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The Role of Genetic Mutation ABCC6 Gene on the Pseudoxanthoma Elasticum (PXE) Syndrome

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Abstract

Pseudoxanthoma elasticum (PXE) is an inherited disorder caused by mutations in the ABCC6 gene that affects connective tissue in some parts of the body. Elastic tissue in the body becomes mineralized. This means that calcium is deposited in the tissue. This can lead to changes in the skin, eyes, cardiovascular system, and digestive tract. PXE causes a variety of signs and symptoms that vary in number, type, and severity from person to person. Some of the effects of PXE can cause serious medical problems, while others are less severe. Effects may include: skin changes, changes in the retina that may lead to significant loss of central vision, changes in the cardiovascular system that may include calcification of blood vessels and decreased blood flow to the arms and legs, or changes in the digestive system that may lead to bleeding in the stomach or intestines. People with PXE can use a tool called an Amsler grid to monitor their central vision. If there is swelling or bleeding in the center of the retina, it may cause the intersecting lines of the Amsler grid to appear distorted. A retina specialist can teach the patient how to use the Amsler grid. Pseudoxanthoma elasticum (PXE) syndrome is caused by mutations in the ABCC6 gene, located on the short arm of chromosome 16 at 16p13.11. This gene provides instructions for the synthesis of a protein called MRP6 (also known as the ABCC6 protein). This protein is found mainly in liver and kidney cells, and in small amounts in other tissues, including the skin, stomach, blood vessels, and eyes. MRP6 is thought to transport certain substances across cell membranes. However, the substances have not been identified. Some studies suggest that the MRP6 protein stimulates the release of a molecule called adenosine triphosphate (ATP) from cells through an unknown mechanism.

Keywords: Pseudoxanthoma Elasticum (PXE), ABCC6 Gene, Skin Disorder, Genetic Dermatology Disease.

Introduction of Pseudoxanthoma Elasticum (PXE) Syndrome

Pseudoxanthoma elasticum (PXE) is an inherited disorder caused by mutations in the ABCC6 gene that affects connective tissue in some parts of the body. Elastic tissue in the body becomes mineralized. This means that calcium is deposited in the tissue. This can lead to changes in the skin, eyes, cardiovascular system, and digestive tract. Doctors first diagnosed PXE more than 100 years ago. Researchers have made significant progress in the past few years [1].

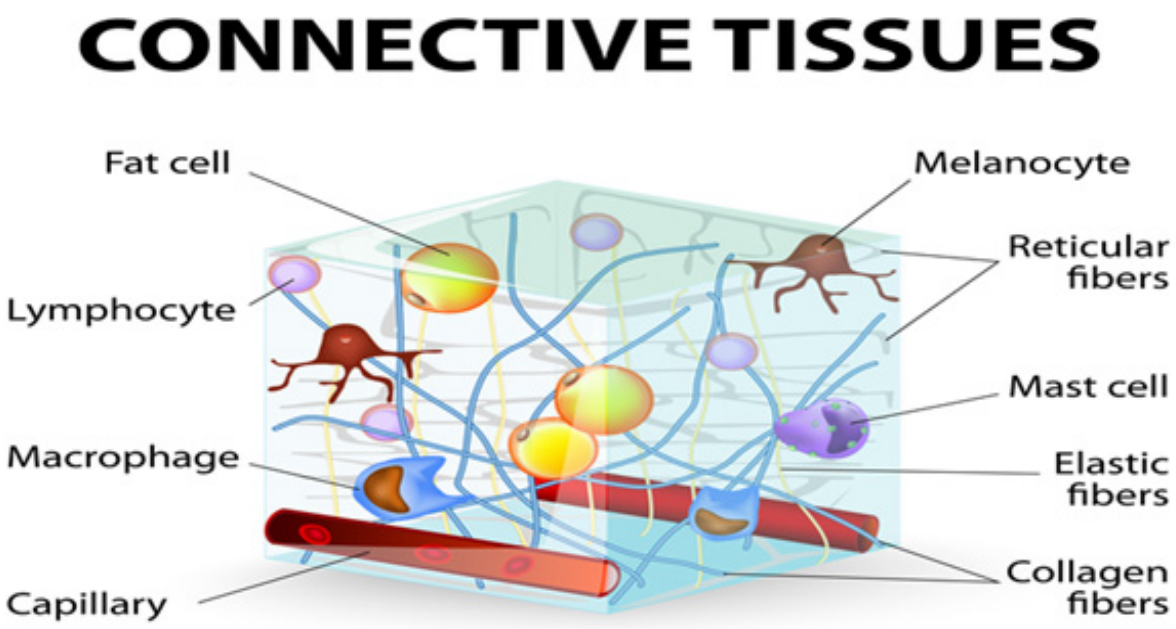

Figure 1: Schematic of the Components of Connective Tissue [1].

Pseudoxanthoma elasticum (PXE) is a progressive disorder characterized by the accumulation of calcium and other mineral deposits (mineralization) in elastic fibers. Elastic fibers are a component of connective tissue that provides strength and flexibility to structures throughout the body [1].

Figure 2: Images of Skin Disorder in PXE Syndrome [1]

In PXE, mineralization can affect elastic fibers in the skin, eyes, and blood vessels, and less commonly in other areas, such as the digestive tract. People with PXE may have yellow bumps called papules on their necks, armpits, and other areas of their skin that are tender when they bend a joint (flexor areas). They may also have eye abnormalities, such as changes in the pigment cells of the retina (the layer of light-sensitive cells at the back of the eye) called pau d'orange. Another eye abnormality known as angioid streaks occurs when tiny gaps develop in the layer of tissue under the retina called Bruch's membrane. Retinal bleeding and scarring may also occur, which can cause vision loss. Mineralization of the blood vessels that carry blood from the heart to other parts of the body (arteries) may cause other signs and symptoms of PXE. For example, people with this disease may develop narrowing of the arteries (atherosclerosis) or a condition called claudication, which is characterized by cramps and pain during exercise due to reduced blood flow to the arms and legs. Rarely, bleeding from blood vessels in the digestive tract may also occur [1].

Figure 3: Another View of the Skin Disorder Associated with PXE Syndrome [1].

PXE causes a variety of signs and symptoms that vary in number, type, and severity from person to person. Some of the effects of PXE can cause serious medical problems, while others are less severe. Effects may include: skin changes, changes in the retina that may lead to significant loss of central vision, changes in the cardiovascular system that may include calcification of blood vessels and decreased blood flow to the arms and legs, or changes in the digestive system that may lead to bleeding in the stomach or intestines. There is currently no way to accurately predict how the disorder will progress for a particular person. Some people do not have skin lesions. Others do not have vision loss. Many people do not experience digestive complications or cardiovascular problems. Some have no symptoms of PXE other than a positive skin biopsy or irregular blood vessel-like streaks (angioids) in the retina. There does not seem to be any discernible pattern to the effects of PXE and how quickly it progresses [1,2].

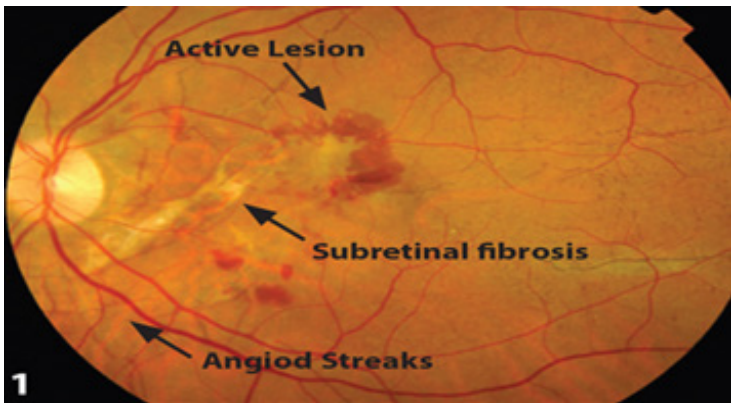

Figure 4: Ophthalmological Image of the Pupil of an Eye with PXE Syndrome [1].

Skin: PXE often causes visible skin changes. These changes vary from person to person. The first changes are usually on the skin on the sides of a person's neck. Small lesions may develop. They may look like a rash or have a "rocky" appearance. These skin lesions tend to progress slowly and unpredictably from the neck down. Skin changes are most often reported in young children. Areas of the body most affected are those that bend a lot. The neck, armpits, the skin inside the elbows, the groin, and the skin behind the knees may be gradually affected, leading to loose folds in these areas. Lesions may appear on the inside of the lower lip or the lining of the rectum or vagina. Some of these effects may be reduced with reconstructive or plastic surgery. You can have PXE and not have any visible skin lesions. In some people, a close examination of the skin by a dermatologist will not reveal any visible signs of lesions, but a positive biopsy indicates a diagnosis of PXE. Given the identification of a mutation in the ABCC6 transporter gene as a cause of PXE, blood analysis can be performed in research centers to confirm the presence or absence of the mutation [1,2].

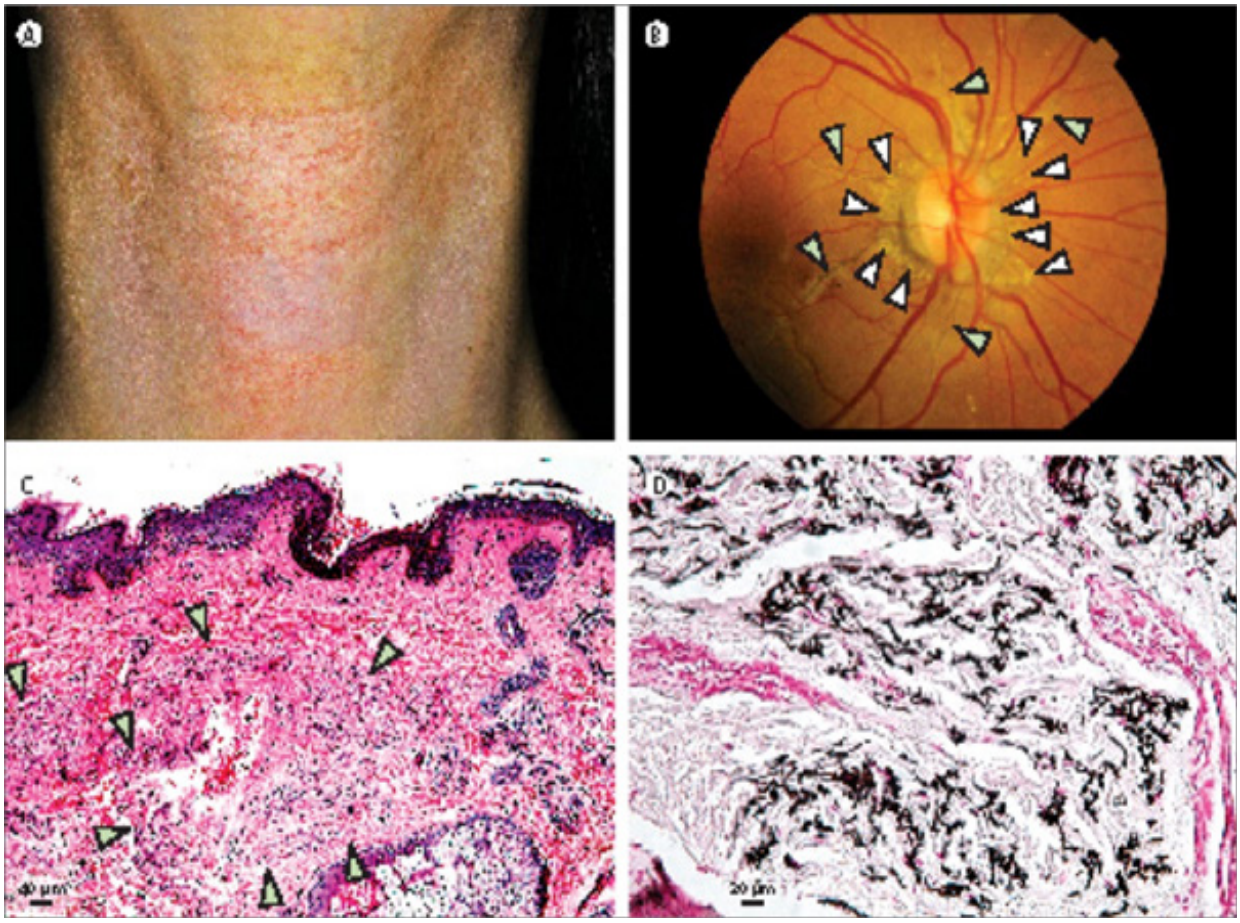

Figure 5: Histopathological Microscopic Images of Skin Tissues Affected by PXE Syndrome [1].

Eyes: PXE affects the retina. The first changes, which can only be seen during an eye exam, are called "peau d'orange" because the retina begins to look like the skin of an orange. The condition does not affect vision, nor do the characteristic irregular streaks called angioid streaks that develop later. These streaks occur when mineralization of the highly elastic membrane behind the retina, called Bruch's membrane, causes it to break. Tiny blood vessels under this layer take advantage of these breaks in the membrane and grow through the membrane. This is called neovascularization. Sometimes, these blood vessels leak and bleed. This bleeding leads to loss of central vision. While people with PXE may lose enough vision to become legally blind, almost all people with PXE still have peripheral vision [1,2].

Figure 6: Image of Skin Tissue Affected by PXE Syndrome [1].

People with PXE can use a tool called an Amsler grid to monitor their central vision. If there is swelling or bleeding in the center of the retina, it may cause the intersecting lines of the Amsler grid to appear distorted. A retina specialist can teach the patient how to use the Amsler grid.1,2

Figure 7: Images of Skin Disorders Associated with PXE Syndrome [1].

Cardiovascular system: Because PXE can cause the blood vessels to mineralize and narrow, people with PXE may experience cramping in their legs when they walk due to reduced blood flow. This reduced blood flow is called intermittent claudication. Reduced blood flow to the arms and legs may mean that a person can no longer feel a pulse in their wrists or feet. Some doctors believe that high blood pressure (hypertension) and mitral valve prolapse may be more common in people with PXE than in the general population. People with PXE should see their doctor periodically to monitor their blood pressure, cholesterol, and pulse in their arms and legs. A heart-healthy lifestyle with a low-fat diet and plenty of exercise is recommended.1,2 Regular exercise may reduce the effects of PXE on blood vessels. Maintaining a normal weight may also be helpful. Smoking should be avoided. Digestive system: Unusually, PXE may cause gastrointestinal bleeding. This is sometimes not immediately recognized and can be life-threatening. Little is known about the gastrointestinal effects of PXE, except that bleeding is usually extensive in the stomach or intestines. In a small number of patients, this bleeding has been mistaken for an ulcer. A person with PXE who experiences any digestive problems should tell their doctor that they have PXE. Some doctors recommend that people with PXE avoid taking nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen, and naproxen [1,2].

Pregnancy: Most women with PXE are thought to have normal pregnancies, and the incidence of pregnancy-related complications is similar to that of the general population. However, some have reported stomach or intestinal complications. Overall, complications affecting the fetus have not been reported. There is no prenatal test to determine whether a fetus has PXE [1,2].

Pseudoxanthoma elasticum (PXE) syndrome is caused by mutations in the ABCC6 gene, located on the short arm of chromosome 16 at 16p13.11. This gene provides instructions for the synthesis of a protein called MRP6 (also known as the ABCC6 protein). This protein is found mainly in liver and kidney cells, and in small amounts in other tissues, including the skin, stomach, blood vessels, and eyes. MRP6 is thought to transport certain substances across cell membranes. However, the substances have not been identified. Some studies suggest that the MRP6 protein stimulates the release of a molecule called adenosine triphosphate (ATP) from cells through an unknown mechanism. ATP can be broken down into other molecules, including adenosine monophosphate (AMP) and pyrophosphate. Pyrophosphate helps control the deposition of calcium and other minerals in the body. Other studies suggest that a substance transported by MRP6 is involved in the breakdown of ATP. This unidentified substance is thought to help prevent tissue mineralization [1,2].

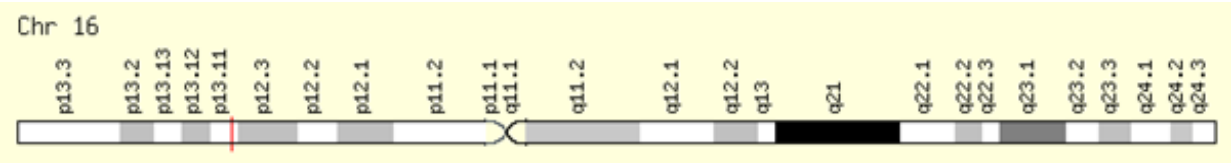

Figure 8: Schematic of the Physical map of Chromosome Number 16, Where the ABCC6 Gene is Located on the Short Arm of this Chromosome as 16p13.11 [1].

Mutations in the ABCC6 gene result in an absent or nonfunctional MRP6 protein. It is not known how the failure of the MRP6 protein to function properly leads to PXE. This deficiency may impair the release of ATP from cells. As a result, little pyrophosphate is produced, and calcium and other minerals accumulate in the elastic fibers of the skin, eyes, blood vessels, and other tis-

sues affected by PXE. Alternatively, the lack of MRP6 function may disrupt the transport of a substance that normally prevents mineralization, leading to the abnormal accumulation of calcium and other minerals characteristic of PXE [1,3].

As mentioned, PXE syndrome is an inherited disorder caused by changes (mutations) in the ABCC6 transporter gene. ABCC6 is one of a group of genes that shuttle certain molecules back and forth across cell membranes. It is not currently known what molecules ABCC6 transmits, but it is thought that they may play a role in keeping elastic fibers in certain tissues of the body healthy [1,3].

PXE is inherited in a recessive pattern. Recessive genetic disorders occur when a person inherits one abnormal gene from each parent. If a person receives one normal gene and one abnormal gene for the disease, the person will be a carrier of the disease, but will usually not show symptoms. The risk of both carrier parents passing on both abnormal genes and having an affected child is 25% with each pregnancy. The risk of having a child who is a carrier like the parents is 50% with each pregnancy. The chance of the child receiving normal genes from both parents is 25%. This risk is the same for men and women [1,3].

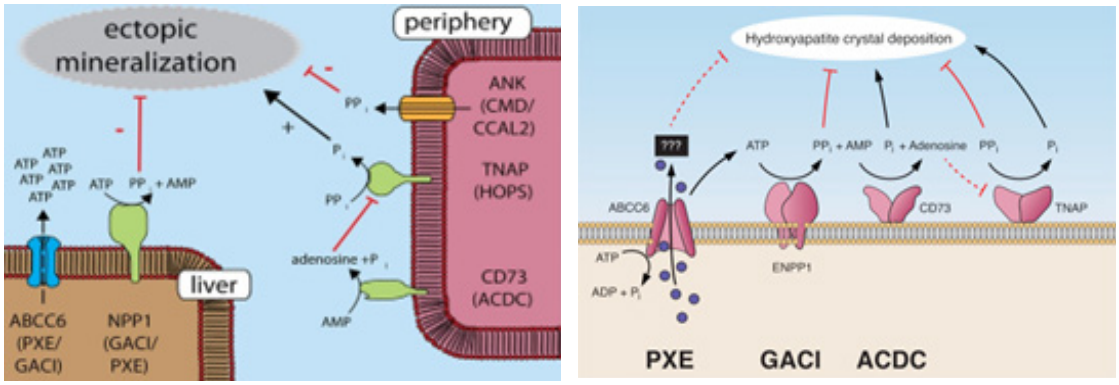

Figure 9: Schematic of the Molecular and Biochemical Mechanism of the ABCC6 Gene in PXE [1].

In some cases, autosomal dominant inheritance has been reported in patients with PXE, but it is not clear whether the dominant pattern is truly dominant or is reported because, by chance, one parent is an asymptomatic carrier of the ABCC6 gene mutation while the other parent has the disorder [1,3].

Dominant genetic disorders occur when only one copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be the result of a mutated (changed) gene in the affected individual. The risk of passing the abnormal gene from an affected parent to a child is 50% for each pregnancy. This risk is the same for men and women [1,4].

Since PXE may be present in other family members but not diagnosed, it is recommended that all close relatives be screened for PXE by an ophthalmologist and dermatologist. The ophthalmologist should look for orange streaks and angioid streaks. If PXE is suspected, a dermatologist should take biopsies from the neck, underarms, and inside of the elbow of a person with suspected PXE. These biopsies may be necessary even if the skin does not show any visible lesions. Even with a negative biopsy, other family members may have PXE. PXE affects each person with great variability. A blood test is available to determine whether a person carries the gene. Estimates of the incidence of PXE vary from 1 in 100,000 to 1 in 25,000. However, the true incidence of PXE in any population is unknown. It is likely that many people with PXE are undiagnosed, especially those with mild PXE symptoms or those whose symptoms are not typical [1,4].

The Symptoms of the Following Disorders may be Similar to Those of Pseudoxanthoma Elasticum (PXE) Syndrome. Comparisons may be Helpful in the Differential Diagnosis:
Ehlers-Danlos syndrome is a rare inherited disorder of connective tissue. It is characterized by the ability of affected individuals to bend their bodies beyond their normal range (joint hypermobility), abnormal skin stretching (increased skin elasticity), and widespread tissue fragility (e.g., skin, blood vessels, and other tissues can tear from even minor trauma). Many forms of Ehlers-Danlos syndrome are inherited as an autosomal dominant genetic trait, but some forms of the disorder are inherited as an autosomal recessive genetic trait or an X-linked recessive genetic trait [1,4].

Marfan syndrome is an inherited disorder that affects the connective tissue of the heart and blood vessels (cardiovascular system). The musculoskeletal system (ligaments and muscles) is also affected. The main symptoms also include abnormal height, large hands and feet, and involvement of the lungs and eyes [1,4].

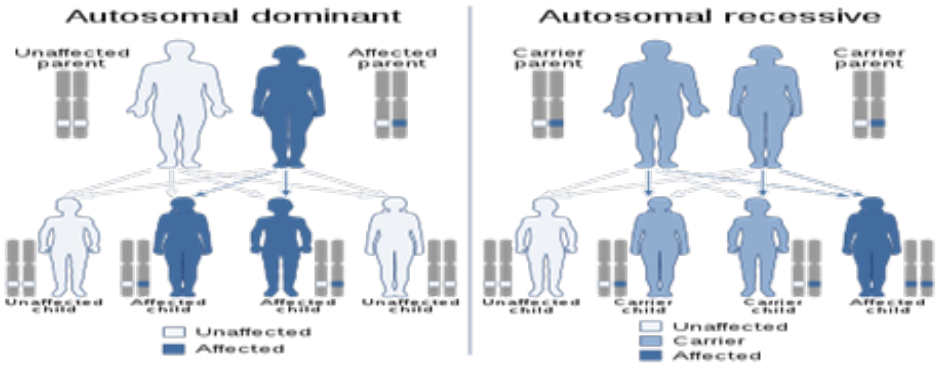

Figure 10: Schematic of the Autosomal Dominant (left) and Autosomal Recessive (right) Inheritance Patterns that PXE Syndrome Follows [1].

Other disorders may be characterized by the development of angioid streaks (e.g., sickle cell disease, hemochromatosis, etc.). There are also other disorders that may have skin changes similar to PXE (e.g., solar elastosis, etc.). These disorders usually have other physical and microscopic features that may distinguish them from PXE [1,4].

Skin changes are usually the first sign of PXE and lead to a definitive diagnosis. Although the symptoms of PXE and the age of onset vary considerably, many people first notice an unusual appearance to their skin, usually on the flanks or back of the neck. Small bumps called lesions may appear. Some people have described these as resembling a rash or an unwashed neck. A small biopsy of the lesion is usually performed to confirm the diagnosis of PXE. This biopsy requires taking a very small piece of skin, about the size of a pencil eraser, from the neck, armpit, or inside of the elbow. The dermatologist sends the sample to a laboratory, where a special stain called von Kossa stain is used to detect calcium in the tissue [1,5].

Sometimes, changes in the eyes are the first noticeable sign of PXE. Early changes in the eyes may only be visible during an eye exam. Later symptoms can include loss of central vision. Some people are first diagnosed with PXE when they notice a distortion in their vision [1,6].

A team of medical specialists (for example, an ophthalmologist, dermatologist, gastroenterologist, and primary care physician) may be needed to help manage PXE and its effects. People affected by PXE should make sure that all healthcare professionals they see are well-informed about the possible consequences of PXE [1,6].

Regular medical checkups by a primary care physician are essential. A careful family history should be taken regarding onset, symptoms that may be related to PXE, and the rest of the family's medical history. The affected person's cholesterol and triglycerides should be checked. Peripheral pulses should also be monitored. A dermatologist is most likely the doctor who will make a definitive diagnosis and make recommendations about reconstructive surgery, if the patient is interested. An ophthalmologist will dilate the eyes to look for orange and angioid streaks. If angioid streaks are found, it may be wise to consult a retina specialist. A cardiologist can perform a baseline EKG and sonogram. In cases involving retinal hemorrhages, laser therapy or injectable medications have been helpful for some people. However, not everyone can benefit from these treatments. In some cases, laser surgery does not restore vision. In others, scarring from bleeding and laser surgery has worsened vision. A variety of visual aids can be provided to help compensate for the loss of vision. It is generally thought that people with PXE should avoid activities that may cause direct damage to the eye. Activities that increase pressure in the eye, such as weightlifting, should also be avoided [1,7].

At this time, genetic research, including studies to identify gene mutations, is underway in several laboratories. Once the mutations are identified, researchers can study the changes caused by PXE and how to correct or compensate for them. Other PXE research includes clinical studies to determine what defines PXE, how it progresses, and what changes it causes in different body systems. In the next few years, it may be possible to tell whether a person has PXE through a blood test. Retina research is advancing rapidly. There are currently many projects investigating angioid streaks, retinal hemorrhages, and what can be used to reduce the bleeding and vision loss that often follows [1,7].

Discussion and Conclusion

Pseudoxanthoma elasticum (PXE) refers to a group of rare inherited disorders that affect the elastic connective tissue of the skin, eyes, and blood vessels. PXE, alternatively called Gronblad-Strandberg syndrome, was first described in 1881 and occurs when abnormal calcification and mineralization of elastic fibres in affected tissues occur. It is characterised by yellow papules and plaques (which may mimic xanthomas), skin laxity, and ocular manifestations that may incur vision loss at later stages. People with PXE can use a tool called an Amsler grid to monitor their central vision. If there is swelling or bleeding in the center of the retina, it may cause the intersecting lines of the Amsler grid to appear distorted. A retina specialist can teach the patient how to use the Amsler grid. Pseudoxanthoma elasticum (PXE) syndrome is caused by mutations in the ABCC6 gene, located on the short arm of chromosome 16 at 16p13.11. This gene provides instructions for the synthesis of a protein called MRP6

(also known as the ABCC6 protein). This protein is found mainly in liver and kidney cells, and in small amounts in other tissues, including the skin, stomach, blood vessels, and eyes. MRP6 is thought to transport certain substances across cell membranes. However, the substances have not been identified. Some studies suggest that the MRP6 protein stimulates the release of a molecule called adenosine triphosphate (ATP) from cells through an unknown mechanism. ATP can be broken down into other molecules, including adenosine monophosphate (AMP) and pyrophosphate. Pyrophosphate helps control the deposition of calcium and other minerals in the body. The most important aspect of treatment is to ensure that complications from blood vessel involvement are prevented or dealt with speedily by the appropriate specialist [1-7].

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