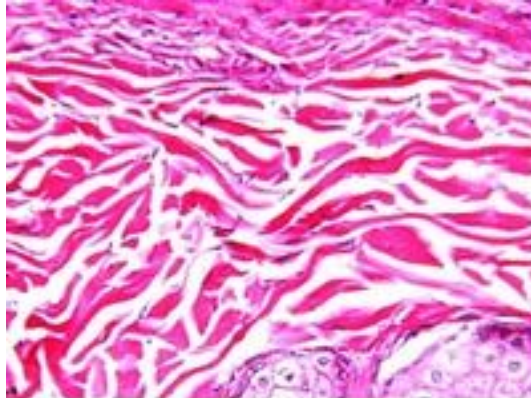


Skin and Connective Tissue



The dermis, shown above, is a layer of cells - mostly fibroblasts - that lies below the epidermis. Together these two layers make up the skin. The dermis is responsible for thermoregulation and the supply of nutrients to the epidermis. The fibroblasts secrete substances such as collagen and elastin, which supports and confers elasticity to the skin. The dermis is the tough connective tissue from which leather is made. (Reproduced from the website of David Hawkins, Ph.D, Exercise Biology Program, UC Davis, with permission.)

The skin is the largest organ in the body — both in weight and in surface area — and separates the body's internal environment from the external environment. The skin has many diverse roles. It acts as a channel of communication with the outside world; protects the body from water loss; uses specialized pigment cells, called melanocytes, to protect the body from ultraviolet radiation; participates in calcium homeostasis by contributing to the body's supply of vitamin D; and helps regulate body temperature and metabolism.

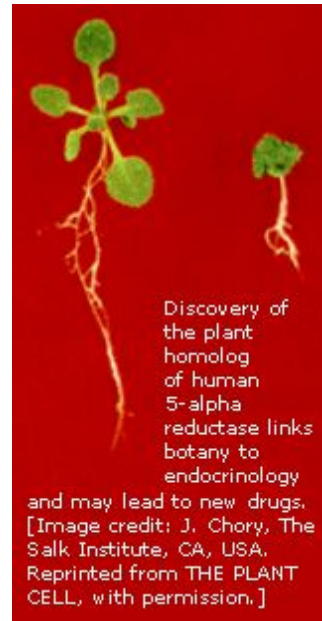
Elastic tissues such as the skin require a strong and resilient structural framework. This framework is called the extracellular matrix, or connective tissue. The orientation of the connective tissues — adipose (fat cells), cartilage, bone, tendons, and ligaments — found beneath the skin are also key for tissue appearance and function. All connective tissue is composed of three major classes of biomolecules: structural proteins (collagen and elastin), specialized proteins (fibrillin, fibronectin, and laminin), and proteoglycans.

Some skin and connective tissue diseases, such as those discussed in this section of genes and disease, are due strictly to genetic inheritance, while others do not have specific gene abnormalities as their sole cause. Many features of skin and connective tissue disorders overlap with each other, and with other disorders, even though they have unique genetic causes.

Male pattern baldness

5-alpha reductase is an enzyme that was first discovered in the male prostate. Here it catalyzes the conversion of testosterone to dihydrotestosterone, which in turn binds to the androgen receptor and initiates development of the external genitalia and prostate. The gene for 5-alpha reductase has been mapped to chromosome 5.

More recently, 5-alpha reductase was found in human scalp and elsewhere in the skin, where it carries out the same reaction as in the prostate. It is thought that disturbances in 5-alpha reductase activity in skin cells might contribute to male pattern baldness, acne, or hirsutism. The discovery of a plant homolog of human 5-alpha reductase may lead to new drugs, and the race is now on to find inhibitors of 5-alpha reductase.



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Diastrophic dysplasia

Diastrophic dysplasia (DTD) is a rare growth disorder in which patients are usually short, have club feet, and have malformed hands and joints. Although found in all populations, it is particularly prevalent in Finland.

The gene whose mutation results in DTD maps to chromosome 5 and encodes a novel sulfate transporter. This ties in with the observation of unusual concentrations of sulfate in various tissues of DTD patients. Sulfate is important for skeletal joints because cartilage—the shock-absorber of joints—requires sulfur during its manufacture. Adding sulfur increases the negative charge within cartilage, which contributes to its shock-absorbing properties.

A great deal of further research must be done before this condition is fully understood and effective therapies are developed.



Radiograph of the hand of a patient with diastrophic dysplasia.
[Image credit: Eric Lander, Whitehead Institute, MIT, USA.]

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Ellis-van Creveld syndrome

Ellis-van Creveld syndrome, also known as "chondroectodermal dysplasia," is a rare genetic disorder characterized by short-limb dwarfism, polydactyly (additional fingers or toes), malformation of the bones of the wrist, dystrophy of the fingernails, partial hare-lip, cardiac malformation, and often prenatal eruption of the teeth.

The gene causing Ellis-van Creveld syndrome, EVC, has been mapped to the short arm of chromosome 4. As yet, the function of a healthy EVC gene is not known; this is one of the most important questions that must be answered about the disease, since it would give an indication as to the molecular mechanism of the disease.

Ellis-van Creveld syndrome is often seen among the Old Order Amish community in Lancaster County, Pennsylvania. Because this group of people is small and isolated, it affords a rare opportunity to observe the passage of this particular disorder from

generation to generation. A pattern of inheritance can be observed that has indicated the disease is autosomal-recessive (i.e. a mutated gene from both parents is required before the effects of the disease to become apparent).



Ellis-van Creveld syndrome. The search for a molecular basis for the disease is on-going. Image credit: Clement D. Erhardt, Jr., Baltimore, MD, USA.

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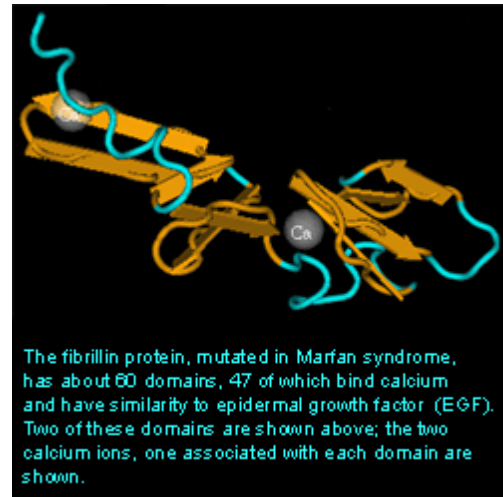
Marfan syndrome

Marfan syndrome is a connective tissue disorder, so affects many structures, including the skeleton, lungs, eyes, heart and blood vessels. The disease is characterized by unusually long limbs, and is believed to have affected Abraham Lincoln.

Marfan syndrome is an autosomal dominant disorder that has been linked to the *FBN1* gene on chromosome 15. *FBN1* encodes a protein called fibrillin, which is essential for the formation of elastic fibres found in connective tissue. Without the structural support provided by fibrillin, many tissues are weakened, which can have severe consequences, for example, ruptures in the walls of major arteries.

Beta blockers have been used to control some of the cardiovascular symptoms of Marfan syndrome; however, they are not effective against the skeletal and ocular problems, which can also be serious. A related disease has been found in mice, and it is hoped that the study of mouse fibrillin synthesis and secretion, and connective tissue formation, will further our understanding Marfan syndrome in humans.

To see the interactive version of this figure requires Cn3D [www.ncbi.nlm.nih.gov/Structure/CN3D/cn3d.shtml], a three-dimensional structure viewer.



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National Marfan Foundation [www.marfan.org/] nonprofit organization

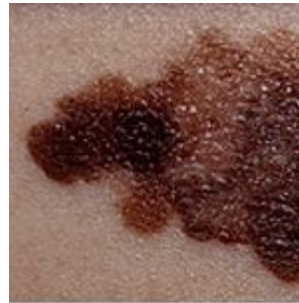
Malignant melanoma

In 1997, it was expected that about 40,300 Americans would be diagnosed with malignant melanoma, the most aggressive kind of skin cancer. Melanomas are more common in people with lightly pigmented skin, and people who have had melanoma once have a high risk of developing new melanomas.

In some cases, the risk of developing melanoma runs in families, where a mutation in the *CDKN2* gene on chromosome 9 can underlie susceptibility to melanoma. *CDKN2* codes for a protein called p16 that is an important regulator of the cell division cycle; it stops the cell from synthesizing DNA before it divides. If p16 is not working properly, the skin cell does not have this brake on the cell division cycle and so can go on to proliferate unchecked. At some point this proliferation can be seen as a sudden change in skin growth or the appearance of a mole.

The most powerful weapons against melanoma are therefore 1) prevention, by using protective clothing and sun screen and 2) early detection, by recog-

nizing changes in skin growths or the appearance of new growths. Insight may also be drawn for other cancer types by studying the molecular biology of p16, since the malfunction of other components of the p16 pathway have also been implicated in other cancers.



Malignant melanoma is associated with mutation of a tumor suppressor gene involved in cell cycle control. [Image credit: National Cancer Institute, NIH, Bethesda, MD, USA .]

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CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

American Cancer Society [www.cancer.org] research and patient support

MEDLINE *plus* [www.nlm.nih.gov/medlineplus/melanoma.html] links on melanoma compiled by the National Library of Medicine

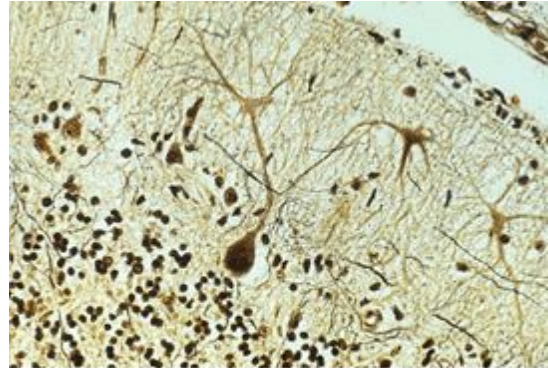
Menkes syndrome

Menkes syndrome is an inborn error of metabolism that markedly decreases the cells' ability to absorb copper. The disorder causes severe cerebral degeneration and arterial changes, resulting in death in infancy. The disease can often be diagnosed by looking at a victim's hair, which appears to be both whitish and kinked when viewed under a microscope.

Menkes' disease is transmitted as an X-linked recessive trait. Sufferers can not transport copper, which is needed by enzymes involved in making bone, nerve and other structures. A number of other diseases, including type IX Ehlers-Danlos syndrome, may be the result of allelic mutations (i.e. mutations in the same gene, but having slightly different symptoms) and it is hoped that research into these diseases may prove useful in fighting Menkes' disease.

If administered within the first few months of life, copper histidinate appears to be effective in increasing the life expectancy of some patients. However,

this treatment only increases life expectancy from three to thirteen years of age, so can only be considered a palliative. A similar condition to Menkes' disease exists in mice; working with these model organisms will help give insight into human copper transport mechanisms, so helping to develop effective treatments for Menkes' sufferers.



Abnormal Purkinje cell dendrites in the brain of a patient with Menkes disease. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

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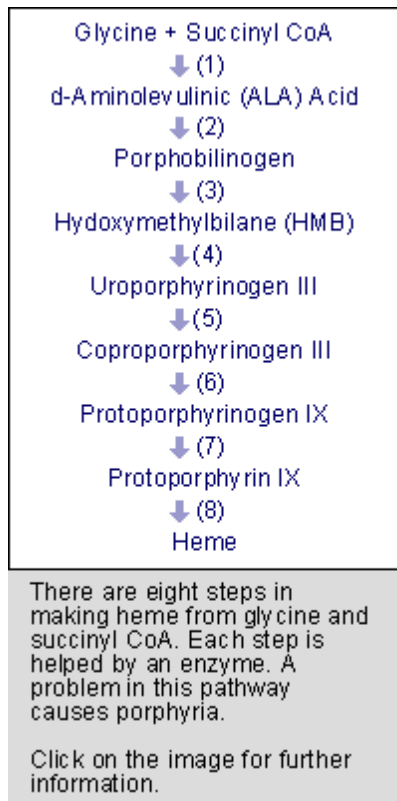
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Porphyria



Porphyria is a diverse group of diseases in which production of heme is disrupted. Porphyria is derived from the Greek word "porphyra", which means purple. When heme production is faulty, porphyrins are overproduced and lend a reddish-purple color to urine.

Heme is composed of porphyrin, a large circular molecule made from four rings linked together with an iron atom at its center. Heme is the oxygen-binding part of hemoglobin, giving red blood cells their color. It is also a component of several vital enzymes in the liver including the group known as

cytochrome P450. This enzyme family is important in converting potentially harmful substances such as drugs to inactive products destined for excretion.

Heme synthesis takes place in several steps, each of which requires a specific enzyme of which there are 8 in total. The genes that encode these enzymes are located on different chromosomes, and mutations of these genes can be inherited in either an autosomal dominant or autosomal recessive fashion, depending on the gene concerned. Affected individuals are unable to complete heme synthesis, and intermediate products, porphyrin or its precursors, accumulate.

Environmental triggers are important in many attacks of porphyria. Example triggers include certain medications, fasting, or hormonal changes. Genetic carriers who avoid a triggering exposure may never experience symptoms.

The cutaneous porphyrias cause sun sensitivity, with blistering typically on the face, back of the hands, and other sun-exposed areas. The most common of these is porphyria cutanea tarda (PCT). Triggering factors are alcohol use, estrogen, iron, and liver disease, particularly hepatitis C.

The acute porphyrias typically cause abdominal pain and nausea. Some patients have personality changes and seizures at the outset. With time the illness can involve weakness in many different muscles.

The cutaneous and acute forms are treated differently. Cure of these genetic diseases awaits the results of ongoing research on the safest and most effective means of gene transfer or correction.

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Fact sheet [<http://digestive.niddk.nih.gov/ddiseases/pubs/porphyria/>]from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH

MedlinePlus [<http://www.nlm.nih.gov/medlineplus/ency/article/001208.htm>]a medical encyclopedia from the National Library of Medicine, NIH

Step in Pathway	Enzyme	Disease caused by enzyme deficiency
1	ALA synthase	
2	ALA dehydratase	ALAD porphyria
3	HMB synthase	Acute intermittent porphyria
4	Uroporphyrinogen synthase (UROS)	Congenital erythropoietic porphyria
5	Uroporphyrinogen decarboxylase (UROD)	Porphyria cutanea tarda
6	Coproporphyrinogen oxidase	Hereditary coproporphyrin
7	Protoporphyrinogen oxidase	Variegate porphyria
8	Ferrochelatase	Erythropoietic protoporphyria