Ocular albinism with absent foveal pits but without nystagmus, photophobia, or severely reduced vision

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A 9-year-old Caucasian girl of northern European ancestry presented with findings suggestive of ocular albinism, although she maintains good visual acuity and lacks nystagmus and photophobia. DNA analysis revealed that the patient is a compound heterozygote for mutations in the tyrosinase gene, which is typically associated with overt, generalized oculocutaneous albinism and severe ocular symptoms. Her particular genotype confers no apparent cutaneous disease and only mild ocular features.

Albinism is characterized by decreased or absent melanin synthesis, resulting in abnormalities of skin and hair pigmentation. Ocular manifestations are characteristic and include reduced visual acuity, typically in the range of 20/100 to 20/400; photophobia; nystagmus; strabismus; iris transillumination defects; and a hypopigmented fundus with an absent foveal pit. Since there are numerous, genetically determined steps in the process of melanin synthesis, albinism can be caused by different mutations with differing patterns of inheritance and phenotypic expression. The ocular form, in which skin and hair pigmentation are relatively normal, is known to occur either by X-linked recessive or by autosomal-recessive inheritance. Autosomal-recessive ocular albinism (AROA), described by O’Donnell and coworkers in 1978, is now known to be associated with mutations and polymorphisms of genes that can also cause oculocutaneous disease.

Case Report

A 9-year-old Caucasian girl, followed by a pediatric ophthalmologist for an accommodative esotropia and mild left amblyopia, was referred for evaluation of worsening visual acuity in both eyes and abnormal macular pigmentation. She had no photophobia. Family history was notable for age-related macular degeneration in the patient’s father’s but slightly paler than her father’s. Her mother was unavailable for comparison. She was thought by her father to tan normally. Best-corrected visual acuity measured 20/32 in both eyes (right eye, +4.00 − 1.50 × 95; left eye, +4.75 − 1.00 × 106). She was orthophoric with her glasses and had excellent stereopsis, measuring to 50 arcsec on the Titmus test. There was no nystagmus on slit-lamp examination. Other tests for nystagmus were not done. Slit-lamp examination was notable, however, for diffuse iris transillumination bilaterally (Figure 1B). Dilated examination revealed markedly albinotic fundi (Figure 2A). Each macula appeared flat and had hundreds of tiny punched-out hypo- and hyperpigmented spots with an absent foveal pit (Figure 2B). No streaks or specks of pigmentation were noted in the periphery of either eye. Examination of the patient’s father was unremarkable.

Foveal sensitivity, as measured by the Humphrey 24-2 threshold test, was 36 dB in the right eye and 37 dB in the left (ie, normal). Farnsworth D-15 color vision testing was relatively normal, with the patient making only 1 mistake in each eye. Fluorescein angiography revealed small foveal avascular zones in both eyes, with no evidence of leakage (Figure 2C and D). Optical coherence tomography (Stratus; Carl Zeiss Meditec, Dublin, CA) confirmed the absence of foveal pits in both eyes (Figure 2A). Each macula appeared flat and had hundreds of tiny punched-out hypo- and hyperpigmented spots with an absent foveal pit (Figure 2B). No streaks or specks of pigmentation were noted in the periphery of either eye. Examination of the patient’s father was unremarkable.

The patient had light brown hair, which appeared normal, and apparently normal skin pigmentation (Figure 1A). Her skin and hair color were similar to her sister’s but slightly paler than her father’s. Her mother was unavailable for comparison. She was thought by her father to tan normally. Best-corrected visual acuity measured 20/32 in both eyes (right eye, +4.00 − 1.50 × 95; left eye, +4.75 − 1.00 × 106). She was orthophoric with her glasses and had excellent stereopsis, measuring to 50 arcsec on the Titmus test. There was no nystagmus on slit-lamp examination. Other tests for nystagmus were not done. Slit-lamp examination was notable, however, for diffuse iris transillumination bilaterally (Figure 1B). Dilated examination revealed markedly albinotic fundi (Figure 2A). Each macula appeared flat and had hundreds of tiny punched-out hypo- and hyperpigmented spots with an absent foveal pit (Figure 2B). No streaks or specks of pigmentation were noted in the periphery of either eye. Examination of the patient’s father was unremarkable.

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Discussion

The enzyme tyrosinase is essential to melanin formation, catalyzing the rate-limiting step of tyrosine hydroxylation. It is not surprising, therefore, that decreased or absent
**FIG 1.** A, External examination revealing light brown hair and slightly reduced skin pigmentation. B, Slit-lamp examination of the right eye with retroillumination demonstrates diffuse iris transillumination defects. Examination of the left eye demonstrated similar findings.

**FIG 2.** A, Ophthalmoscopic examination of the right eye demonstrating albinotic fundus; note the prominence of choroidal vessels, indicative of decreased melanin in the retinal pigment epithelium and choroid. B, Numerous, small hypo- and hyperpigmented spots in the macula. Note the absent foveal pit. Examination of the left eye demonstrated similar findings. C, Fluorescein angiography transiting the right eye demonstrates an abnormally small but present foveal avascular zone. D, Late frames of the right eye reveal multiple, tiny areas of punctate hyperfluorescence corresponding to areas of retinal pigment epithelial hypopigmentation, representing “window defects.” Mid- and late frames of the left eye demonstrated similar findings. There was no leakage.
tyrosinase causes albinism. Despite having abnormalities in both alleles of the tyrosinase gene, our patient does not demonstrate any of the typical nonocular findings of oculocutaneous albinism. The most likely reason is that the polymorphic allele with the guanine to adenine substitution at the 1205 position of the TYR gene results in some functional tyrosinase enzyme, permitting some degree of skin and hair pigmentation. This particular substitution has been shown to yield a thermolabile tyrosinase enzyme with only 25% of normal catalytic activity at body temperature of 37°C. At higher temperatures, there is more inactivation of the tyrosinase enzyme. Our patient, who carries this hypomorphic allele and another mutant allele, therefore, has approximately 12% to 13% of normal tyrosinase activity. Her eyes are presumably more severely affected than her skin because their postnatal (and even intrauterine) development occurs at temperatures slightly higher than that of skin and hair.

AROA was first described in 1978, when it was noted that several patients presented with the findings of ocular albinism but without cutaneous manifestations. All of these patients had markedly diminished visual acuity, nystagmus, photophobia, and strabismus. Pedigree analysis was consistent with recessive inheritance. Since this initial description, many more such patients have been identified, and the genetics of this entity have been better characterized. In the most comprehensive study of AROA to date, 56% of the 36 patients studied were found to have mutations in the TYR (OCA1) gene, as in our patient. Twenty percent were found to have mutations in other genes associated with albinism, such as the pink-eyed dilution (P) gene or tyrosinase-related protein 1 (TRYP1) gene, also known as OCA2 or OCA3, respectively. No mutation could be identified in the others. Most of the patients in this study were severely affected.

Review of the supplemental data from this study shows that only 2 of 20 patients with AROA and TYR mutations had good visual acuity (better than 20/40) with no nystagmus. These 2 individuals were also compound heterozygotes with 1 mutant allele and the same hypomorphic allele that affects our case. This polymorphism has also recently been reported in another albinism patient who also may have lacked nystagmus.

We present this case to emphasize that oculocutaneous albinism gene mutations can cause phenotypic variation not only in the presence and type of cutaneous findings but also in the severity and type of ocular disease. Ophthalmologists should, therefore, suspect and evaluate this diagnosis in patients with minimal or atypical ocular findings of albinism, such as apparently isolated foveal hypoplasia.

Interestingly, our patient retains good visual acuity despite the absence of foveal pits. A recent study by Marmor and colleagues suggests that the foveal pit may not be necessary for cone specialization, making it somewhat visually insignificant. Their study demonstrated normal central cone number, architecture, and cone function, as determined by electroretinography in 4 patients, 2 of whom had oculocutaneous albinism. Newer modalities such as the scanning laser ophthalmoscope and spectral domain OCT have also been used to better evaluate foveal hypoplasia. Since there is no published long-term follow-up of patients with mild oculocutaneous albinism, we cannot be certain about our patient’s prognosis, but these findings suggest that she may retain relatively good visual acuity.

References