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Pseudoxanthoma Elasticum

Synonym: PXE

Sharon F Terry, MA[1] and Jouni Uitto, MD, PhD[2]

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Summary

Clinical characteristics

Pseudoxanthoma elasticum (PXE) is a systemic disorder that affects the elastic tissue of the skin, the eye, and vascular system. Individuals most commonly present with angioid streaks of the retina found on routine eye examination or associated with retinal hemorrhage and/or characteristic papules in the skin. The most frequent cause of morbidity and disability in PXE is reduced vision due to complications of subretinal neovascularizations and macular atrophy. Other manifestations include premature gastrointestinal angina and/or bleeding, intermittent claudication of arm and leg muscles, stroke, renovascular hypertension, and cardiovascular complications (angina/myocardial infarction). Most affected individuals live a normal life span.

Diagnosis/testing

The clinical diagnosis of PXE is established in a proband with characteristic skin lesions and at least one characteristic retinal finding. When eye findings are characteristic, but skin findings are equivocal, identification of calcified dystrophic elastic fibers using a von Kossa or similar stain on a biopsy of potentially lesional skin establishes the diagnosis.

The molecular diagnosis of PXE is established in a proband by the presence of biallelic *ABCC6* pathogenic variants identified on molecular genetic testing.

Management

Treatment of manifestations: Management requires coordinated input from multidisciplinary specialists; care by a retina specialist including intraocular injection of anti-angiogenic drugs for the treatment of macular neovascularization when indicated; standard-of-care interventions for gastrointestinal bleeding, claudication, stroke, renovascular hypertension, and cardiovascular complications (angina and/or myocardial infarction).

Surveillance: Routine examination by a retina specialist; follow up as recommended by treating physicians for vascular manifestations.

Author Affiliations: 1 PXE International, Washington, DC; Email: sterry@pxe.org. 2 Thomas Jefferson University, Philadelphia, Pennsylvania; Email: jouni.uitto@jefferson.edu.

Agents/circumstances to avoid: Contact sports or racquet sports without appropriate eye and head protection; aspirin and nonsteroidal anti-inflammatory medications because of increased risk of gastrointestinal bleeding; smoking because of its vasoconstrictive properties.

Pregnancy management: Vaginal delivery appears safe for the retina of women with PXE if no active choroidal neovascularization (CNV) is present. Women with PXE should have a retinal examination to check for active CNV, as angioid streaks alone are not an indication for medical interventions during delivery.

Genetic counseling

PXE is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic heterozygote (carrier), and a 25% chance of being unaffected and not a carrier. If both *ABCC6* pathogenic variants have been identified in the family, carrier testing for at-risk family members, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for pseudoxanthoma elasticum (PXE) have been established [Uitto et al 2014].

Suggestive Findings

PXE **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings

- **Skin**
  - Papules (darker than the skin color), usually seen on the lateral aspect of the neck or the flexural creases, such as the antecubital fossae, axillae, groin, or popliteal fossae
  - Plaques formed by coalescence of papules
  - Loose, slack, or droopy, redundant skin (especially of the neck, axilla, and groin) that occurs with time
- **Eye**
  - *Peau d'orange* generally appearing in the first decade and the late second decade, characterized by diffuse mottling of the fundus
  - Retinal angioid streaks often appearing in the second decade, consisting of broad grayish to reddish-brown irregular lines caused by breaks in Bruch's membrane* that appear to radiate outward from the optic disk or peripapillary region in a pattern that resembles blood vessels; hence the term "angioid"

    * Bruch's membrane is the elastin-rich tissue layer of the choroid between the retina and the choriocapillaris.

    Note: Fluorescein angiography may be necessary to confirm this retinal finding.
- **Gastrointestinal bleeding,** particularly the stomach. The characteristic yellow mucosal lesions of PXE can be seen on gastroscopy.
- **Vascular.** Beginning in the second decade of life, almost all individuals with PXE develop intermittent claudication.

Family history is consistent with autosomal recessive inheritance. Note: Pseudodominant inheritance (i.e., an autosomal recessive condition present in individuals in two or more generations) has been reported in some families [Bergen 2006, Ringpfeil et al 2006, Legrand et al 2017].

Establishing the Diagnosis

The diagnosis of PXE can be **established** in a proband based on clinical findings or by identification of biallelic pathogenic (or likely pathogenic) variants in *ABCC6* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *ABCC6* variants of uncertain significance (or of one known *ABCC6* pathogenic variant and one *ABCC6* variant of uncertain significance) does not establish or rule out the diagnosis.

Clinical Diagnosis

The diagnosis of PXE is established in an individual with characteristic skin lesions on the neck, axillae, and/or antecubital fosse and at least one characteristic retinal finding (*peau d'orange*, angioid streaks, or choroidal vascularization). When eye findings are characteristic but skin findings are equivocal or subtle, identification of calcified dystrophic elastic fibers using a von Kossa or similar stain on a biopsy of potentially lesional skin establishes the diagnosis.

Molecular Diagnosis

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those in whom the diagnosis of PXE has not been considered are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1

- **Single-gene testing.** Sequence analysis of *ABCC6* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Sequence analysis is performed first; if only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis is performed to detect intragenic deletions or duplications.

  Note: (1) Presence of the pseudogenes *ABCC6P1* (which has high homology to exons1-9) and *ABCC6P2* (high homology to exons 1-4) interferes with both sequence analysis and deletion/duplication analysis. (2) Multiplex ligation-dependent probe amplification (MLPA) analysis to detect intragenic deletions or duplications using a widely available commercial kit does not include probes for exons 1, 3, 6, 16, 19-20, 29, and 31. Therefore, deletion or duplications confined to these exons cannot be detected by this assay. This technical challenge likely contributes to the disease alleles not detected in affected individuals (see Table 1).(3) Targeted testing for the most common pathogenic variants may be performed first (see Table 7).

- **A multigene panel** that includes *ABCC6* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain

significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing. When the diagnosis of PXE has not been considered, comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is often an option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Pseudoxanthoma Elasticum (PXE)

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ABCC6	Sequence analysis [3]	~75%-86% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	~10%-13% [4, 7]
Unknown	NA	~4%-12%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Chassaing et al [2007], Iwanaga et al [2017], Legrand et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Miksch et al [2005] and Kringen et al [2015]) may not be detected by these methods.
6. Note, MLPA analysis using a widely available commercial kit does not include probes for exons 1, 3, 6, 16, 19-20, 29, and 31.
7. A deletion of exons 23-29 is common (~11% of alleles in affected individuals) in European populations [Legrand et al 2017], and a deletion of exons 1-4 is common (~10% of alleles in affected individuals) in the Japanese population [Iwanaga et al 2017].

Clinical Characteristics

Clinical Description

Pseudoxanthoma elasticum (PXE) is a systemic disorder that affects the elastic tissue of the skin, the eye, and the cardiovascular and gastrointestinal systems. Individuals can present as early as age five years with papules in the skin and/or between ages ten and 30 years with angioid streaks of the retina found on routine eye examination

or associated with retinal hemorrhage. Manifestations of other vascular involvement include gastrointestinal angina and/or bleeding, intermittent claudication of arm and leg muscles, stroke, and renovascular hypertension, especially at an unexpectedly young age.

Table 2. Select Features of Pseudoxanthoma Elasticum (PXE)

Feature	% of Persons with Feature	Comment
Skin lesions	100%	In advanced stages, skin can become lax & redundant; sometimes reconstructive surgery is necessary.
Retinal involvement	100%	Subretinal neovascularization w/hemorrhage can cause significant visual impairment.
Vascular (arterial arrowing)	60%	Can cause claudication, small strokes, intestinal angina, renovascular hypertension, angina &/or myocardial infarction
GI bleeding	10%	Most commonly in the upper GI tract

Based on Uitto et al [2014]
GI = gastrointestinal

Skin. Skin lesions are generally the first sign and are present between the first and second decade of life, but are often not recognized as a sign of PXE. The primary skin lesion is a papule that is somewhat darker than the person's natural skin tone, i.e., yellowish on white skin, black on brown skin, usually seen on the lateral aspect of the neck or the flexural creases (e.g., the antecubital fossae, axillae, groin, or popliteal fossae). Occasionally, there is periumbilical involvement.

The papules gradually coalesce to form plaques, and eventually the skin, especially of the neck, axilla, and groin, becomes loose, lax, and redundant.

Mucous membranes can show similar yellowish lesions, most commonly the inner aspect of the lower lip and the vaginal mucosa.

Eye. The earliest ocular finding is a diffuse mottling of the fundus known as *peau d'orange*, generally appearing between adolescence and the late second decade.

In nearly every person with PXE, angioid streaks develop between the first and second decade.

Neither angioid streaks nor *peau d'orange* affects visual acuity; however, spontaneous subretinal neovascularization and hemorrhage can occur and lead to visual distortion (metamorphopsia) and decreased visual acuity, resulting in disciform scarring and, when the macula or fovea is involved, permanent loss of central vision. In some cases, atrophy similar to geographic atrophy in age-related macular degeneration develops and can be the cause of vision loss [Gliem et al 2016, Risseeuw et al 2019].

Gastrointestinal. The most common site of bleeding is the upper gastrointestinal tract, particularly the stomach. The cause of bleeding is not well understood; one theory is that it may begin with superficial bleeding from erosive gastritis, then becomes massive and uncontrolled due to defective vasoconstriction of affected arteries. Diffuse punctate bleeding and erosions can be seen on gastroscopy, but an exact source of the hemorrhage may be difficult to locate.

Vascular. Mineralization of the internal elastic lamina of medium-sized arteries, predominantly in peripheral arteries (arms, legs) and intracranial internal carotid arteries, resulting in arterial narrowing occurs frequently in PXE. Arterial narrowing can lead to asymmetric or diminished pulses in the limbs and, if severe enough, can cause intermittent claudication of the leg and arm muscles, small strokes (cerebrovascular arteries), intestinal angina (celiac or mesenteric arteries), and renovascular hypertension (renal arteries).

Although one small series suggested an increased incidence of mitral valve prolapse in individuals with PXE [Lebwohl et al 1982], this has never been replicated.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *ABCC6* have been identified.

In addition, the phenotype does not differ between individuals with biallelic *ABCC6* pathogenic variants and those who meet clinical diagnostic criteria but who do not have a known genetic cause.

Nomenclature

Earlier reports sometimes referred to PXE as Gröndblad-Strandberg syndrome.

Prevalence

Prevalence data are not available.

Common disease-associated variants have been identified in individuals of European descent [Pfendner et al 2007, Legrand et al 2017] and in Japanese populations [Iwanaga et al 2017]. A founder variant was also identified in the Afrikaner population [Le Saux et al 2002]. See Table 7 for details about notable variants.

Genetically Related (Allelic) Disorders

A few individuals with generalized arterial calcification of infancy (GACI) without detectable pathogenic variants in *ENPP1* have been reported to have biallelic pathogenic variants in *ABCC6* [Nitschke et al 2012].

Differential Diagnosis

Hereditary Disorders

Table 3. Genes of Interest in the Differential Diagnosis of Pseudoxanthoma Elasticum (PXE)

Gene(s)	Disorder	MOI	Clinical Features Overlapping w/PXE	Differentiating Features
ATP6V0A2 *EFEMP2* *ELN* *FBLN5* *LTBP4* [1]	Cutis laxa (See *ATP6V0A2*-Related Cutis Laxa, *FBLN5*-Related Cutis Laxa, *EFEMP2*-Related Cutis Laxa, *ELN*-Related Cutis Laxa, and *LTBP4*-Related Cutis Laxa.)	AR AD	Loose & sagging skin mimicking PXE; no discrete papules or plaques	Skin lesions appear over the entire body; in PXE they are limited to the flexor areas.
ENPP1	Generalized arterial calcification of infancy (GACI)	AR	• Severe arteriopathy • Children w/GACI may also develop the typical cutaneous & ocular phenotype of PXE. [2]	GACI is very severe in children; PXE is very mild & often not apparent in childhood.
FGF23 *GALNT3* *KL*	Hyperphosphatemic familial tumoral calcinosis	AR	Angioid streaks in the retina [3]	Skin lesions are present in PXE.
GGCX	PXE-like disorder w/multiple coagulation factor deficiency (OMIM 610842)	AR	Cutis laxa-like skin changes w/ histolopathologic changes of PXE & deficiency of vitamin K-dependent clotting factors	No issues w/clotting in PXE

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features Overlapping w/PXE	Differentiating Features
HBB	Beta-thalassemia	AR	PXE-like phenotype (skin, eye [angioid streaks in the retina [3]], & cardiovascular)	Although similar, the angioid streaks are not concurrent w/skin lesions.
HBB	Sickle thalassemia (See Sickle Cell Disease.)	AR	Angioid streaks in the retina [3]	Although similar, the angioid streaks are not concurrent w/skin lesions.
LEMD3	Buschke-Ollendorf syndrome (BOS) (OMIM 166700)	AD	Osteopoikilosis assoc w/ cutaneous papules w/ accumulation of elastin in dermis	• On skin biopsy, PXE does not have the same extent of abnormal collagen fibers near the calcified elastic fibers. • The skin lesions in BOS do not calcify histopathologically. • No osteopoikilosis in PXE
PDB4 *SQSTM1* *TNFRSF11A* *TNFRSF11B* *ZNF687*	Paget disease of bone (OMIM PS167250)	AD AR	Angioid streaks in the retina [3]	No skin lesions in Paget disease of bone

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. Cutis laxa may also be associated with pathogenic variants in *ALDH18A1*, *ATP6V1A*, *ATP6V1E1*, or *PYCR1* (see OMIM Cutis Laxa Phenotypic Series).

2. Nitschke et al [2012]

3. PXE is the most common cause of angioid streaks of the retina.

Acquired Disorders and Disorders without a Known Genetic Cause

Skin

The skin lesions of pseudoxanthoma elasticum (PXE) are mimicked by those in the following acquired conditions:

- White fibrous papulosis of the neck and papillary dermal elastolysis, both signs of intrinsic aging, associated with thinning or loss of elastic fibers and focal thickening of the collagen fiber network (collectively known as fibroelastolytic papulosis)
- Solar elastosis, in which yellowish-white papules occur in the skin of the neck and chest as a result of photoaging
- Late-onset focal dermal elastosis

Long-term D-penicillamine treatment (used in the treatment of Wilson disease and prevention of cysteine kidney stones in cystinuria results in skin lesions that clinically resemble PXE but do not exhibit elastic fiber mineralization histologically [Bécuwe et al 2005].

Eyes

In high myopia, lacquer cracks may resemble angioid streaks.

Subretinal neovascularization with hemorrhage can be seen in the absence of angioid streaks in age-related macular degeneration, high myopia, and presumed ocular histoplasmosis. Macular atrophy can also be seen in age-related macular degeneration.

Recurrent Gastrointestinal Bleeding

PXE should be considered in the differential diagnosis of recurrent gastrointestinal bleeding of unknown cause [Dalle & Geboes 2002].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with pseudoxanthoma elasticum (PXE), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Pseudoxanthoma Elasticum (PXE)

System/Concern		Evaluation	Comment
Skin		Complete skin exam w/biopsy (if not done previously) by dermatologist	To establish a baseline
Eye		Complete exam by retinal specialist incl best corrected visual acuity, Amsler grid, OCT, [1] & retinal exam for neovascularization & macular atrophy	Early recognition of choroidal neovascularization assoc w/angioid streaks allows prompt treatment w/anti-angiogenesis drugs & appropriate surveillance.
Reduced vision		Consultation w/agencies for the visually impaired [1]	Use of low vision aids [2]
Gastrointestinal (bleeding, angina)		Obtain past medical history & medical records for findings consistent w/these potential complications	Referral to gastroenterologist
Vascular	**Claudication of leg &/or arm muscles**	Obtain past medical history & medical records for findings consistent w/these potential vascular complications	Referral to vascular clinic
	Stroke		Referral to neurologist/stroke clinic
	Renovascular hypertension		Referral to nephrologist
Cardiovascular assessment		Referral to cardiologist for baseline exam	Cardiovascular issues (if present) may be exacerbated by PXE.
Other		Consultation w/clinical geneticist &/or genetic counselor	

OCT = optical coherence tomography

1. In the US, publicly funded agencies at the state level provide services for the blind or those with progressive eye disorders; services include vocational training, mobility training, and skills for independent living.

2. Low vision aids such as magnifiers and closed-circuit television may provide useful reading vision for individuals with reduced central acuity.

Treatment of Manifestations

No specific treatment for PXE exists.

Management of PXE requires coordinated input from multidisciplinary specialists (see Table 5). Support groups can benefit affected individuals and their families by providing accurate information and education and reducing isolation.

Table 5. Treatment of Manifestations in Individuals with Pseudoxanthoma Elasticum (PXE)

System/Concern		Treatment	Considerations/Other
Skin		Reconstructive surgery [1]	Reconstructive surgery may be indicated to improve skin changes of the face, neck, axilla, & groin that are causing infection & inflammation.
Eye		Current treatment for macular neovascularization, incl intravitreal injection of anti-angiogenic drugs [2]	Consult a retinal specialist immediately for any distortion in vision or ↓ in visual acuity.
Gastrointestinal		Surgical intervention may be indicated for Gl bleeding. [3]	Avoid use of aspirin & NSAIDs to ↓ risk of GI bleeding.
Vascular	**Claudication of leg &/or arm muscles**	Per treating vascular clinic/surgeon [4]	
	Stroke	Per treating stroke clinic/neurologist	
	Renovascular hypertension	Per treating nephrologist [4]	
Cardiovascular complications (angina, MI)		Mgmt of angina &/or prior MI per treating cardiologist/cardiovascular surgeon [5]	

GI = gastrointestinal; MI = myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs
1. As directed by a dermatologist or plastic surgeon
2. Mimoun et al [2017], Battaglia Parodi et al [2019]
3. Bleeding may be difficult to control without surgery [Dalle & Geboes 2002].
4. See Anderson et al [2013] for clinical practice guidelines on the management of individuals with peripheral artery disease.
5. See Fihn et al [2012] and Fihn et al [2014] for clinical practice guidelines on the management of individuals with stable ischemic heart disease.

Surveillance

Table 6. Recommended Surveillance for Individuals with Pseudoxanthoma Elasticum (PXE)

System/Concern		Evaluation	Frequency
Skin		Consultation w/cosmetic dermatologist or reconstructive surgeon if redundant skin presents risk of infection	Per patient
Eye		Retinal exam by retinal specialist	Annually or more frequently per treating ophthalmologist when retinal neovascularization is active &/or treatment is ongoing
		Patient use of Amsler grid to monitor for central visual disturbances	Daily
Gastrointestinal		Per treating gastroenterologist	Per treating gastroenterologist
Vascular	**Claudication of leg &/or arm muscles**	Per treating vascular clinic/surgeon	Per treating vascular clinic/surgeon
	Stroke	Per treating stroke clinic/neurologist	Per treating stroke clinic/neurologist
	Renovascular hypertension	Per treating nephrologist	Per treating nephrologist
Cardiovascular complications angina, MI)		Per treating cardiologist	Per treating cardiologist

MI = myocardial infarction

Agents/Circumstances to Avoid

Racquet and contact sports carry an increased risk for ocular and head trauma, both of which have been reported to precipitate retinal hemorrhage in patients with angioid streaks; participation in such activities should be discouraged.

Individuals with PXE who participate in sports and physical recreation should wear appropriate protective eyewear such as polycarbonate sports goggles and/or protective helmets with eye shields.

Aspirin and nonsteroidal anti-inflammatory medications should be avoided whenever possible to reduce the risk of gastrointestinal bleeding.

Smoking is strongly discouraged because of its vasoconstrictive properties.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of medical management and preventive measures. In those without a molecular diagnosis, at-risk sibs should be screened by clinical examination, medical history, and detailed review of cardiovascular systems. Evaluations can include:

- Retinal examination for *peau d'orange* and angioid streaks, which are usually evident by the first or second decade, and skin examination for characteristic skin lesions if the pathogenic variants in the family are not known;
- Molecular genetic testing if the *ABCC6* pathogenic variants in the family are known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Most women with PXE have normal pregnancies; PXE is not associated with markedly increased fetal loss or adverse reproductive outcomes. The incidence of gastrointestinal bleeding and retinal complications (<1%) is lower than previously thought [Bercovitch et al 2004]. Retinal examination during pregnancy and prompt attention to any visual symptoms are advised. Vaginal delivery appears safe for the retina of women with PXE if no active choroidal neovascularization is present. Angioid streaks alone are not an indication for medical interventions during delivery.

In the series of 795 pregnancies examined by Bercovitch et al [2004], a history of pregnancy did not have a statistically significant effect on the severity of manifestations of PXE in women older than age 40 years. This was confirmed in a 2016 review of the literature [Camacho et al 2016].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Pseudoxanthoma elasticum (PXE) is inherited in an autosomal recessive manner.

Note: Pseudodominant inheritance (i.e., an autosomal recessive condition present in individuals in two or more generations) is reported in some families [Bergen 2006, Ringpfeil et al 2006, Legrand et al 2017].

Risk to Family Members

Parents of a proband

- If the parents of a proband are clinically unaffected, they are obligate heterozygotes (i.e., presumed to be carriers of one *ABCC6* pathogenic variant based on family history).
- In populations with a high carrier rate and/or a high rate of consanguinity, it is possible that affected children will be born to an affected individual and a carrier (or even to two affected individuals) resulting in pseudodominant inheritance.
- In very rare instances, only one parent is a carrier and the proband has PXE as the result of one inherited *ABCC6* pathogenic variant and one *de novo ABCC6* pathogenic variant [Legrand et al 2017].
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for an *ABCC6* pathogenic variant and to allow reliable recurrence risk assessment.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ABCC6* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Intrafamilial clinical variability in PXE is observed; thus, sibs who inherit biallelic *ABCC6* pathogenic variants may be more or less severely affected than the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an affected individual's reproductive partner also has PXE or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ABCC6*.
- In populations with a high carrier rate and/or a high rate of consanguinity, the reproductive partner of the proband may have two *ABCC6* pathogenic variants or be heterozygous. Thus, the risk to offspring is most accurately determined after molecular genetic testing of the proband's reproductive partner.

Other family members. If both parents of the proband are known to be heterozygous for an *ABCC6* pathogenic variant, each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ABCC6* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for clarification of genetic status, determination of genetic risk, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *ABCC6* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early confirmation or exclusion of the diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**

  Pseudoxanthoma elasticum

- **PXE International, Inc.**

  4301 Connecticut Avenue, NW

  Suite 404

  Washington DC 20008-2369

  Phone: 202-362-9599

  Fax: 202-966-8553

  Email: info@pxe.org

  www.pxe.org

- **PXE International BioBank and Clinical Data Registry**

  www.pxe.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Pseudoxanthoma Elasticum: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

ABCC6	16p13.11	ATP-binding cassette sub-family C member 6	ABCC6 @ LOVD	ABCC6	ABCC6

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Pseudoxanthoma Elasticum (View All in OMIM)

177850	PSEUDOXANTHOMA ELASTICUM, FORME FRUSTE
264800	PSEUDOXANTHOMA ELASTICUM; PXE
603234	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 6; ABCC6

Molecular Pathogenesis

ABCC6 encodes multidrug resistance-associated protein 6 (also known as ATP-binding cassette sub-family C member 6, ABCC6). Although the mechanism of action is not completely understood, there is evidence that disease-associated low levels of inorganic pyrophosphate in the blood cause mineralization in peripheral tissue.

Mechanism of disease causation. Loss of ABCC6 function causes the disease.

***ABCC6*-specific laboratory technical considerations.** The presence of the two following pseudogenes interferes with both sequence analysis and deletion/duplication analysis:

- *ABCC6P1*, which has high homology to exons 1-9
- *ABCC6P2*, which has high homology to exons 1-4

Multiplex ligation-dependent probe amplification (MLPA) analysis to detect intragenic deletions or duplications using a widely available commercial kit does not include probes for exons 1, 3, 6, 16, 19-20, 29, and 31. Therefore, deletion or duplications confined to these exons cannot be detected by this assay. This technical challenge likely contributes to the disease alleles not detected in affected individuals (see Table 1).

Table 7. Notable *ABCC6* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001171.5 NP_001162.4	c.3421C>T	p.Arg1141Ter	Most common (in descending order) disease-associated variants in European populations [Legrand et al 2017]
NM_001171.5	Exon 23-29 deletion	--	
NM_001171.5 NP_001162.4	c.2542delG	p.Val848CysfsTer83	Most common (in descending order) pathogenic variants in the Japanese population [Iwanaga et al 2017]
	c.1132C>T	p.Glu378Ter	
NM_001171.5	Exon 1-4 deletion	--	
NM_001171.5 NP_001162.4	c.4015C>T	p.Arg1339Cys	Founder variant that accounts for ~50% of disease alleles in the Afrikaner population [Le Saux et al 2002]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Sharon F Terry, MA, is the co-founder of PXE International and co-investigator on more than 30 PXE clinical studies. Her publications exceed 170 peer-reviewed papers. She has given more than 500 presentations at national and international meetings. She manages the International PXE Research Consortium. She is the founder of the PXE BioBank and Registry. She is also the president and CEO of Genetic Alliance.

Dr Jouni Uitto is internationally recognized for his research on connective tissue biochemistry and molecular biology in relation to cutaneous diseases. Dr Uitto's publications include 725 original articles in peer-reviewed journals, 352 textbook chapters and review articles, and 1,048 abstracts on presentations at national and international meetings.

Author History

Jouni Uitto, MD (2020-present)
Lionel G Bercovitch, MD; Brown University (2001-2020)
Charles D Boyd, PhD; University of Hawaii (2001-2006)
Sharon F Terry, MA (2001-present)

Revision History

- 4 June 2020 (bp) Comprehensive update posted live
- 14 June 2012 (me) Comprehensive update posted live
- 2 April 2007 (st) Revision: Molecular Genetic Testing – targeted mutation analysis changed to deletion analysis
- 11 December 2006 (me) Comprehensive update posted live
- 5 November 2003 (me) Comprehensive update posted live
- 14 March 2002 (st) Author revision
- 5 June 2001 (me) Review posted live
- September 2000 (st) Original submission

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