both brown eyelashes and eyebrows, whereas the two others exhibited light brown hair, eyelashes, and eyebrows. Fitzpatrick phototype was ranged between I and II. A nystagmus (INS) was present in all patients, one of them (patient 2) exhibiting an asymmetrical periodic alternating form, with an alternat-

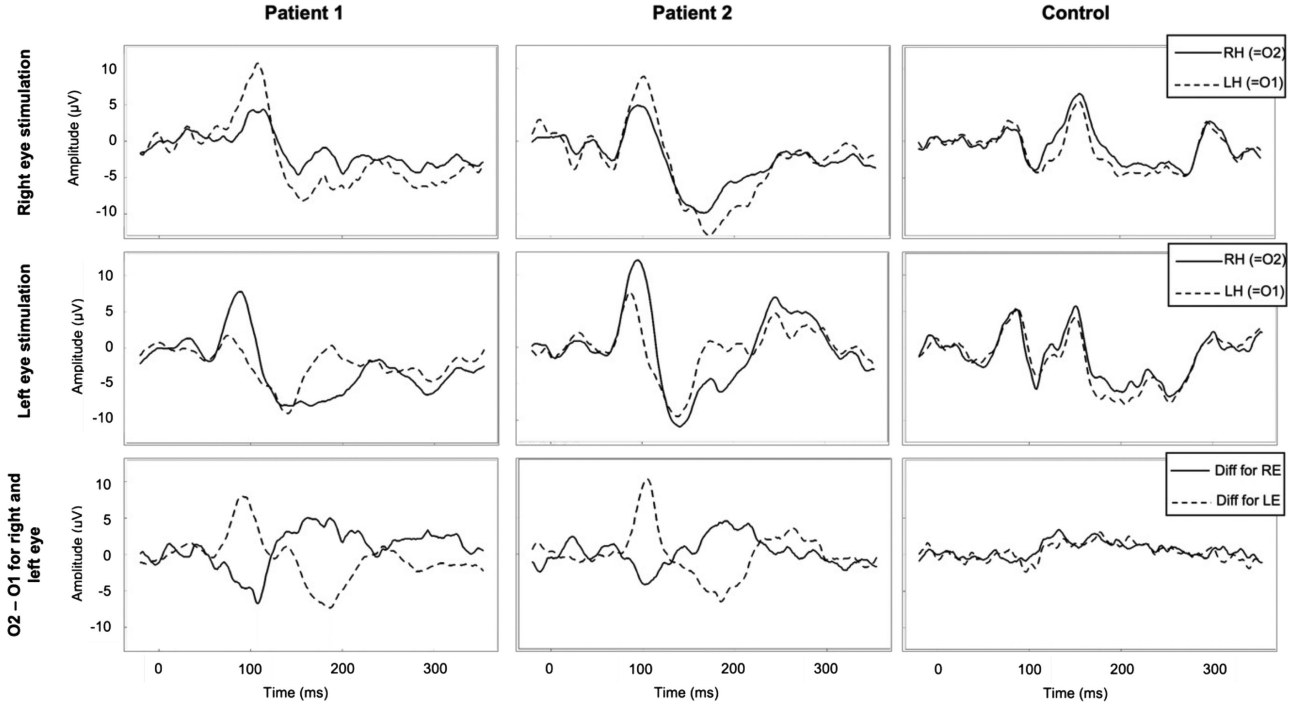

Figure 5. Visual evoked potentials responses for the two first patients. Control is presented in the last column. RH = right hemisphere (O2 response); LH = left hemisphere (O1 response); RE = right eye; LE = left eye.

ing position of the null-zone. The two others exhibited a centered null-zone. Visual acuity of the two tested patients was reduced (respectively, 0.1 and 0.2 logMAR for the right and left eyes of patient 1 and 0.4 logMAR for both eyes of patient 2). An associated strabismus was found on two patients (one exo- and one esotropia); patient 2 seemed to be phoric, although no stereopsis was found.

All of patients presented the three cardinal ophthalmological signs: iris transillumination (grade 3 for all patients), macular hypopigmentation (respectively, grades 2, 2, and 1), and foveal hypoplasia (grade 3 for all patients). Two patients (patients 1 and 3) exhibited an out-of-range angle lambda on both eyes, with a value that ranged between +9.2 degrees and +15.95 degrees. Last, VEPs performed on the two older patients highlighted a highly asymmetrical chiasmal coefficient (respectively, −0.97 and −0.90).

Discussion

Here, we characterized the ocular and skin phenotype of three patients with OCA8. All presented with very mild skin manifestations, their skin phenotype being similar to that of the general population in our consultation. In contrast, the cardinal ophthalmological signs of albinism were present, although with significant heterogeneity.

An INS was present in all of them. In the absence of an obvious dermatological phenotype, this sign is usually the first warning leading to the genetic diagnosis of albinism. Additionally, one patient exhibited an INS clinical peculiarity, known as asymmetrical periodic alternating nystagmus (APAN), which occurs in 10% of total INS cases, but in up to 37% of INS cases resulting from albinism.[24] Two out of the three patients also exhibited strabismus, which is also a frequently associated sign – the prevalence of strabismus in albinism ranging from 53% to 90.5%.[25,26] Macular hypopigmentation was present in all three patients, as was iris transillumination – with grades ranging from 1 to 2 (as opposed to the other scales, grade 1 is the worst phenotype in the macular hypopigmentation grading) and grade 3, respectively. Last, foveal hypoplasia was always present – grade 3 in all patients, as expected in albinism.[5] This is in accordance with the intermediate visual acuities, ranging from 0.4 to 0.1 LogMAR. These gradings define a mild phenotype.[8]

Additionally, an out-of-range positive angle lambda was found in two of the three patients – no conclusion can be drawn from angle lambda in the second patient, as she exhibited high myopia and had undergone refractive surgery. Beyond its impact on the visual presentation of strabismus, such positive angle lambda is a strong clinical indicator of albinism,[11–13] as it reflects the chiasmal misrouting and its effects on the location of the fovea. In this study, VEP revealed a significant fiber misrouting for the two tested patients. In the Volk et al. study, no conclusion could be reached regarding the quantification of chiasmal decussation by VEP, as none of the three patients recorded exhibited interpretable responses for pattern stimulations, whereas in the two cases having undergone flash stimulations, discordant results were obtained.[19] In our two patients, the chiasmal coefficient was close to −1. According to Jansonius et al., it normally ranges between −1 and +1, where −1 means maximal asymmetry of the signal recording between the two hemispheres, and +1 a perfect symmetry of the signal among the two hemispheres, and therefore a normal chiasmal decussation.[22,27]

Our results therefore reinforce the hypothesis of an unexpected involvement of DCT in axonal guidance of the ganglion cells from the neural retina to the chiasm. So far, L-Dopa, the first intermediate of pigment synthesis, is described as the key factor that links melanogenesis in the retinal pigment epithelium (RPE) and axonal guidance of the

retinal ganglion cells.[28] Patients with OCA1 lack tyrosinase, which is required to initiate melanin biosynthesis by converting tyrosine to L-Dopa. Because ophthalmological anomalies can be rescued by L-Dopa in murine models of OCA1, L-Dopa has been proposed as a major factor in retinogenesis and optic nerve guidance.[29–31] Different modes of action are being investigated to further assess the steps in retinal differentiation that would depend directly on the presence of L-Dopa. This has led clinicians to consider L-Dopa for pharmacological interventions on newborns with albinism, based on promising vision rescue on murine model.[32,33] In healthy pigment cells, dopachrome tautomerase encoded by *DCT* acts downstream of L-Dopa converting dopachrome into DHICA, an intermediate of eumelanins.[28] Thus, loss-of-function mutations in *DCT* are not expected to affect levels of L-Dopa in pigmented cells. Unexpectedly, however, we have recently found that optic cups of *Dct*$^{-/-}$ OCA8 murine models have 50% less L-Dopa than wild-type controls, indicating that levels of L-Dopa may be limiting in the developing retina of patients with OCA8.[29] The present evidence of chiasm misrouting in patients with OCA8 supports this hypothesis and suggests an action of DCT upstream of L-Dopa, either directly or through indirect feedback loops. Further studies will be needed to better understand the complex pathway of eumelanin synthesis and its contribution to retinogenesis.

Conclusions

Recently, pathogenic variants in the *DCT* gene were proven to cause oculocutaneous albinism. Although patients with OCA8 exhibit a milder dermatological phenotype than patients with other OCA types, their vision was initially described as significantly impaired. The present report on three OCA8 cases confirms previous findings and identifies chiasmal misrouting in the two adults that could undergo electrophysiological recordings. This, together with recent findings in the murine model, supports the hypothesis that DCT regulates levels of L-Dopa and downstream signaling in the developing retina. These results convey critical future therapeutic implications.

Acknowledgments

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