Genetics

What Is PXE?
Pseudoxanthoma elasticum, (PXE), is an inherited disorder that causes some tissue in the body to become mineralized, that is, calcium and other minerals are deposited in the tissue. This can result in changes in the skin, eyes, cardiovascular system and gastrointestinal system. PXE was recognized over a hundred years ago. A number of significant advances have been made in the past few decades.

What Are the Effects of PXE?
PXE results in a variety of signs and symptoms. The number, type, and severity of signs of PXE are different for each person. Certain effects of PXE can cause serious medical problems while others have less impact. The effects of PXE may include: skin changes, changes in the retina of the eye that may result in significant loss of central vision; changes in the cardiovascular system that may involve calcification of arteries and decreased blood flow in the arms and legs; and/or changes in the gastrointestinal system that may lead to bleeding in the stomach or intestines.

Genetics of PXE
DNA is genetic information. Genes are chunks of DNA that have instructions for your body. These instructions allow your body to carry out its functions. Genes can have changes, which are called variants. For example, a person's eye color, hair color, and whether or not they have freckles are all examples of physical features caused by genetic variation. Some of these variants can turn off the gene, or reduce the gene's function. Sometimes that doesn't matter, and sometimes this can cause problems. This change is called a mutation.

The gene associated with PXE is called ABCC6. Most living plants and animals have the gene called ABCC6. People affected by PXE also have the ABCC6 gene. It is not true that people affected by PXE have the "PXE gene", instead they have a mutation in the gene associated with PXE (ABCC6) that causes the gene to not function properly.

All of our genes come in pairs, so we all have two copies of every gene. Some genes are dominant, meaning that a mutation in just one copy of the gene will cause a sign or a symptom. Some genes are recessive, meaning that both genes must have a mutation in order to cause a sign or symptom.

PXE is a recessive trait, so an individual will only have PXE if they have mutations in both copies of ABCC6. A person is a carrier of PXE if they have a mutation in only one copy of ABCC6.

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How many mutations cause PXE?
Over 300 different variants in ABCC6 that cause PXE have been identified. This is by no means exhaustive, as new variants are being identified and further characterized all the time thanks to advances in scientific technology and by the efforts of dedicated researchers.

Does knowing my mutation help understand how PXE will progress? Will knowing my mutation help get me the right treatment (now and in the future)?
As mentioned before, variants in a gene called ABCC6 cause PXE. This gene regulates the amount of something called pyrophosphate (PPi), a protein in the body. When PPi is low, then tissue can mineralize. PXE mostly affects the skin and eyes. We don't know yet why these specific areas are affected and not others.

In some conditions we can use someone's variant to predict their symptoms. This is called a genotype-phenotype correlation. This link, this correlation, has not been found for people with PXE.

In 2007, scientists at the PXE International Center of Excellence in Research and Clinical Care at Jefferson looked for a link between variants and symptoms in PXE. 270 people affected by PXE had genetic testing to find what variants were present. These patients also filled out a survey about their symptoms. 82 different variants were found at that time, 39 of which had not been found before. None of the variants predicted the symptoms or severity of PXE.

Now that we have more than 300 variants catalogued, we will redo this study and see if we can find any associations between variants and symptoms or how PXE progresses. Stay tuned.

If we find a treatment that works on a specific subset of mutations, then knowing your mutation will be helpful. If we do find such classes of mutations are important, then we will test everyone before we begin to offer treatments.

Inheritance
As previously mentioned, all of our genes come in pairs, so we all have two copies of every gene. One copy is passed down, or inherited, from each parent. In order to have PXE, both parents need to pass down a gene that causes PXE. You can read more about how PXE is passed down from parent to child in the *inheritance bulletin.*

If I am a carrier, should I get genetic testing for my partner before having children?
Most people carry many genes that have a mutation, most of these do not cause you a problem. This usually only becomes an issue if both you and your partner have a mutation in the same gene, as seen below.

Example:
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 an individual 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**).

When this happens, even though neither of you have any symptoms, there is a 1 in 4 chance for each pregnancy that your child will be affected by the condition associated with the gene. The risk of you passing on PXE is much lower than many other conditions since it is so rare to have mutations in ABCC6 to start with. If you or your family are concerned about these recessive conditions, and would like to screen for them, ask your obstetrician to order a carrier screen panel for you and your partner. It will not likely test for PXE since it is so rare, but would test for other genes, all of which are much more common. If you are concerned about PXE, you will have to ask your healthcare provider to order carrier screening specifically for variants in the ABCC6 gene and you will likely pay for yourself, except in certain countries where such screening is routine.