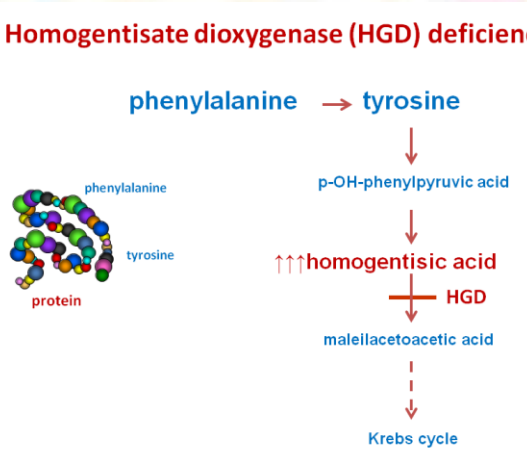
ALKAPTONURIA

WHAT IS ALKAPTONURIA?

Alkaptonuria (AKU) is an **inborn error of metabolism: a genetic disease** caused by a lack of the enzyme **homogentisate dioxygenase** (HGD). Without HGD, patients cannot break down protein to amino acids, such as tyrosine and phenylalanine, which causes a build up of **homogentisic acid** (HGA) in the bones, cartilage and urine. Alkaptonuria is characterized by the presence of black urine, ochronosis (black bones and cartilage) and a degenerative arthritis of the joints.



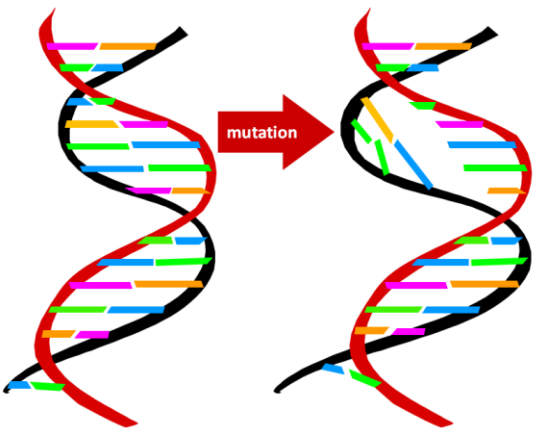
WHAT IS HOMOGENTISIC ACID?

Homogentisic acid is an intermediate in the degradation pathway of the amino acids (phenylalanine and tyrosine) to the Krebs cycle. It is the substrate for the enzyme HGD and under normal conditions, is virtually undetectable in blood and urine.

WHEN DOES HOMOGENTISIC ACID ACCUMULATE?

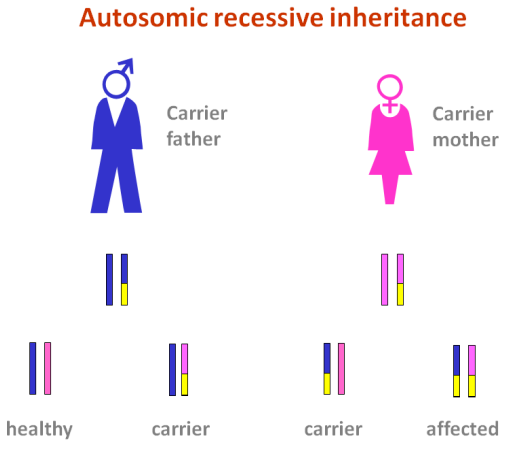
Without a working **HGD enzyme**, homogentisic acid accumulates in the blood and is eliminated in large amounts in the urine. In contact with air, HGA reacts with oxygen and turns the urine black. This is caused by a black pigment called “alkapton”, and leads to the name **alkapton**-uria. This same black pigment, in a process called ochronosis, causes tissue and bone to darken and degenerate. This causes painful and disabling joint disease, known as **osteoarthritis.**

WHAT CAUSES HGD DEFICIENCY?



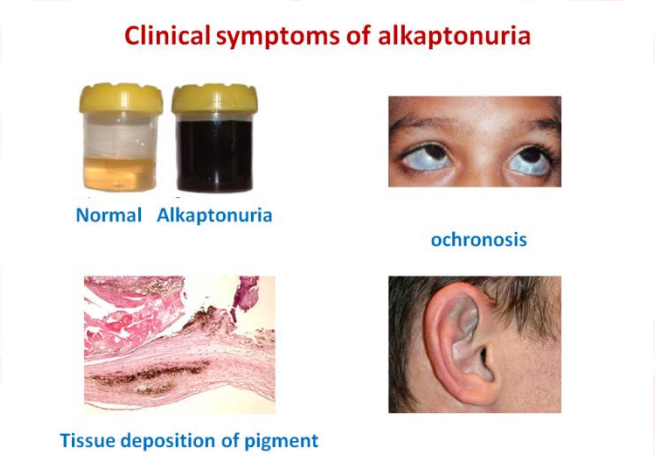
HGD deficiency occurs due to **mutations** in the ***HGO* gene**. It is passed down when both the mother and father carry the mutated gene.

This is called an **autosomal recessive inheritance**, i.e. both parents are carriers of the gene, although they do not suffer any symptoms of the disease. If both parents pass this gene to their child, they will suffer from **alkaptonuria**.



WHICH ARE THE CLINICAL SYMPTOMS OF ALKAPTONURIA?

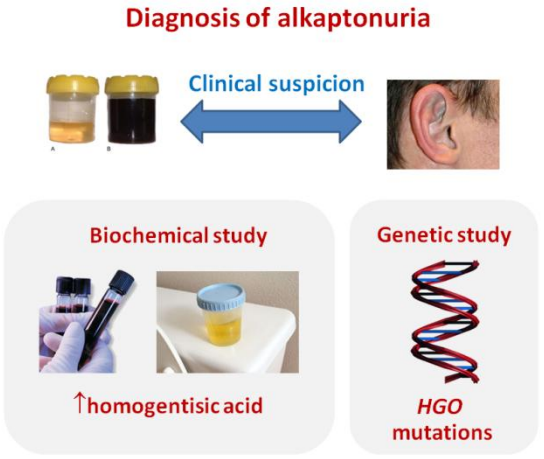
The symptoms of AKU are:



1. **Black urine**, which appears from birth and can lead to early diagnosis of the disease.
2. **Osteoarthritis**. This is caused when homogentisic acid builds up in the connective tissue of patients, causing black and brittle bones and cartilage. This can be extremely painful and gets worse with age.
3. **Black spots** in the eyes, discoloured ears and dark earwax also affect AKU patients. However these symptoms do not affect vision or hearing, and are often used for diagnostic purposes later in life. This process of ochronosis may also occur under the nails, on the face and hands.
4. **Kidney**, **prostate** and **bladder** stones may occur due to the build-up of HGA in the **genito-urinary tract**, during the production of urine.
5. The build-up of HGA can also cause **heart** complications. In severe cases, it may cause heart disease and patients may require heart valve replacements.

HOW IS ALKAPTONURIA DIAGNOSED?

Initial diagnosis is based on **clinical symptoms** such as urine colour and joint pain. This can then be confirmed through a urine test or blood test for HGA. Genetic testing is also performed in some cases.



CAN ALKAPTONURIA BE TREATED?

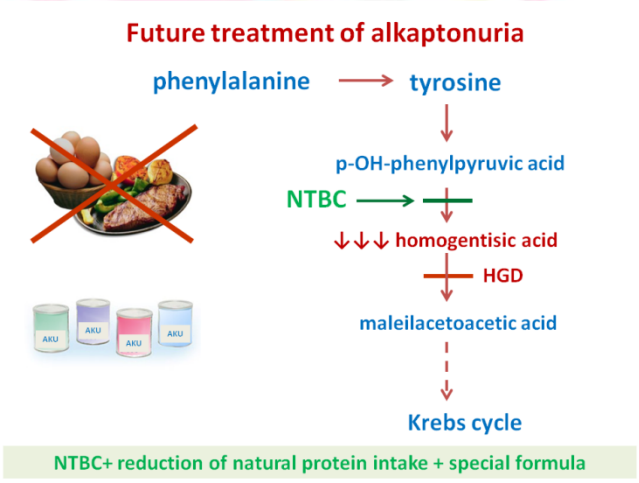
The classic treatment is **symptomatic**, to reduce the **complications** of alkaptonuria. Pain control and certain types of exercise can reduce pain and improve mobility. Patients often need surgery such as joint replacements or repair of tendon rupture. Some patients may also need heart valve replacements.

There are anecdotal reports that a diet low in protein can delay joint problems. However, there have been no formal clinical trials and there is no proof it is beneficial. Maintaining a low-protein diet is extremely difficult to do.

Some alkaptonuria patients take vitamin C as an anti-oxidant. However, this has not been shown to have any effect and vitamin C has no proven effect on AKU in humans.

However, **nitisinone**, currently approved for treatment of tyrosinemia type 1, is a promising future treatment as it stops the build up of HGA. A clinical study of 40 adult patients showed reduced HGA, even though evidence for a clinical effect was not strong enough. However, this therapy may be effective if administered at an early stage of the disease. Nitisinone is currently being tested in a series of international clinical trials.

Alkaptonuria is an inherited disease which can lead to severe consequences. Early diagnosis and new treatments can enhance the quality of life of patients suffering from this disease.



Translation supervised by
Hana Ayoob, AKU Society
http://www.akusociety.org/index.html

Passeig Sant Joan de Déu, 2
08950 Esplugues de Llobregat
Barcelona, Spain
Tel: +34 93 203 39 59
www.hsjdbcn.org / www.guiametabolica.org