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Pseudoxanthoma Elasticum: A Novel Mutation in the *ABCC6* Gene That Affects Eye Manifestations of the Disease

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ABSTRACT

Purpose: To determine whether a correlation between *ABCC6* mutations and ocular phenotypic expressions exists.

Methods: In this study, 28 relatives of a consultand with known pseudoxanthoma elasticum were recruited for evaluation of the ocular manifestations of the disease, including peau d'orange appearance, angioid streaks, choroidal neovascular membranes, peripapillary atrophy, and retinal drusen. Comprehensive eye examinations were documented for all patients, who were then evaluated for the presence of known mutations in the aforementioned *ABCC6* gene.

Results: Statistically significant correlations were noted between the gene and peau d'orange appearance ($P = 0.0016$), angioid streaks ($P < 0.0001$), and choroidal neovascular membranes ($P = 0.0016$).

Conclusions: A statistically significant association was documented between the R39G mutation of the ABCC6 protein and 3 of 6 known manifestations of pseudoxanthoma elasticum. Although mutations of this gene are clearly associated with angioid streaks, the mechanism by which the transporter affects development of this pathology is speculative.

INTRODUCTION

Pseudoxanthoma elasticum (PXE) is an inherited disorder with multiple systemic manifestations involving the skin, vascular system, and Bruch's membrane of the eye. Histopathology has demonstrated the mineralization and fragmentation of elastic fibers in these tissues. Of interest, 43 mutations in the *ABCC6* gene have been noted in approximately 80% of patients with PXE.[1] This particular gene encodes an adenosine triphosphate–binding cassette protein.

Ocular involvement has been noted in most patients, with a typical sequence of findings that includes peau d'orange appearance of the retinal pigment epithelium (RPE), angioid streaks, peripapillary atrophy, retinal drusen, and, ultimately, comet-like tails. Although there are no known deleterious effects noted from peau d'orange appearance and comet-like tails, the visual prognosis associated with angioid streaks is poor. It has been noted that 75% of those with angioid streaks develop disciform macular scars.[2]

Bruch's membrane is an elastin- and collagen-rich membrane and is the attachment site for the RPE; it also functions in the bidirectional transport of nutrients and metabolites between the RPE and choriocapillaris. Angioid streaks are ruptures in pathologically thickened and calcified Bruch's membrane; breaks in Bruch's membrane lead to atrophy of the overlying RPE and photoreceptors.

Most patients with PXE have been noted to have sporadic mutations, including 43 mutations of the *ABCC6* gene. The disease has been localized to an 820-kilobase region of chromosome 16p13.1.[3] Adenosine triphosphate–binding cassette proteins are involved in signal transduction, protein secretion, drug and antibiotic resistance, and the antigen presentation cascade. The physiologic function of ABCC6 remains unclear, although it has been proposed that the protein functions in the regulation of the extracellular matrix movement between the inner retina and the photoreceptor RPE–Bruch's membrane complex.[4] Faulty active transport of anions could affect the transport properties and distribution of molecules, thereby producing pathology in Bruch's membrane. Of note, ABCC6 is highly expressed in the liver and kidney, while less expression can be found in tissues affected by PXE.

METHODS

This study was performed in conjunction with the Department of Endocrinology at the Ochsner Clinic

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Key Words: ABCC6 *gene, angioid streaks, choroidal neovascular membranes, drusen, peau d'orange appearance, peripapillary atrophy, phenotypic expression, pseudoxanthoma elasticum*

Table 1. Ocular Findings Noted During Clinical Examinations of 28 Relatives of the Consultand

Peau d'Orange Appearance	Angioid Streaks	Choroidal Neovascular Membranes	Peripapillary Atrophy	Comet-like Tails	Retinal Drusen	Genotype[a]
X	X	X	X		X	2 (Homozygous)
						2
	X		X			Both
			X			1
						1
						1
						1
	X	X	X			Both
			X		X	1
					X	Neither
						2
						1
						1
						1
						Both
			X			1
						1
			X			1
X						Both
X	X	X	X			Both
						1
						Neither
X	X	X	X			Both
						1
						Neither
				X		Neither
			X			1
			X		X	1

[a]Numeral 1 indicates R39G(e9), and 2 indicates R1138W(e24).

Foundation. One of us investigated the role of 2 *ABCC6* mutations (R39G and R1138W) associated with bone density loss in patients with PXE (A.B., unpublished data). A total of 28 family members of a consultand with these mutations from southeastern Louisiana with known PXE were recruited for the study; of these, 22 were female, and 6 were male. The study was observational and prospective in design. Researchers were blinded to genotypic findings until all clinical information was obtained. Informed consent was obtained from all 28 subjects. For patients to be included in the study, the following examinations were required: best-corrected visual acuity, intraocular pressure, dilated fundus examination, fundus photography, and intravenous fluorescein angiography. Blood samples were sent to the Molecular Diagnostics Laboratory of the Department of Dermatology and Cutaneous Biology at Thomas Jefferson University, Philadelphia, PA, to be evaluated for the presence of the aforementioned mutations in the *ABCC6* gene. One investigator was responsible for reviewing all color fundus photographs and intravenous fluorescein angiography photographs.

Table 2. Spearman Rank Correlation Coefficients Among 24 Relatives of the Consultand With the R39G Mutation[a]

Peau d'Orange Appearance	Angioid Streaks	Choroidal Neovascular Membranes	Peripapillary Atrophy	Retinal Drusen
0.51640	0.65158	0.51640	0.24140	−0.21822
0.0098	0.0006	0.0098	0.2558	0.3057

[a] Coefficients represent probability greater than |r| under H0; $\rho = 0$.

RESULTS

The ocular findings noted during the clinical examinations of 28 subjects included the following: peau d'orange appearance (4 patients), angioid streaks (5 patients), choroidal neovascular membranes (4 patients), peripapillary atrophy (11 patients), comet-like tails (1 patient), and retinal drusen (4 patients) (Table 1). A statistically significant association between the presence of peau d'orange appearance ($P = 0.0016$), angioid streaks ($P < 0.0001$), and choroidal neovascular membranes ($P = 0.0016$) was discovered with respect to the R39G mutation of the ABCC6 protein (Table 2).

DISCUSSION

R1138W is an established mutation in a large intracellular loop of *ABCC6* in which mutants are often identified. To our knowledge, no specific ophthalmic associations with the R39G gene of interest have been reported previously. If the R39G mutation could be evaluated further, it might provide insight into the pathogenesis of angioid streaks and, ultimately, related choroidal neovascular membranes, as discovered in PXE. Further studies could similarly evaluate angioid streak formation in other known systemic diseases such as Ehlers-Danlos syndrome, Paget disease, and sickle cell anemia. Effective therapy remains challenging.[5]

Although the statistics of this study demonstrated significant findings, 28 patients were included, and the study thereby lacked power. In addition, only 2 of the known mutations of ABCC6 protein were explored. It would be helpful to repeat the study to look at all known mutations and to evaluate any associations.

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REFERENCES

1. Le Saux O, Beck K, Sachsinger C, et al. A spectrum of *ABCC6* mutations is responsible for pseudoxanthoma elasticum [published corrections appear in *Am J Hum Genet*. 2001;69(6):1413 and 2002;71(2):448]. *Am J Hum Genet*. 2001;69(4):749–764.
2. Secrétan M, Zografos L, Guggisberg D, Piguet B. Chorioretinal vascular abnormalities associated with angioid streaks and pseudoxanthoma elasticum. *Arch Ophthalmol*. 1998;116(10): 1333–1336.
3. Le Saux O, Urban Z, Göring HH, et al. Pseudoxanthoma elasticum maps to an 820-kb region of the p13.1 region of chromosome 16 [published correction appears in *Genomics*. 2000;63(3):439]. *Genomics*. 1999;62(1):1–10.
4. Hu X, Plomp AS, van Soest S, Wijnholds J, de Jong PT, Bergen AA. Pseudoxanthoma elasticum: a clinical, histopathological, and molecular update. *Surv Ophthalmol*. 2003;48(4):424–438.
5. Finger RP, Charbel Issa P, Ladewig MS, et al. Pseudoxanthoma elasticum: genetics, clinical manifestations and therapeutic approaches. *Surv Ophthalmol*. 2009;54(2):272–285.