Recognizing
The National
Bone and Joint Decade
2002–2011

Questions & Answers about . . .

Heritable Disorders of Connective Tissue

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
National Institutes of Health
Public Health Service • U.S. Department of Health and Human Services

For Your Information

This publication contains information about medications used to treat the health condition discussed here. When this booklet was printed, we included the most up-to-date (accurate) information available. Occasionally, new information on medication is released.

For updates and for any questions about any medications you are taking, please contact the U.S. Food and Drug Administration at 1–888–INFO–FDA (1–888–463–6332, a toll-free call) or visit their Web site at www.fda.gov.

Additional copies of this booklet are available from:

National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIAMS/National Institutes of Health
1 AMS Circle
Bethesda, MD 20892–3675

You can also find this booklet on the NIAMS Web site at www.niams.nih.gov.

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Information Box

This booklet generally describes a family of more than 200 disorders that affect connective tissues. These disorders result from alterations (mutations) in genes, and thus are called "heritable." All of these diseases are directly related to mutations in genes that are responsible for building tissues. Alterations in these genes may change the structure and development of skin, bones, joints, the heart, blood vessels, lungs, eyes, and ears. Some mutations also change how these tissues work.

Some other connective tissue problems are not directly linked to mutations in tissue-building genes, although some people may be genetically predisposed to becoming affected.

The disorders discussed in this fact sheet are called heritable (genetic) disorders of connective tissue (HDCTs). Many, but not all, of them are rare. (See the box for a description of some of the more common HDCTs.)

Some Common Heritable Disorders of Connective Tissue

Physicians and scientists have identified more than 200 heritable connective tissue disorders. Some of the more common ones are listed below. Some of these are really groups of disorders and may be known by other names.

Ehlers-Danlos syndrome – The problems present in Ehlers-Danlos syndrome (EDS), a group of more than 10 disorders, include changes in the physical properties of skin, joints, blood vessels, and other tissues such as ligaments and tendons. People with EDS have some degree of joint looseness, fragile small blood vessels, and abnormal scar formation and wound healing. Soft, velvety skin stretches excessively but returns to normal after being pulled. Some forms of EDS can present problems with the spine, including a curved spine, and the eyes. EDS can also lead to weak internal organs, including the uterus, intestines, and large blood vessels. Mutations in several different genes are responsible for varying symptoms in the several types of EDS. In most cases, the genetic defect involves collagen, the major protein-building material of bone.

Epidermolysis bullosa – The characteristic feature of epidermolysis bullosa (EB) is blistering of the skin. Some forms of the disease may involve the gastrointestinal tract, the pulmonary system, the muscles, or the bladder. Most forms are evident at birth. This disorder

can be both disabling and disfiguring, and some forms may lead to early death. Blisters result when skin layers separate after minor trauma. Defects of several proteins within the skin are at fault.

Marfan syndrome – People with Marfan syndrome tend to have excessively long bones and are commonly thin, with long, "spider-like" fingers. Other problems include skeletal malformations; abnormal position of the lens of the eye; and enlargement at the beginning part of the aorta, the major vessel carrying blood away from the heart. If left untreated, an enlarged aorta can lead to hemorrhage and even death. This disorder results from mutations in the gene that determines the structure of fibrillin-1, a protein important to connective tissue.

Osteogenesis imperfecta – People with osteogenesis imperfecta (OI) have bones that fracture easily, low muscle mass, and joint and ligament laxity. There are six major types of OI, ranging in severity from mild to lethal. The appearance of people with OI varies considerably. Individuals may have a blue or gray tint to the sclera (whites of the eyes), thin skin, growth deficiencies, and fragile teeth. They may develop scoliosis, respiratory problems, and hearing loss. Also known as "brittle bone disease," this disorder arises from mutations in the two genes that make type I collagen, a protein important to bones and skin. These mutations cause the body to make either too little or poor-quality type I collagen.

What Is Connective Tissue and What Does Heritable Disorders Mean?

Connective tissue is the material between the cells of the body that gives tissues form and strength. This "cellular glue" is also involved in delivering nutrients to the tissue, and in the special functioning of certain tissues. Connective tissue is made up of dozens of proteins, including collagens, proteoglycans, and glycoproteins. The combination of these proteins can vary between tissues.

The genes that encode these proteins can harbor defects or mutations, which can affect the functioning of certain properties of connective tissue in selected tissues. When this occurs, the result can be a heritable disorder – one that can be inherited, or passed from parent to child – of connective tissue.

How Do People Get Gene Alterations?

People with heritable disorders of connective tissue inherit an altered gene either from one or from both parents. We have two copies of most genes: one inherited from each parent. Males have one copy of each gene on the X chromosome, because they have only one X chromosome; and one copy of each gene on the Y chromosome. In contrast, females have two copies of X chromosome genes because they have two X chromosomes.

Some genetic disorders require that only a single copy of a gene be altered. These disorders can be seen in many generations of a family because the altered copy of the gene is passed from parent to child (dominant inheritance). The same disorder can occur in an individual without a family history of the condition if there is a new mutation in the right gene at conception. Some disorders are seen only when the individual has received an altered copy of the gene from each parent (recessive inheritance); in these families, the person with only a single copy is called a "carrier" and is not actually affected.

If a mutation occurs on an X chromosome, it generally produces a condition in which the pattern of affected individuals in a family is unusual. Often, women are carriers (that is, they have only a single altered copy of the gene), but males show the condition because they do not have a second protective copy of the gene. Such a condition is referred to as "X-linked."

Who Gets HDCTs?

By one estimate, more than a half million people in the United States are affected by the more than 200 heritable disorders of connective tissue. Generally, these conditions affect people of all ethnic groups and ages, and both sexes are affected. Many of these disorders are rare. Some may not be evident at birth, but only appear after a certain age or after exposure to a particular environmental stress.

Does Anything Increase the Chances of Having a Genetic Disease?

Several factors increase the likelihood that a person will inherit an alteration in a gene. If you are concerned about your risk, you should talk to your health care provider or a genetic counselor.

The following factors may increase the chance of getting or passing on a genetic disease:

- parents who have a genetic disease
- a family history of a genetic disease
- parents who are closely related or part of a distinct ethnic or geographic community
- parents who do not show disease symptoms, but "carry" a disease gene in their genetic makeup (this can be discovered through genetic testing).

How Does Genetic Counseling Help?

People seek genetic counseling to make better decisions about their lives and families. Because genetic counselors understand how genetic disorders are passed on through families, they can help couples estimate the risks of having children with genetic diseases. They can also tell parents about tests to determine if they are carrying certain altered

genes, tests for newborns who may have inherited certain altered genes, and tests that can be done in early pregnancy to determine if a fetus either carries an altered copy of a gene or is affected with a disorder. The information derived from all these studies can facilitate family planning.

Your health care team can help you find genetic counseling if you wish to better understand your or your child's disease or risk of disease.

What Are the Symptoms of a HDCT?

Each disorder has different symptoms. Some diseases cause bone growth problems. People with bone growth disorders may have brittle bones or bones that are too long or too short. Some disorders cause people to be unusually tall (Marfan syndrome) or short (chondrodysplasias, osteogenesis imperfecta), or to have head and facial structure malformations (Apert syndrome, Pfeiffer syndrome). In some of these disorders, joint looseness or joints that are too tight can cause problems.

The skin can be affected as well. Ehlers-Danlos syndrome results in stretchy or loose skin, while in another connective tissue disorder, cutis laxa, deficient elastic fibers cause the skin to hang in folds. Epidermolysis bullosa results in blistered skin. Pseudoxanthoma elasticum causes skin, eye, and heart problems, and closed-off or blocked blood vessels. Marfan syndrome and some forms of Ehlers-Danlos syndrome lead to weak blood vessels.

It is critical for affected individuals and their family members to work closely with their health care teams. Symptoms of HDCTs are extremely variable, and some disorders can pose severe health risks even when affected individuals have no symptoms.

How Do Doctors Diagnose HDCTs?

Diagnosis always rests first on a combination of family history, medical history, and physical examination. Because many of these conditions are uncommon, the family physician may suspect a diagnosis but be uncertain about how to confirm it. At this point, referral to experienced clinicians, often medical geneticists, can be extremely valuable to either confirm or exclude the suspected diagnosis. Laboratory tests are available to confirm the diagnosis for many HDCTs, but not for all. Once a diagnosis is made, laboratory studies may be available to provide some or all of the following:

- prenatal testing to identify an affected fetus and assist in family planning
- newborn screening to spot a condition that may become evident later in life
- carrier testing to identify adults who, without symptoms, carry a genetic mutation for a disease
- predictive testing to spot people at risk for developing a genetic connective tissue disease later in life. These tests are helpful for diseases that run in the family.

What Treatments Are Available?

The term heritable disorders of connective tissue refers to a wide range of disorders, each requiring a specific program for management and treatment. In most instances, regular monitoring is important to assess, for example, the diameter of the aorta in people with Marfan syndrome, the extent of scoliosis (spine curvature) in people with OI and those with some forms of EDS, and whether there is protrusion of the spine into the base of the skull in people with OI. For some conditions, specific metabolic treatment is useful (for example, vitamin B6 in people with homocystinuria, a metabolic disorder resulting from a liver enzyme deficiency). In others, systemic treatment with drugs like beta blockers is appropriate. Maintaining general health is also important for people with all HDCTs.

What Research Is Being Done on HDCTs?

Scientists are working to better understand these disorders at several levels: (1) to identify the genes in which the mutations reside, (2) to identify the mutations that result in the clinical condition, (3) to understand how these mutations result in the condition, and (4) to use all available information about the condition to plan new therapies and test their use and value, both in animal models and in affected individuals. Because most of these conditions are uncommon, and individuals with them are widely scattered, it is often difficult to gather information about the clinical course of the disorder and assemble enough people to plan effective clinical trials.

The **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**, a part of the Department of Health and Human Services' National Institutes of Health (NIH), is the lead Federal agency for connective tissue research. Several other NIH institutes are also studying HDCTs. NIAMS supports research through grants to scientists around the country, in national and international clinical trials, and at the NIH campus. This is some of the research underway:

- NIAMS is conducting an in-depth natural history study of people who have Marfan syndrome (which leads to abnormally long bones), nail-patella syndrome (a congenital skeletal disorder), Stickler syndrome (which causes eye and joint problems), and Ehlers-Danlos syndrome (which causes skin and blood vessel problems). All of these disorders have multiple, interrelated symptoms. NIAMS scientists are closely observing the people in this study over a long period to get a more complete picture of the diseases. They hope to improve their understanding of the genetic origins of the symptoms, of disease progression, and of mutations in patients and their relatives. Scientists expect their findings to apply to other HDCTs as well.

  Specific areas of research and findings arising from this long-term study include:

  – examining the efficacy of screening for dural ectasia (an enlargement of the membrane that sur-

rounds the spinal cord) in the diagnosis of Marfan syndrome

- analyzing the prevalence of spinal and hip abnormalities in Stickler syndrome, and their relationship to chronic pain
- documenting an increased risk of failure of the femoral head (the ball portion at the top of the thigh bone) in children with Stickler syndrome
- developing proposed diagnostic criteria for Stickler syndrome based on clinical and molecular studies in this population
- identifying a connective tissue disorder with features resembling Marfan syndrome, Stickler syndrome, and Ehlers-Danlos syndrome
- studying the mechanism of chronic musculoskeletal pain in people with HDCTs and exploring ways, including mindfulness-based stress reduction, to ameliorate it
- looking at some specific musculoskeletal complications of aging in patients with HDCTs, such as the prevalence and severity of osteoporosis and osteoarthritis
- using molecular genetic studies to identify both new genes contributing to Stickler syndrome and Ehlers-Danlos syndrome, and mutations in previously recognized genes.

- NIAMS is examining gene defects that lead to abnormal elastin, the connective tissue protein that allows arteries, muscles, and other organs to respond in certain ways to movement. So far, the investigators have shown how elastin gene mutations cause two specific diseases: a skin disease (cutis laxa) and a blood vessel disease (supravalvular aortic stenosis). Scientists hope to learn more about how mutations affect elastin fiber and tissue growth. They also hope to find out how gene defects lead to the development of elastin disease.

- NIAMS is supporting a study looking for ways to treat diseases such as osteogenesis imperfecta by using gene therapy. Stem cells, which have the potential to develop into more specialized cells, would replace bone cells that have gene defects. This research is being conducted on specially bred mice.

- NIAMS is encouraging the establishment of new research registries for connective tissue disorders and other conditions. Through these registries, demographic and medical data from patients and families could be collected and used in research on disorders. Epidermolysis bullosa is one of the disorders for which the Institute has already established a research registry.

- Other NIAMS-supported research pertains to:
  - the chemistry and biology of elastin genes
  - collagen gene defects (several types) that cause bone diseases

  - collagen IV gene defects in mice and humans (Alport syndrome)
  - proteoglycans, a group of proteins that maintain tissue stiffness
  - fibroblasts, cells that form the fibrous tissues in the body
  - cartilage, joints, and skin layers.

- Ongoing studies of aneurysms (weak spots in blood vessel walls that threaten to burst) are taking place at several NIH Institutes. Aneurysms can prove deadly to people with Marfan syndrome and other HDCTs. NIAMS has supported these studies by pioneering development of a breed of mice prone to aneurysms. Scientists hope the mutant mice will improve understanding of aneurysms and ways to prevent them.

- The **National Heart, Lung, and Blood Institute** supported the14th Gordon Research Conference on Elastin and Elastic Fibers, which brought together basic scientists and clinicians to exchange data on the makeup of and problems associated with these critical components of connective tissue. The conference produced new insights and stimulated interdisciplinary discussions that could potentially help those living with the more than 200 connective tissue diseases.

- Studies have shown that the blood pressure medication losartan prevents aortic aneurysms in a mouse model of Marfan syndrome. New studies receiving

funding from the **National Heart, Lung, and Blood Institute** are now underway to determine whether the drug has the same beneficial effect in people.

- At the **National Institute of Child Health and Human Development**, scientists are working with young patients who have osteogenesis imperfecta. They hope to learn more about the genetics of the disease and the natural history of the many secondary features involved, as well as rehabilitation techniques. Animal models and human clinical trials are also evaluating the use of bisphosphonates to treat this condition. Bisphosphonates are a group of drugs now used widely to treat osteoporosis.

- The **National Human Genome Research Institute** is conducting a clinical study of mind-body therapy for chronic pain in people with Ehlers-Danlos syndrome.

- The **National Eye Institute** is supporting research on alterations in the gene that causes pseudoxanthoma elasticum (PXE). Researchers are also studying how differences in the alterations cause varying symptoms for people with this condition.

- Scientists at the **National Institute of Dental and Craniofacial Research** are carrying out clinical studies on fibrous dysplasia of bone.

Where Can People Find More Information About HDCTs?

People with HDCTs can contact professional and support groups that can supply more detailed information than is found here. Most of them also have Internet Web sites. Some major groups are listed below.

- **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**
  National Institutes of Health
  1 AMS Circle
  Bethesda, MD 20892-3675
  Phone: 301–495–4484 or
  877–22–NIAMS (226–4267) (free of charge)
  TTY: 301–565–2966
  Fax: 301–718–6366
  E-mail: niamsinfo@mail.nih.gov
  www.niams.nih.gov

- **American Academy of Orthopaedic Surgeons**
  P.O. Box 2058
  Des Plaines, IL 60017
  Phone: 847–823–7186 or
  800–824–BONE (2663) (free of charge)
  Fax: 847–823–8125
  www.aaos.org

- **Coalition for Heritable Disorders of Connective Tissue**
  4301 Connecticut Ave, N.W., Suite 404
  Washington, DC 20008–2369
  Phone: 202–362–9599
  Fax: 202–966–8553
  E-mail: chdct@pxe.org
  www.chdct.org

- **Genetic Alliance**
  4301 Connecticut Avenue, N.W., Suite 404
  Washington, DC 20008–2369
  Phone: 202–966–5557 or
  800–336–GENE (4363) (free of charge)
  Fax: 202–966–8553
  E-mail: info@geneticalliance.org
  www.geneticalliance.org

- **National Organization for Rare Disorders, Inc.**
  55 Kenosia Ave.
  P.O. Box 1968
  Danbury, CT 06813–1968
  Phone: 203–744–0100 or
  800–999–6673 (free of charge, voicemail only)
  Fax: 203–798–2291
  E-mail: orphan@rarediseases.org
  www.rarediseases.org

- **National Society of Genetic Counselors, Inc.**
  401 N. Michigan Avenue
  Chicago, IL 60611
  Phone: 312–321–6834
  Fax: 312–673–6972
  E-mail: nsgc@nsgc.org
  www.nsgc.org

- **Dystrophic Epidermolysis Bullosa Research Association (DebRA) of America**
  5 West 36th Street, Suite 404
  New York, NY 10018
  Phone: 212–868–1573 or
  (866) DEBRA76 (332–7276) (free of charge)
  Fax: 212–868–9296
  E-mail: staff@debra.org
  www.debra.org

- **Ehlers-Danlos National Foundation**
  3200 Wilshire Boulevard, Suite 1601, South Tower
  Los Angeles, CA 90010
  Phone: 213–368–3800
  Fax: 213–427–0057
  E-mail: staff@ednf.org
  www.ednf.org

- **National Association for Pseudoxanthoma Elasticum**
  8760 Manchester Road, Suite 200
  St. Louis, MO 63144–2724
  Phone: 314–962–0100
  Fax: 314–962–0100
  E-mail: NAPEStLouis@sbcglobal.net
  www.pxenape.org

- **National Marfan Foundation**
  22 Manhasset Avenue
  Port Washington, NY 11050–2023
  Phone: 516–883–8712 or
  800–8–MARFAN (862–7326) (free of charge)
  Fax: 516–883–8040
  E-mail: staff@marfan.org
  www.marfan.org

- **Osteogenesis Imperfecta Foundation**
  804 West Diamond Avenue, Suite 210
  Gaithersburg, MD 20878–1414
  Phone: 301–947–0083 or
  800–981–2663 (free of charge)
  Fax: 301–947–0456
  E-mail: bonelink@oif.org
  www.oif.org

- **PXE International**
  4301 Connecticut Avenue NW, Suite 404
  Washington, DC 20008–2369
  Phone: 202–362–9599
  Fax: 202–966–8553
  E-mail: info@pxe.org
  www.pxe.org

Key Words

Apert syndrome – One of a group of genetic disorders, called acrocephalosyndactyly, characterized by malformations of the skull, face, hands, and feet. Apert syndrome is an autosomonal dominant trait due to a mutation in a gene called FGFR2 (fibroblast growth factor receptor 2).

Beta blockers – A class of medications also known as beta-andrenergic blockers that affect the body's response to certain nerve impulses. This, in turn, decreases the rate and force of the heart's contractions, which lowers blood pressure and reduces the heart's demand for oxygen. In addition to treating high blood pressure, beta blockers may be used for angina, and to prevent heart attacks, migraine headaches, and glaucoma.

Carrier – A person who carries a gene for a recessive genetic disorder. The person has the potential to pass the disorder on to his or her child, but is not personally affected by the disorder.

Collagen – The principal protein of the skin, bones, cartilage, tendons, and other connective tissues.

Chondrodysplasias – Once referred to as dwarfism. A group of genetic disorders, often caused by a single gene variation that affects the structure or metabolism of the bone, cartilage, or connective tissue.

Cutis laxa – Latin for loose or lax skin, cutis laxa refers to an extremely rare connective tissue disorder in which the skin lacks elasticity and hangs in loose folds. Caused by underlying genetic defects in connective tissue structure, the disorder can

also result in serious problems with vocal cords, bones, cartilage, blood vessels, and vital internal organs.

Dominant – A genetic trait (or genetically transmitted disorder) that is evident when only one copy of the gene for that trait is present. Most dominant traits are due to genes on the autosomes (nonsex chromosomes). They affect males and females equally.

Dural ectasia – An enlargement of the dura, a primary membrane of connective tissue that covers the spine and contains the spinal fluid. Common in people with Marfan syndrome, dural ectasia occurs mainly in the lower spine and can cause low back pain, abdominal pain, headaches, leg pain, and perineal pain and numbness.

Ehlers-Danlos syndrome – A heritable connective tissue disease characterized by easy bruising, joint laxity (the ability to bend beyond normal range of motion), lax skin, and tissue weakness.

Epidermolysis bullosa – A potentially disabling, disfiguring, and sometimes lethal connective tissue disorder caused by defects of several proteins in the skin, resulting in skin blistering. Some forms of the disease may involve the gastrointestinal tract, the pulmonary system, muscles, or the bladder.

Glycoprotein – An organic compound composed of a protein and a carbohydrate joined together. In the body, these compounds have many uses and comprise many of the proteins released by cells into the blood and other fluids.

Heritable – Capable of being transmitted from parent to child through genes.

Homocystinuria – A genetically transmitted disease in which an enzyme deficiency permits the buildup of the amino acid homocyteine. The result, if not treated, can be mental retardation, blood vessel disease, and atherosclerosis (hardening of the arteries).

Mutations – Changes in genes that can occur randomly or as a result of some factor in the environment.

Marfan syndrome – A heritable disorder of connective tissue resulting from mutations in the gene that specifies the genetic code for fibrillin-1, a protein important to connective tissue. The disorder is characterized by excessively long leg bones and long "spider-like" fingers. Other problems include skeletal malformations, abnormal position of the lens of the eye, and enlargement at the beginning part of the aorta, the major vessel carrying blood away from the heart. If left untreated, an enlarged aorta can lead to hemorrhage and even death.

Nail-patella syndrome (NPS) – A rare genetic disorder that causes abnormalities of bones, joints, fingernails, and kidneys. NPS is commonly characterized by absent or underdeveloped kneecaps and thumbnails. It is estimated to occur in one in 50,000 newborns.

Osteogenesis imperfecta – A condition that results from mutation in two genes that make type I collagen, a protein important to bones and teeth. These mutations cause the body to either make too little collagen or poor-quality collagen. The result includes bones that fracture easily, low muscle mass, and joints and ligaments that move beyond their intended range of motion.

Pfeiffer syndrome – Also called type V acrocephalosyndactyly, Pfeiffer syndrome is one of a group of genetic disorders characterized by malformations of the skull, face, hands, and feet. Like the more common Apert syndrome, Pfeiffer syndrome is caused by a mutation in the FGFR2 (fibroblast growth factor receptor 2) gene.

Proteoglycans – A class of glycoproteins that perform various functions and serve as the "filler" substance between the cells. An inability to break down proteoglycans is characteristic of a series of genetic disorders called mucopolysaccharidoses.

Pseudoxanthoma elasticum (PXE) – A rare disorder of degeneration of the elastic fibers with tiny areas of calcification in the skin, the back of the eyes (retinae), and the blood vessels. PXE typically causes skin abnormalities, eye abnormalities that can lead to blindness, atherosclerosis (hardening of the arteries), mitral valve prolapse, and fragile blood vessels that can lead to problems with circulation and abnormal bleeding into internal organs, including the bowel. PXE is inherited either as an autosomal recessive or as an autosomal dominant trait.

Recessive – A genetic trait or disorder that is usually expressed when only two copies of a gene for that trait, one from each parent, are present.

Scoliosis – A lateral side-to-side curvature of the spine. In most cases the cause is not known, but it may be more common in people who have a family history of the condition. Treatment can include braces, physical therapy, and, in some cases, surgery.

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