# PXE Guide

# Genetics and Inheritance

## PXE Guide: Genetics and Inheritance

### What Is PXE?

Pseudoxanthoma elasticum (PXE) is an inherited condition that causes abnormal mineralization in some elastic tissues of the body. Mineralization means that tiny deposits of calcium and other minerals build up where they do not usually belong.

PXE most often affects the skin, eyes, and arteries. Less commonly, it may affect the gastrointestinal system. The signs and symptoms of PXE vary widely from person to person, even within the same family.

### What Gene Is Associated With PXE?

The gene associated with PXE is called *ABCC6*.

Everyone has the *ABCC6* gene. People with PXE do not have "the PXE gene." Rather, they have changes in both copies of *ABCC6* that keep the gene from working properly.

Genes are instructions used by the body. Most genes come in pairs: one copy is inherited from the mother and one copy is inherited from the father. A change in a gene is now usually called a variant. Some people also use the older word mutation. In this guide, we use "variant" unless we are explaining older terminology. Variants that cause disease are called pathogenic variants.

Some variants do not cause disease. These are not pathogenic. Others reduce or stop the gene from functioning properly. In PXE, pathogenic variants in *ABCC6* reduce the normal function of *ABCC6*.

### What Does *ABCC6* Do?

*ABCC6* is involved in the body's control of mineralization. It is involved in the production of inorganic pyrophosphate (PPi). PPi is a naturally occurring substance in everyone's blood

that helps prevent unwanted mineralization. In people with PXE, PPi is too low because the gene is not working properly. When PPi is too low, mineralization can occur in elastic tissues, especially in the skin, eyes, and arteries.

This is why PXE is sometimes described as a disorder of ectopic mineralization. “Ectopic” means in the wrong place.

### How Is PXE Inherited?

PXE is inherited in an autosomal recessive pattern.

This means that a person usually has PXE only when both copies of *ABCC6* have disease-causing variants: one inherited from each parent.

A person with one disease-causing *ABCC6* variant and one working copy of *ABCC6* is called a carrier. Carriers do not have PXE. Some research suggests that carriers may occasionally have subclinical findings, meaning some mineralization, but it never impacts the person.

### How does a person end up with two copies of the *ABCC6* gene carrying pathogenic variants?

For a person to have two copies of pathogenic variants in *ABCC6* both parents are carriers. Neither parent has PXE.

When both parents are carriers, each pregnancy has:

- a 25% chance that the child will have PXE
- a 50% chance that the child will be a carrier
- a 25% chance that the child will neither have PXE nor be a carrier

These chances are the same for each pregnancy. They do not “even out” across a family. For example, a family could have more than one child with PXE, or no children with PXE, even when both parents are carriers. Just like a coin can be flipped 10 times and heads can come up 10 times.

## Other Inheritance Situations

If one parent is a carrier and the other parent is not a carrier, each child has a 50% chance of being a carrier and a 50% chance of not being a carrier. The child would not have PXE.

If one parent has PXE and the other parent is a carrier, each child has a 50% chance of having PXE and a 50% chance of being a carrier.

If both parents have PXE, all of their children are expected to inherit two pathogenic *ABCC6* variants and have PXE.

These situations are far less common than the carrier-parent pattern.

## Does Having a Pathogenic *ABCC6* Variant Mean Someone Has PXE?

Not always.

A person with only one pathogenic, disease-causing, *ABCC6* variant is usually a carrier and is not considered to have PXE.

A person with two pathogenic *ABCC6* variants may have PXE, but the diagnosis should still be interpreted in the context of clinical findings. This means without skin and eye findings, the person is not considered to have PXE. This is especially important when genetic testing was done for another reason, and PXE was not suspected.

Sometimes a genetic report shows one disease-causing *ABCC6* variant and one variant of uncertain significance, or VUS.

A VUS means there is not enough evidence to know whether that variant causes disease. A VUS should not be treated as definitely disease-causing unless it is later reclassified. Genetic reports should be reviewed with a geneticist or genetic counselor when possible. PXE International keeps a database of variants and submits them to the international repositories.

## Genetic Diagnosis in Adolescents and Adults

Sometimes PXE is first suspected because a person receives a genetic test report showing two *ABCC6* variants, or one disease-causing *ABCC6* variant and one VUS.

For an adolescent or adult with pathogenic variants in *ABCC6*, the next step is usually to look for physical signs of PXE. This may include:

- a skin biopsy to look for mineralization and changes in the elastic fibers in the mid-dermis; and/or
- a dilated eye exam to look for peau d'orange or angioid streaks.

If an adolescent or adult has no PXE-related skin findings on biopsy and no PXE-related eye findings, they do not have PXE based on a genetic report alone.

## Genetic Findings in Babies and Young Children

In infants and young children, genetic testing may be performed due to developmental delay, congenital illness, or concern for another genetic condition. In this situation, *ABCC6* findings must be interpreted carefully.

Typical PXE does not cause newborn symptoms, developmental delay, or debilitating early-childhood symptoms. A baby's or child's actual symptoms and medical findings are more important than the possibility of later-onset PXE.

However, there is a related condition called generalized arterial calcification of infancy, or GACI. GACI can sometimes be caused by two disease-causing variants in ABCC6. GACI differs from typical PXE and can cause severe arterial mineralization in infancy.

If a newborn or infant has two *ABCC6* disease-causing variants and signs of illness, vascular calcification, heart problems, high blood pressure, or other serious symptoms, the child should be evaluated promptly by specialists familiar with GACI and disorders of ectopic mineralization. PXE International can help you find someone and connect you with the support group for GACI.

## Does My Variant Predict How PXE Will Affect Me?

At this time, knowing a person's *ABCC6* variants usually does not predict how PXE will progress.

In some genetic conditions, the exact variant can help predict symptoms or severity. This is called a genotype–phenotype correlation. In PXE, no reliable genotype–phenotype correlation has been established.

This means that two people with the same *ABCC6* variants may have different symptoms. Even siblings with PXE may be affected differently.

Genetic information may become more important as treatments are developed. If a future treatment works only for certain types of variants, knowing a person's *ABCC6* variants may help determine eligibility for that treatment or clinical trial.

## How Many *ABCC6* Variants Cause PXE?

Hundreds of variants in *ABCC6* have been reported. New variants continue to be identified as more people receive genetic testing.

Some variants are clearly disease-causing. Some are benign. Others are uncertain and may be reported as VUS. Variant interpretation can change over time as more information becomes available.

## Does everyone with PXE have Two Pathogenic Variants in *ABCC6* have PXE?

No. Some people who have skin and eye signs of PXE do not have two pathogenic variants in *ABCC6*. Some have one such variant, some have none. Some have pathogenic variants in another gene. Some we cannot find any genetic anomaly.

## Should Family Members Be Tested?

Family testing depends on the situation.

Siblings of a person with PXE may also have PXE, because both parents are carriers. If a sibling has not been evaluated, they may wish to have an eye exam since this is the easiest non-invasive testing. Even if they have a genetic test, unless the exact variants are known in the affected sibling, genetic testing might not find any variants.

Parents of a person with PXE are carriers. Siblings of the parents and one of the parents of the may also be carriers.

Genetic counseling can help families understand who may be at risk, which tests are useful, and what the results may mean. Often it takes a long time to get a genetics appointment and so PXE International would be happy to talk to you about testing.

## Should My Partner Be Tested Before Having Children?

If a person with PXE or a known *ABCC6* carrier is planning to have children, partner testing may be interesting.

If one partner has PXE and the other partner is not a carrier, their children are expected to be carriers but not to have PXE.

If one partner has PXE and the other partner is a carrier, each child has a 50% chance of having PXE.

If both partners are carriers, each child has a 25% chance of having PXE.

ABCC6 may not be included on every carrier screening panel. If PXE is a specific concern, ask whether ABCC6 is included or whether targeted ABCC6 testing is needed.

## Questions to Ask a Genetic Counselor

You may wish to ask:

- Do I have one or two *ABCC6* variants?
- Are the variants classified as pathogenic, likely pathogenic, variation of unknown significance (VUS), likely benign, or benign?

- Are the variants known to be on opposite copies of the gene, meaning one from each parent?
- Does this result confirm PXE, or do I need skin or eye evaluation?
- Should my siblings or children be tested?
- Should my partner be tested before pregnancy?
- Is *ABCC6* included on the carrier screening panel being offered?
- Could this result suggest GACI or another disorder of mineralization in an infant or young child?
- Could the interpretation of my variant change in the future?

## Key Points

- PXE is usually caused by disease-causing variants in both copies of *ABCC6*.
- Everyone has the *ABCC6* gene; people with PXE have variants that affect its function.
- PXE is usually inherited in an autosomal recessive pattern.
- Carriers usually do not have PXE.
- If both parents are carriers, each pregnancy has a 25% chance of resulting in a child with PXE.
- A VUS is not the same as a disease-causing variant.
- In adults, a genetic report should be interpreted along with skin and eye findings.
- PXE does not cause severe symptoms or developmental delay in newborns.
- GACI is a related but distinct condition that can sometimes be caused by *ABCC6* variants and requires urgent specialist care in infants.
- Knowing one's *ABCC6* variants does not usually predict PXE severity, but it may become important for future treatments or trials.

**Inheritance**
In the examples below, 'a' means there is a change in *ABCC6*, while 'A' means there is no change or mutation. By drawing a small chart, called a Punnett square, we can see all the possible combinations of gene pairs.

**Symbols Used**
A = ABCC6 gene with no change or mutation a = ABCC6 gene with a change or mutation

AA = not a carrier, doesn't have PXE
Aa = carrier
aa = has PXE

**Possible combinations**
Note that these are the odds each and every pregnancy. That means you can have one of these combinations occur more than the odds would suggest. Just like you have 50% odds of getting heads or tails, but you can flip a coin and get heads 10 times in a row.

**Example 1:**
Neither parent has PXE.
Parent 1 is a carrier and is symbolized with Aa
Parent 2 doesn't have PXE and is not a carrier and is symbolized with AA

| | A | a |
|---|---|---|
| A | **AA** | **Aa** |
| A | **AA** | **Aa** |

Each of the four boxes represents the odds for each pregnancy so you can see that this hypothetical couple has a 50% chance that a child will not be a carrier (**AA**) and a 50% chance that a child will be a carrier (**Aa**)

**Example 2:**
Neither parent has PXE.
Parent 1 is a carrier and is symbolized with Aa
Parent 2 is also a carrier and is symbolized with Aa
**This is the most common scenario by far, and likely why someone has PXE.**

| | A | a |
|---|---|---|
| A | **AA** | **Aa** |
| a | **aA** | **aa** |

Each of the four boxes represents the odds for each pregnancy so you can see that this hypothetical couple has a:
25% (one out of four boxes) chance that a child will not have PXE and not be a carrier (**AA**);
50% chance that a child will be a carrier (**Aa**); or
25% chance that a child will be affected by PXE (**aa**).

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**Example 3:**
One parent has PXE.
Parent 1 is a carrier and is symbolized with Aa
Parent 2 has PXE and is symbolized with aa
**This is the reason some families have two generations with PXE, we have never found one with three generations.**

| | A | a |
|---|---|---|
| a | **aA** | **aa** |
| a | **aA** | **aa** |

Each of the four boxes represents the odds for each pregnancy so you can see that this hypothetical couple has a:
50% (two out of four boxes) chance that a child be a carrier (**aA**); and
50% chance that a child will be affected by PXE (**aa**).

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**Example 4:**
Parent 1 has PXE and is symbolized with aa
Parent 2 has PXE and is symbolized with aa
**There is no question here, all of the children will have PXE.**

| | a | a |
|---|---|---|
| a | **aa** | **aa** |
| a | **aa** | **aa** |

Each of the four boxes represents the odds for each pregnancy so you can see that this hypothetical couple has a:
100% (four out of four boxes) chance that a child will be affected by PXE (**aa**).

# PXE International

PXE International provides information, support, and research opportunities for individuals and families affected by pseudoxanthoma elasticum.

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