ELASTIN METABOLISM

What is Elastin?

There is only one tropoelastin gene (ELN) in humans.

Elastin has been shown to have a half-life of about 74 years and is the longest lasting protein in the body.

One of the most amazing facts about elastin is that it is not made after we reach the age of 12 or 13.

Composition

Elastin is made by linking many soluble tropoelastin protein molecules, in a reaction catalyzed by lysyl oxidase, to make a massive insoluble, durable cross-linked array.

The tropoelastin is subjected to oxidation by lysyl oxidase enzymes at a subset of lysines which subsequently participate in aldol condensation and Schiff base reactions to form cross-links.

Lysyl oxidase is an extracellular copper enzyme that catalyzes formation of aldehydes from lysine residues in elastin precursors.

Cutis laxa?

This disease is characterized by loose, sagging skin; an increased risk of an abnormal bulging (an aneurysm) in a large blood vessel called the aorta; and a lung disease called emphysema, which can make it difficult to breathe.

What genes are related to cutis laxa?

Cutis laxa can be caused by mutations in the ATP6V0A2, ATP7A, EFEMP2, ELN, or FBLN5 gene. Most of these genes are involved in the formation and function of elastic fibers.

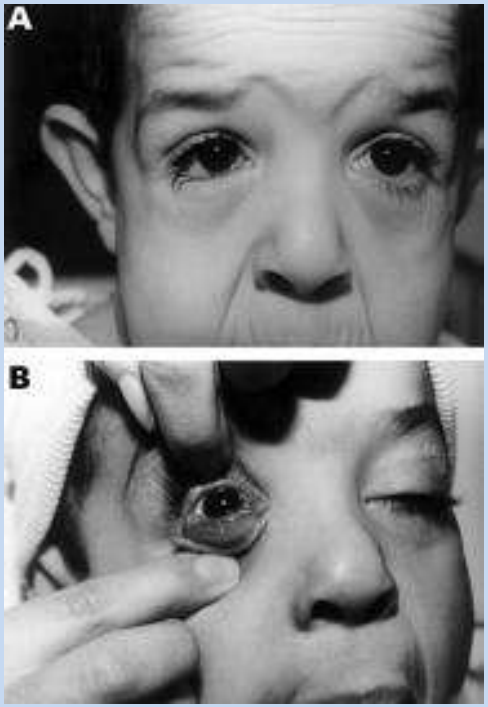
ATP7A gene provides instructions for making a protein that is important for regulating copper levels in the body.

The causes of acquired cutis laxa are unclear, although it may occur as a side effect of treatment with medications that remove copper from the body (copper chelating drugs).

cutis laxa forms are often distinguished by their pattern of inheritance: autosomal dominant, autosomal recessive, or X-linked.

In general, the autosomal recessive forms of cutis laxa tend to be more severe than the autosomal dominant form.

The X-linked form of cutis laxa is often called occipital horn syndrome. This form of the disorder is considered a mild type of Menkes syndrome, which is a condition that affects copper levels in the body.



Supravalvular aortic stenosis (SVAS)

caused by mutations in the *ELN* gene. At least 60 mutations in the *ELN* gene have been found to cause supravalvular aortic stenosis (SVAS),

It is a heart defect present from birth that is characterized by a narrowing of the large blood vessel that carries blood from the heart to the rest of the body (the aorta).

Over time, the wall of the aorta can become damaged. Aortic narrowing causes the heart to work harder to pump blood through the aorta, which can lead to shortness of breath, chest pain, and ultimately heart failure.

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Williams syndrome

Is associated with the *ELN* gene. The *ELN* gene is located in a region of chromosome 7 that is deleted in people with Williams syndrome.

This loss reduces the production of elastin by half, which disrupts the normal structure of elastic fibers in many connective tissues.

***CLIP2*, *ELN*, *GTF2I*, *GTF2IRD1*, and *LIMK1* are among the genes that are typically deleted in people with Williams syndrome.**

Researchers have found that loss of the *ELN* gene is associated with the connective tissue abnormalities and cardiovascular disease found in many people with this disease.

Williams syndrome is considered as an autosomal dominant condition because one copy of the altered chromosome 7 in each cell is sufficient to cause the disorder.

Marfan syndrome

Is a genetic disorder of the connective tissue. People with Marfan tend to be unusually tall, with long limbs and long, thin fingers.

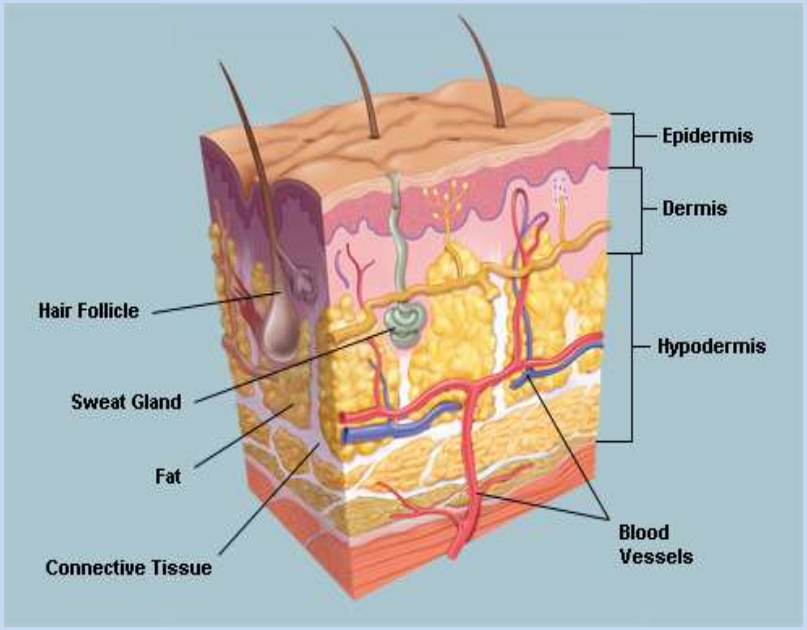
The syndrome is inherited as a dominant trait, carried by the gene *FBN1*, which encodes the connective protein fibrillin-1 (Fibrillin-1 protein is essential for the proper formation of the extracellular matrix, including the biogenesis and maintenance of elastic fibers).

Marfan syndrome has a range of expressions, from mild to severe.

The most serious complications are defects of the heart valves and aorta. It may also affect the lungs, the eyes, the skeleton and the hard palate.

Human skin

The human skin is the outer covering of the body. In humans, it is the largest organ of the integumentary system.



Pigments

There are at least five different pigments that determine the colour of the skin.

1-Melanin: It is brown in colour.

2-Melanoid: It resembles melanin but is present diffusely throughout the epidermis.

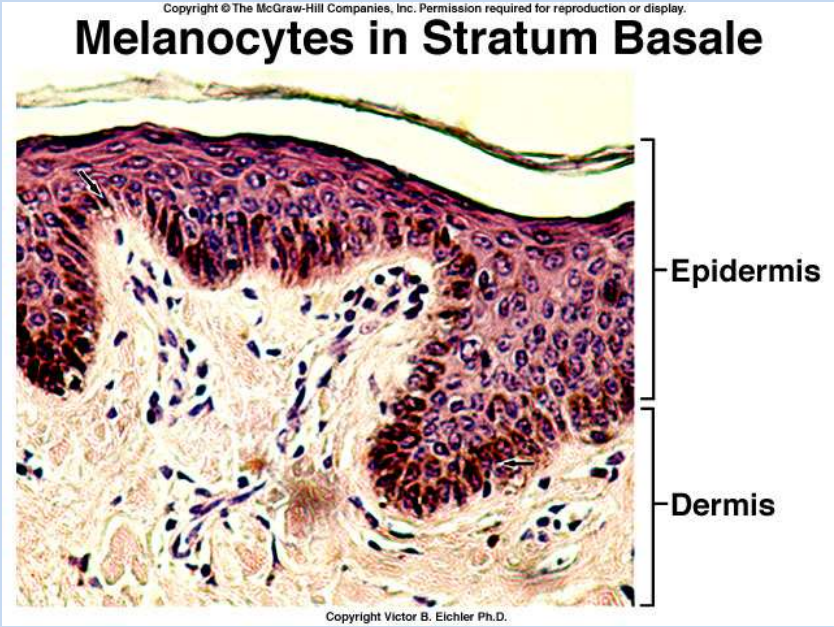
3-Keratin: This pigment is yellow to orange in colour.

4-Hemoglobin: It is found in blood and is not a pigment of the skin but develops a purple color.

5-Oxyhemoglobin: It is also found in blood and is not a pigment of the skin. It develops a red color.

Melanin

Melanin is a natural pigment found in most organisms. In animals melanin pigments are derivatives of the amino acid tyrosine.



Melanin is brown, non-refractile, and finely granular with individual granules having a diameter of less than 800 nanometers.

The most common biological melanin is **eumelanin:** This is a brown-black polymer of dihydroxyindole carboxylic acids and their reduced forms.

Another common form of melanin is **pheomelanin:** a cysteine-containing red-brown polymer of benzothiazine units largely responsible for red hair and freckl.

Melanin synthesis

Special cells known as melanocytes produce melanin in the outer layer of the skin.

The greater expression of the gene creates an increase in the synthesis of melanin.

Precursor

L-tyrosine is a precursor of melanin. This means that certain biochemical pathways convert L-tyrosine into melanin through the use of numerous "intermediate molecules" that are systematically modified into the end product.

Upon exposure to UV radiation, DNA damage triggers cytokines, growth factors and other inflammatory factors to stimulate melanin production.

Melanocytes, by increasing the production of intracellular nitric oxide (NO), they trigger signal transduction cascades to initiate melanogenesis through a series of oxidative reactions involving the amino acid tyrosine in the presence of the enzyme tyrosinase.

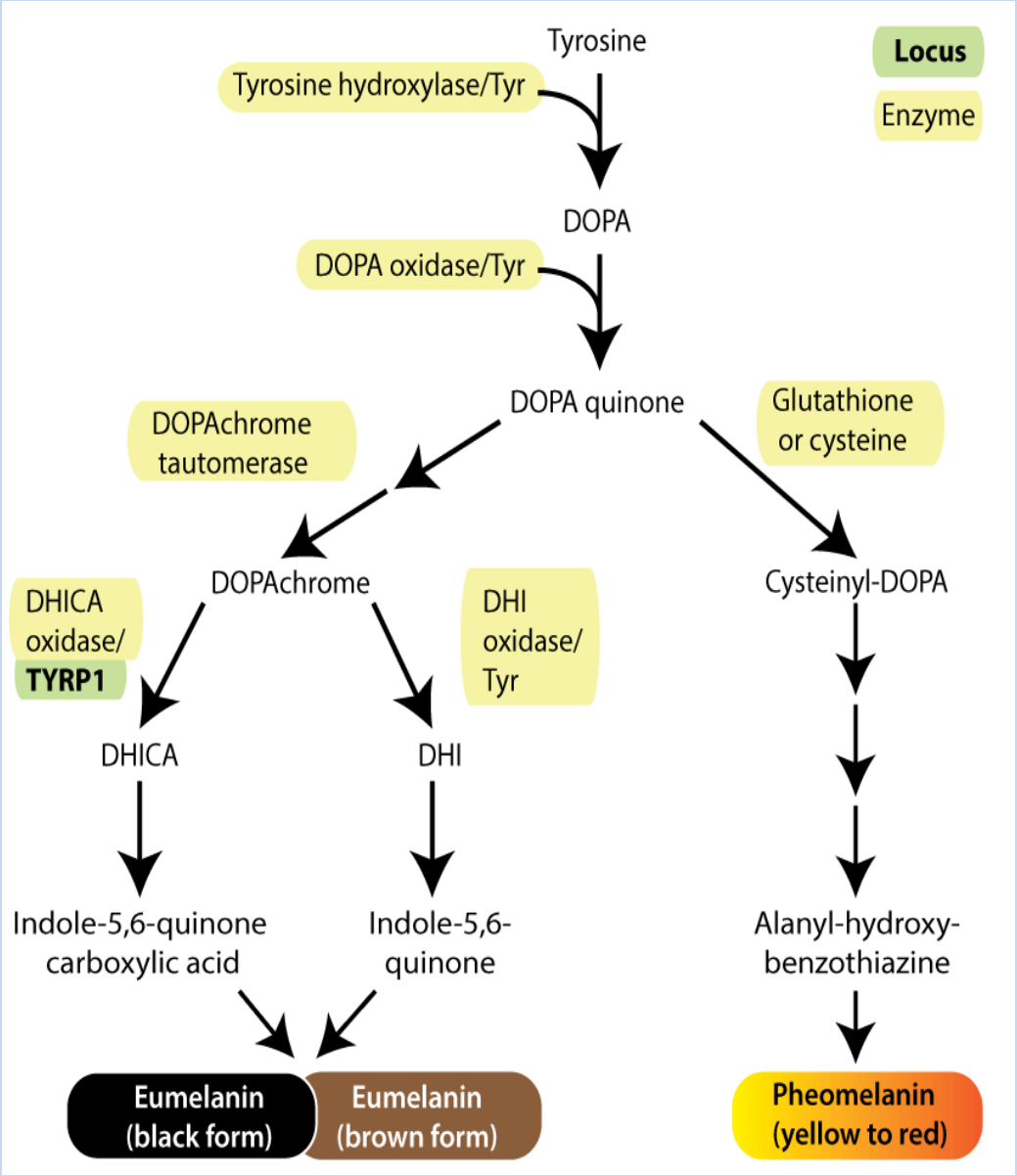
The process of melanin synthesis

Melanin synthesis begins in the liver where phenylalanine is converted to tyrosine by the action of phenylalanine hydroxylase.

The oxidation of L-Tyrosine to L-DOPA is then catalysed by the action of tyrosine hydroxylase enzyme.

In the next step L-DOPA is oxidized to DOPAquinone by DOPA oxidase enzyme

From DOPAquinone, the melanin synthesis pathways diverge to produce either eumelanin or pheomelanin.

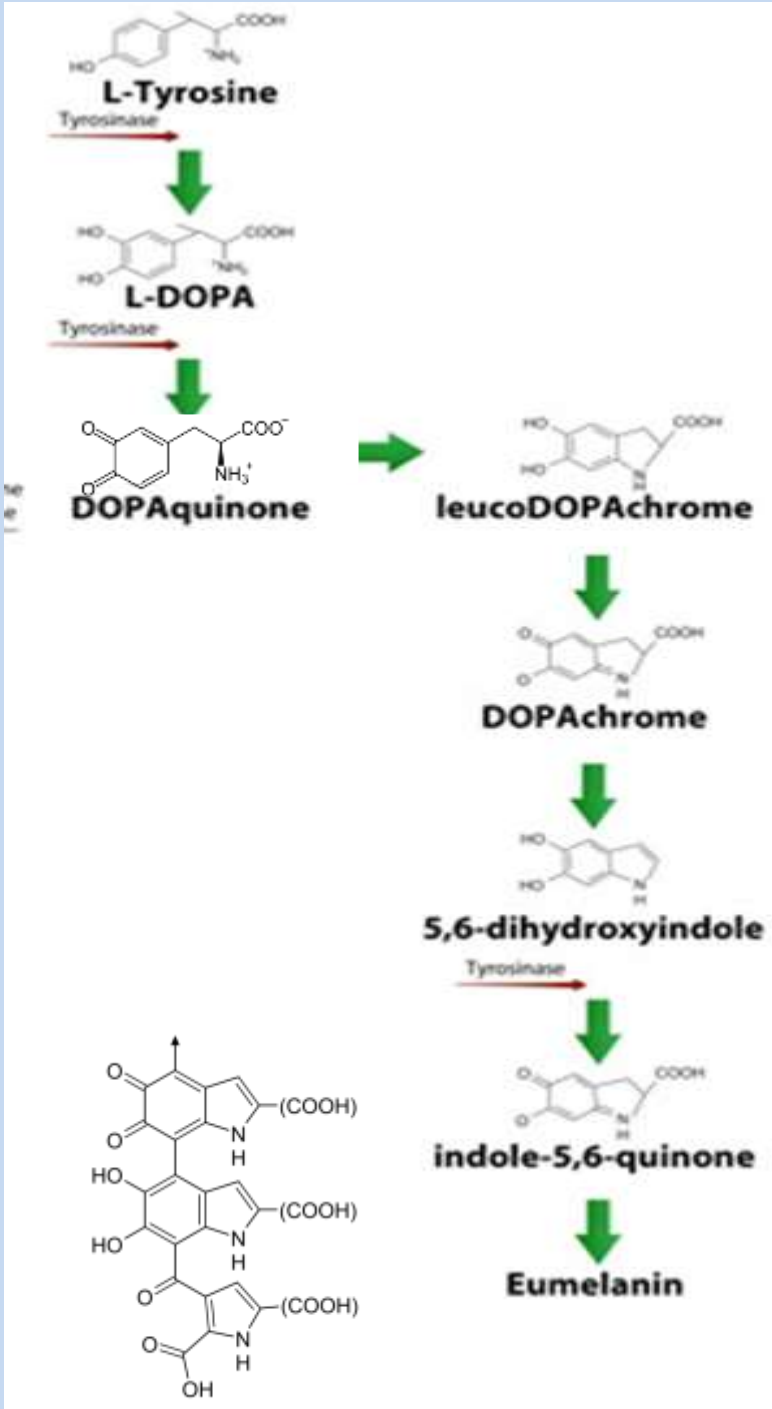


Eumelanin

Firstly, DOPAquinone is converted to leucoDOPAchrome and then DOPAchrome through auto-oxidation,

and subsequently in the presence of DOPAchrome tautomerase and dihydroxyindole-2-carboxylic acid oxidase, DOPAchrome is converted to 5,6-dihydroxyindole.

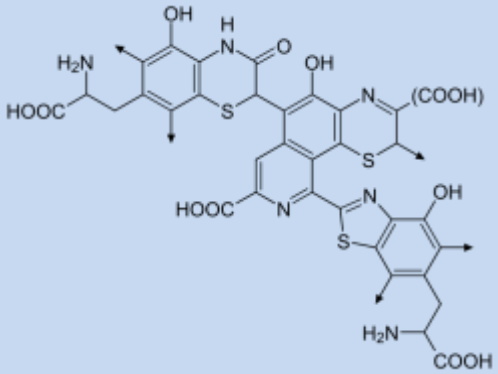
Finally, the oxidation of 5,6-dihydroxyindole (DHI) to indole-5,6-quinone by tyrosinase leads to the formation of eumelanin (brown-black pigment).

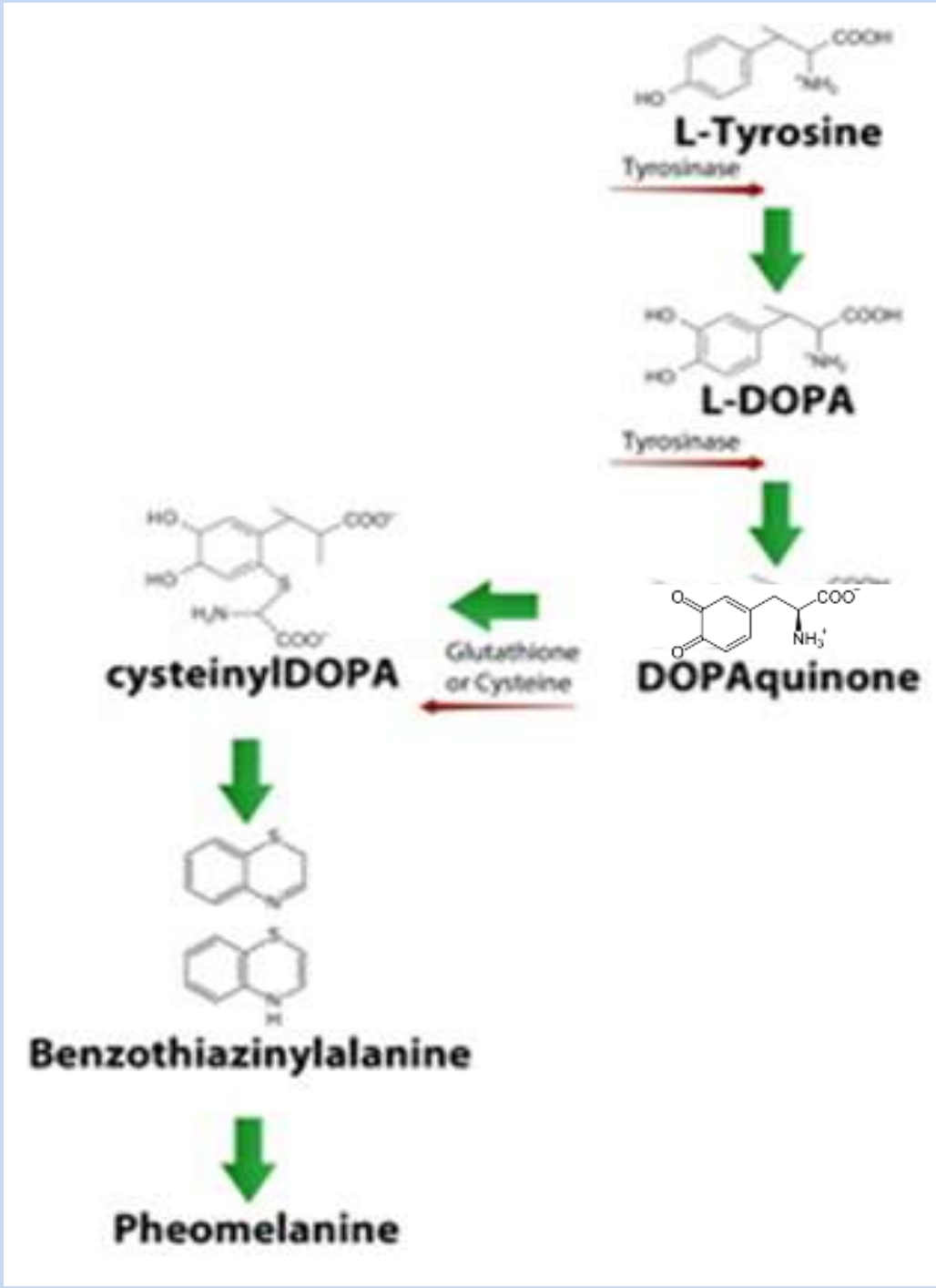


Pheomelanin

In the presence of cysteine or glutathione, DOPAquinone is converted to cysteinyl DOPA

Subsequently, pheomelanin, a yellow-red pigment, is formed through the oxidative polymerization of cysteinylDOPA via 1,4-benzothiazinylalanine intermediates.





Melanin and UV

Ultraviolet (UV) light is a form of radiation that acts as a mutagen, an agent that causes mutations in DNA. Exposure to ultraviolet light causes chemical changes that alter the shape of your DNA, and the process that corrects DNA's shape can also cause changes to the DNA code.

Distortion

The bases in the double strand of DNA always pair up with the same partners on the opposite strand: a thymine with an adenosine, and a cytosine with a guanine (Cytosine and thymine are called pyrimidine bases)

Exposure to UV light can cause two pyrimidine bases sitting next to each other on the same strand to bind to each other, instead of binding to their partner on the opposite strand. That chemical glitch is called a pyrimidine dimer, and it produces a bulge in DNA wherever it occurs.

Mutations

Your cells cannot read past or copy the bulges in DNA.

A cellular process called excision repair will fix the bulge so that the DNA can make proteins and copy itself.

One base of the pyrimidine dimer is snipped out of the strand, and a new base is substituted in.

The replacement base, however, is inserted randomly, and there is only a 1 in 4 chance that it is the same as the base that was removed.

The excision repair process introduces DNA mutations, and every mutation increases your risk for developing skin cancer.

The lighter someone's natural skin color, the less melanin it has to absorb UV rays and protect itself. The darker a person's natural skin color, the more melanin it has to protect itself.

Photoprotection

"The term Photoprotection designates the mechanisms that nature has developed to minimize the damages that the human body suffers when exposed to UV-irradiation.

Photoprotection of the human skin is achieved by extremely efficient internal conversion of DNA, proteins and melanin. Internal conversion is a photochemical process that converts the energy of the UV-photon into small amounts of heat.

This small amount of heat is harmless. If the energy of the UV-photon were not transformed into heat, then it would lead to the generation of free radicals or other harmful reactive chemical species (e.g. singlet oxygen, or hydroxyl radical).“

VITAMIN D AND MELANIN

There is a relationship between the amount of melanin in your skin and vitamin D levels. Your body can synthesize vitamin D when your skin is exposed to direct sunlight.

Because melanin blocks the effects of sunlight, increased levels of melanin can impair your ability to make new vitamin D.

As a result, people with dark skin often have lower levels of vitamin D than lighter-skinned people.

Albinism

Albinism is a group of genetic conditions that causes a lack of pigment. It can effect only the eyes or both the eyes and skin. Most types of albinism are inherited when an individual receives the albinism gene from both parents.

Description

- Due to the defect in tyrosine metabolism it results in a deficiency of melanin production and partial or full absence of pigment from the skin, hair, and eyes
- It may be inherited by one of several modes: autosomal recessive, autosomal dominant.
- Affected people may appear to have white hair, skin & iris color. They may have vision defects and photophobia.
- Oculocutaneous albinism is most severe form resulting from a deficiency of tyrosinase activity, causing a total absence of pigment from the hair, eyes & skin

Causes

- Albinism is caused by an alteration of the gene that regulates the melanin pigment synthesis.

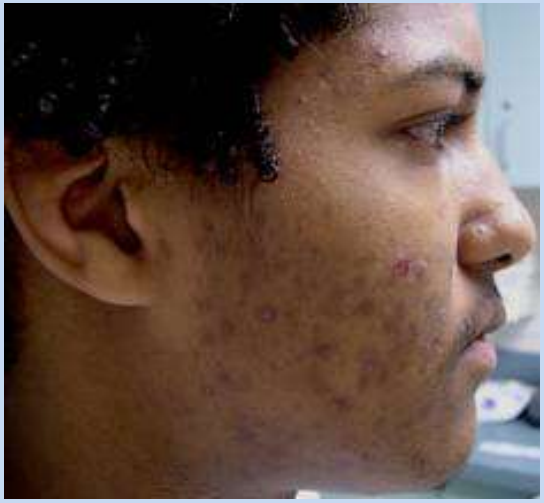
Symptoms

- Absence of pigment from the hair, skin, or iris of eyes
- Lighter than normal skin and hair or complete albinism
- Most forms of complete albinism have some of the following possible symptoms:
  - Rapid eye movements
  - Strabismus (eyes not tracking properly)
  - Photophobia (avoidance of light because of discomfort)
  - Decreased visual acuity
  - Functional blindness

Complications

- Skin cancer
- Decreased vision, blindness

hyperpigmentation



hyperpigmentation is the darkening of an area of skin or nails caused by increased melanin.

Hyperpigmentation is a common, usually harmless condition in which patches of skin become darker in color than the normal surrounding skin.

Causes

Hyperpigmentation may be caused by sun damage, inflammation, or other skin injuries, including those related to acne vulgaris.

Many forms of hyperpigmentation are caused by an excess production of melanin.

As the body ages, melanocyte distribution becomes less diffuse and its regulation less controlled by the body. UV light stimulates melanocyte activity, and where concentrations of the cells are denser than surrounding areas, hyperpigmentation is effected.