GENEReviews

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Pseudoxanthoma Elasticum

[*PXE, Gronblad-Strandberg Syndrome*]

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Summary

Disease characteristics. Pseudoxanthoma elasticum (PXE) affects the skin, eye, cardiovascular system, and gastrointestinal system. Individuals most commonly present with papules in the skin and/or with angioid streaks of the retina found on routine eye examination or associated with retinal hemorrhage. Rarely, individuals may present with vascular signs and symptoms: gastrointestinal bleeding or intermittent claudication. The most frequent cause of morbidity and disability in PXE is reduced vision from macular hemorrhage and disciform scarring. Most affected individuals live a normal life span.

Diagnosis/testing. The diagnosis of PXE is suspected in individuals with characteristic skin and ocular findings and is established by histologic findings on biopsy of lesional skin. *ABCC6 (MRP6*), which encodes the ATP-binding cassette protein multidrug resistance-associated protein 6, is the only gene known to be associated with PXE. Molecular genetic testing detects mutations in about 80% of affected individuals.

Management. *Treatment of manifestations:* coordinated care by a multidisciplinary team (dermatologist, primary care physician, ophthalmologist, cardiologist, vascular surgeon, plastic surgeon, genetics professional, nutritionist); contact with support groups for accurate information and to reduce the sense of isolation; surgical intervention as indicated for gastrointestinal bleeding and severe peripheral vascular disease. Current treatment for subretinal neovascularization and hemorrhage appears to be effective. *Surveillance:* Routine examination by an ophthalmologist with expertise in retinal disease; routine physical examination with attention to the cardiovascular system. *Agents/circumstances to avoid:* contact sports; aspirin and nonsteroidal anti-inflammatory medications (NSAIDs) because of gastrointestinal bleeding risk.

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 carrier, and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3. Prenatal testing using molecular genetic techniques may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

Current minimal criteria for the clinical diagnosis of pseudoxanthoma elasticum (PXE) are the presence of retinal angioid streaks in combination with characteristic skin lesions with or without a positive family history of PXE. However, carriers with a positive family history may have mild ocular and cutaneous findings [Bacchelli et al 1999, Sherer et al 2001].

Note: The minimal criteria for the diagnosis of PXE are likely to change once molecular genetic testing becomes more widely available.

- **Angioid streaks** are breaks in Bruch's membrane, the tissue layer between the retina and the choriocapillaris. Angioid streaks radiate from the optic disk in a pattern that resembles blood vessels, hence, the term 'angioid'. Angioid streaks are best observed on examination of the retina with an ophthalmoscope through a dilated pupil. Fluorescein angiography may be needed on occasion.
- **Typical skin lesions** are yellowish papules, usually seen on the lateral aspect of the neck or the flexural creases, such as the antecubital fossae, axillae, groin, or popliteal fossae. With time, the papulesf coalesce to form plaques and the skin becomes loose and redundant.
- **A positive family history** is defined as two or more family members with clinically diagnosed PXE.

Testing

Skin biopsy. Calcification of fragmented elastic fibers in a biopsy of lesional skin, confirmed by von Kossa stain, is diagnostic.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *ABCC6(MRP6)*, which encodes the ATP-binding cassette protein multidrug resistance-associated protein 6, is the only gene known to be associated with PXE both in families with autosomal recessive inheritance and in families with two-generation involvement (see Genetic Counseling: Evidence in support of AR inheritance pattern) [Struk et al 1997, van Soest et al 1997, Le Saux et al 2000, Bergen et al 2000].

Clinical use

- Confirmatory diagnostic testing

Clinical testing

- **Sequence analysis/mutation scanning.** These methods detect missense mutations, the most prevalent mutations in *ABCC6* [Le Saux et al 2001], as well as nonsense mutations, frameshift mutations, and small deletions and insertions, which have also been described. Testing strategies may involve screening of select exons (e.g., exons 24 and 28, in which a large number of mutations are located) before proceeding to sequencing of the remainder of the coding region [Hu et al 2004].
- **Deletion analysis.** A 16.4 kb deletion involving *ABCC6* exons 23-29 is a recurrent mutation found in multiple populations with varying frequency. It has been shown to represent approximately 30% of alleles in the US and about 5% of alleles in Europe [Le Saux et al 2001].

Research testing

- **Direct DNA.** Molecular genetic testing for *ABCC6* deletions and point mutations is available on a research basis only.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Pseudoxanthoma Elasticum

Test Methods	Mutations Detected	Mutation Detection Frequency[1]	Test Availability
Sequence analysis/mutation scanning and deletion analysis	*ABCC6* sequence variants; *ABCC6* del23-29	80% [2]	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

2. Hu et al 2004

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- Inheritance is autosomal recessive; however, in 20% of cases, no mutations are found.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in the *ABCC6(MRP6)* gene.

Although an increased risk of premature coronary artery disease among carriers of the *ABCC6* p.R1141X mutation has been suggested [Wegman et al 2005], this has not been confirmed. Struk et al (2006), testing thousands of carriers, showed no association of coronary heart disease and *ABCC6* mutations.

Clinical Description

Natural History

Pseudoxanthoma elasticum (PXE) primarily affects the skin, eye, cardiovascular system, and gastrointestinal system. Individuals with PXE most commonly present with papules in the skin and/or with angioid streaks of the retina found on routine eye examination or associated with retinal hemorrhage. Rarely, individuals may present with vascular signs and symptoms: gastrointestinal bleeding or intermittent claudication. The most frequent cause of morbidity and disability in PXE is reduced vision from macular hemorrhage and disciform scarring. Most affected individuals live a normal life span.

Skin. The primary skin lesion is a yellowish papule, usually seen on the lateral aspect of the neck or the flexural creases, such as 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 and redundant. Mucous membranes can show similar 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 the second and third decades, angioid streaks develop. These broad grayish to reddish-brown irregular lines radiate outward from the optic nerve. They result from fractures in a mineralized Bruch's membrane, an elastin-rich layer of the choroid. Neither angioid streaks nor peau d'orange affects visual acuity; however, spontaneous subretinal neovascularization and hemorrhage can occur and lead to disciform scarring, and loss of central vision when the macula or fovea are involved.

Cardiovascular. Mineralization of the internal elastic lamina of medium-sized arteries resulting in arterial narrowing occurs frequently in PXE. Arterial narrowing can lead to asymmetric or diminished pulses in the limbs, causing intermittent claudication of the leg and arm muscles, or angina or myocardial infarction (coronary arteries), small strokes (cerebrovascular arteries), intestinal angina (celiac or mesenteric arteries), and renovascular hypertension (renal arteries). At least one small series suggested an increased incidence of mitral valve prolapse in individuals with PXE [Lebwohl et al 1982]. However, this has yet to be confirmed by larger prospective controlled studies.

Gastrointestinal. The most common site of bleeding is the upper gastrointestinal tract, particularly the stomach. The characteristic yellow mucosal lesions of PXE can be seen on gastroscopy. The cause of bleeding is not well understood; it may be the result of defective arterial constriction in response to erosive gastritis and superficial bleeding. Diffuse punctate bleeding and erosions can be seen and an exact source of the hemorrhage may be difficult to locate. Bleeding may be difficult to control without surgery.

Pregnancy. Most women with PXE have normal pregnancies. PXE is not associated with markedly increased fetal loss or adverse reproductive outcomes. The incidence of gastric bleeding and retinal complications (<1%) is lower than previously thought [Bercovitch et al 2004].

Genotype-Phenotype Correlations

To date, no genotype-phenotype correlations are known.

Nomenclature

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

Prevalence

The exact prevalence is unknown. Published reports estimate prevalence from 1:25,000 to 1:100,000.

A few populations have an increased risk, such as the Afrikaners in South Africa, who display a founder effect [Le Saux et al 2002].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Individuals with beta-thalassemia may present with a phenotype (skin, eye, and cardiovascular) that is similar to pseudoxanthoma elasticum (PXE) but in the absence of *ABCC6* mutations.

Skin. The skin lesions of PXE are mimicked by those in the following conditions:

- Buschke-Ollendorf syndrome (osteopoikilosis associated with cutaneous papules with extensive accumulation of elastin in the dermis)
- 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
- Cutis laxa

D-penicillamine treatment (see Wilson disease) results in skin lesions that clinically resemble PXE but do not exhibit elastic fiber mineralization histologically [Becuwe et al 2005].

Eyes. PXE is the most common cause of angioid streaks of the retina. Angioid streaks in the retina can also be seen in the following:

- Sickle thalassemia (see Sickle Cell Disease)
- Beta-thalassemia
- Paget's disease
- High myopia
- Acromegaly
- Familial hyperphosphatemia

Subretinal neovascularization with hemorrhage can be seen in the absence of angioid streaks in age-related macular degeneration and presumed ocular histoplasmosis.

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 in an individual diagnosed with pseudoxanthoma elasticum (PXE):

- Complete skin examination, including a biopsy of potentially lesional skin from the axilla or neck. It should be stained with a von Kossa stain, looking for calcified fragmented elastic fibers.
- Complete dilated eye examination by a retinal specialist, particularly looking for peau d'orange and angioid streaks. A fluorescein angiogram may be necessary to confirm the diagnosis.
- Baseline cardiovascular examination with periodic follow-up for individuals with pseudoxanthoma elasticum (PXE), including, as clinically indicated (depending on age, physical findings, and exercise level): echocardiography, cardiac stress testing, and Doppler evaluation of peripheral vasculature

Treatment of Manifestations

No specific treatment for PXE exists.

Management of PXE requires coordinated input from a multidisciplinary team of specialists including a dermatologist, primary care physician, ophthalmologist, cardiologist, vascular surgeon, plastic surgeon, genetics professional, and nutritionist. Support groups can benefit affected individuals and their families by providing accurate information and education and reducing isolation.

Current treatment for macular degeneration, especially the intraocular injection of anti-angiogenic drugs, appears to be effective in PXE. A retinal specialist should be consulted immediately when the individual experiences any distortion in vision.

Surgical intervention may be indicated for gastrointestinal bleeding, severe peripheral vascular disease (if correctable), and the improvement of changes of the skin of the face, neck, axilla,

and groin that are of cosmetic concern. Although wound healing seems to be uncomplicated in PXE, cosmetic acceptability of surgery involving the skin is less predictable [Viljoen et al 1990].

Prevention of Primary Manifestations

Weight control, avoidance of smoking, and aggressive management of hypertension and lipid disorders may reduce the risk of vascular complications by reducing the risk of comorbidity resulting from atherosclerosis. Reduction in risk has not been confirmed in controlled studies.

Prevention of Secondary Complications

Individuals with PXE who have coexistent mitral valve prolapse should have antibiotic prophylaxis for dental, gastrointestinal, and genitourinary procedures.

Surveillance

- Routine examination by an ophthalmologist with expertise in retinal disease. Affected individuals benefit from learning to use the Amsler grid to monitor for central visual disturbances.
- Routine physical examination with specific attention to the cardiovascular system
- Monitoring by patient for black tarry stool
- Periodic monitoring of serum lipid concentrations

Agents/Circumstances to Avoid

- Avoidance of contact sports
- Wearing of appropriate protective goggles to prevent eye injuries
- Avoidance when possible of aspirin and nonsteriodal anti-inflammatory medications (NSAIDs) to reduce the risk of gastrointestinal bleeding

Testing of Relatives at Risk

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

Therapies Under Investigation

Pentoxifylline and cilostazol may be of value in managing intermittent claudication; however, controlled studies of these drugs in individuals with PXE-related peripheral arterial disease have not been conducted.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Although it has been reported that high calcium intake in adolescence may correlate with the overall severity of PXE [Renie et al 1984], this has not been confirmed by prospective controlled studies and remains controversial.

The AREDS study for macular degeneration suggested that a regimen of antioxidant vitamins could prove beneficial in that disease. It is possible (although not confirmed) that the same recommendation can be made for PXE [Clemons et al 2004].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of the proband

- The parents of an affected individual are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) may have minimal or mild clinical findings.
- It is not known at this time to what degree parents who are carriers of a mutant allele causing PXE are at risk for some manifestations of the disorder. The presence of calcified elastic fibers on biopsy of lesional skin and limited ocular and cutaneous signs of PXE in parents may be consistent with the heterozygous carrier state [Sherer et al 2001].
- It is suggested that parents of a proband undergo thorough ocular and skin examination for signs of PXE and possibly biopsy of axillary, antecubital fossae, or neck skin, even in the absence of overt lesions. Most relatives will have peau d'orange and/or angioid streaks by the first or second decade if they are affected. Of note, positive findings must be interpreted with caution.

Sibs of the proband

- At conception, each sib of an individual with autosomal recessive PXE has a 25% chance of being affected, a 50% chance of being an symptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Most relatives will have peau d'orange and/or angioid streaks by the first or second decade if they are affected. Heterozygotes (carriers) may have minimal clinical findings.

Offspring of the proband. The offspring of an individual with autosomal recessive PXE are obligate heterozygotes (carriers) for a mutant allele causing PXE (see heterozygotes).

Other family members of the proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Heterozygotes. Heterozygotes (carriers) are usually asymptomatic; however, subclinical, but detectable, abnormalities of elastic fibers have been observed on skin biopsy and are difficult to interpret. In apparently unaffected individuals, skin biopsy may reveal subtle abnormalities of elastic fibers suggesting expression of the genetic changes that cause the classic PXE phenotype [Bacchelli et al 1999]. Such studies are currently ongoing.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

Evidence in support of autosomal recessive inheritance pattern. Although early literature on PXE suggests autosomal dominant inheritance based on the observation of two-generation familial occurrence of PXE, these cases have been shown to be pseudodominant [Bergen 2006, Ringpfeil et al 2006]. No three-generation affected pedigrees have been reported. Autosomal dominant inheritance has not been confirmed.

The traditional mechanisms used to determine mode of inheritance (pedigree analysis combined with skin biopsy and eye examination) may be inconclusive because carriers may exhibit characteristic changes resulting in the appearance of two-generation involvement [Sherer et al 2001].

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service. PXE International also offers DNA banking for individuals with PXE.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of PXE are listed in the Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Pseudoxanthoma Elasticum

Gene Symbol	Chromosomal Locus	Protein Name
ABCC6	16p13.1	Multidrug resistance-associated protein 6

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Pseudoxanthoma Elasticum

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

Table C. Genomic Databases for Pseudoxanthoma Elasticum

Gene Symbol	Entrez Gene	HGMD
ABCC6	3166 (MIM No. 603234)	ABCC6

For a description of the genomic databases listed, click here.

Normal allelic variants: The normal gene is approximately 100 kb in size with 31 exons. *ABCC6(MRP6*) is a member of the ATP-binding cassette superfamily and shows 45% sequence homology with *ABCC1*, encoding a multidrug resistant protein, in the same chromosomal region. The entire sequence of the normal *ABCC6* gene is currently available in GenBank. Normal allelic variants detected to date are missense variants encoded by neutral polymorphic changes in exons at the 3' end.

Pathologic allelic variants: Several recurrent nonsense mutations in unrelated individuals with pseudoxanthoma elasticum (PXE) result in premature stop codons and a few reported missense variants that appear to be disease causing have been reported. Some reports of large deletions involving the *ABCC6* gene appear to result in hemizygosity. At least one example exists of a splice variant that arises through a mutation within the conserved sequence of an intron-exon boundary.

Normal gene product: Multidrug resistance-associated protein 6, the protein encoded by *ABCC6(MRP6*, comprises 1503 amino acids; its physiologic function is unknown [Kool et al 1999]. However, MRP1, the prototypical MRP protein, functions as an efflux pump for amphipathic anionic conjugates.

Abnormal gene product: The role of the abnormal gene product is unknown.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Association for Pseudoxanthoma Elasticum, Inc (NAPE)
8764 Manchester Road Suite 200
St Louis MO 63144-2724
Phone: 314-962-0100
Email: pxenape@napxe.org
www.napxe.org

National Library of Medicine Genetics Home Reference
Pseudoxanthoma elasticum

PXE International
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

Medline Plus
Connective Tissue Disorders

Genetic Alliance BioBank
A centralized biological and data [consent/clinical/environmental] repository to enable translational genomic research on rare genetic diseases.
Phone: 202-966-5557
Email: sterry@geneticalliance.org
www.biobank.org

PXE International Blood and Tissue Registry
PXE Registry

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Author Notes

Sharon Terry, Founding Executive Director of PXE International, manages the 19-lab PXE International Research consortium, 54 offices worldwide, and the PXE International Blood and Tissue Bank. She is co-investigator for studies occuring in all of the labs. She is also

President & CEO of Genetic Alliance, a coalition of 600 disease advocacy organizations representing 1000 diseases.

Lionel Bercovitch, MD, Medical Director of PXE International and Clinical Professor of Dermatology at Brown Medical School, coordinates all of the research that PXE International initiates and oversees the production of educational materials for affected individuals and health professionals.

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- 2 April 2007 (st) Revision: Molecular Genetic Testing - targeted mutation analysis changed to deletion analysis
- 11 December 2006 (me) Comprehensive update posted to live Web site
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