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My46 Trait Profile

Alkaptonuria

Alkaptonuria is a metabolic disorder caused by an inability to break down a chemical in the body called homogentisic acid. The buildup of this chemical causes dark urine, arthritis of the spine and joints, and dark spots on and under the skin. It is caused by mutations in the HGD gene that makes the homogentisate 1,2 dioxygenase enzyme.

Characteristics of Alkaptonuria

Alkaptonuria is a rare genetic condition characterized by the body's inability to break down a chemical in the body called homogentisic acid (HGA). All of the symptoms of alkaptonuria are caused by the accumulation of HGA in the body. The first sign is typically dark-colored urine. This is usually the only symptom that is present in children and typically leads a healthcare provider to suspect the diagnosis of alkaptonuria. As a person with alkaptonuria gets older, he/she typically develop pain in the spine, hips, and knees due to arthritis (i.e., joint inflammation). This is progressive -- this means that the arthritis becomes more severe and affects more parts of the body over time. Spinal arthritis can cause other problems with the bones of the spine (i.e. vertebrae), such as spinal curvature (kyphoscoliosis), and changes in bone shape that can cause compression of the spinal cord. These spine changes may make a person with alkaptonuria feel stiff and impair their movements and breathing. Over time, people with alkaptonuria develop blue-black spots on and under their skin, as well as on their eyes and ears. These spots are caused by ochronosis, which is a collection of dark pigment in one spot. HGA can collect in the heart and cause arrhythmias (i.e. abnormal heart beats). A minority of people with alkaptonuria develop heart failure. In some affected individuals, HGA also collects in the kidneys and inside the ears, and can cause kidney stones and hearing loss.

Diagnosis/Testing

Individuals with alkaptonuria have changes or mutations in the HGD gene. This gene makes an enzyme called homogentisate 1,2 dioxygenase. The normal function of this enzyme is to break down HGA. Mutations in the HGD gene decrease the amount of the enzyme in the body, thus causing HGA to accumulate.

A urine test called gas-chromatography mass spectrometry analysis can determine the amount of HGA in the urine. People with alkaptonuria typically have very high amounts of HGA in their urine. High HGA in the urine is enough to confirm a diagnosis of alkaptonuria in an individual. Genetic testing of the HGD gene can also confirm the diagnosis of alkaptonuria.

Management/Surveillance

Management of alkaptonuria is mainly symptomatic – this means that each symptom is treated individually when it occurs. Some people with alkaptonuria receive physical and occupational therapy to help strengthen their muscles and increase flexibility. For people who experience pain, medications or other therapies such as massage and acupuncture can be helpful.

Surgery is often required for joint replacements and kidney stone removal. Some affected individuals also have heart surgery to replace their heart valves if too much HGA has accumulated. It is recommended that people with alkaptonuria have a heart evaluation by a heart doctor (i.e. cardiologist) every 2 to 3 years.

People with alkaptonuria are typically advised to eat a diet that is low in protein. This is because HGA is made when the body breaks down (i.e. metabolizes) protein from food. This diet can reduce the amount of HGA in the blood,

but has not been very effective for preventing symptoms of alkaptonuria.

Mode of inheritance

Alkaptonuria is inherited in an autosomal recessive pattern. This means that an individual has to inherit two HGD mutations (i.e., one from each parent) to be affected with alkaptonuria. If both parents are carriers of an HGD mutation, they have a 1 in 4 (25%) chance with each pregnancy of having a child with alkaptonuria.

Risk to family members

Parents of a child with alkaptonuria are carriers of alkaptonuria. If a sibling of a child with alkaptonuria is unaffected, he/she has a 66% (2/3) chance of being a carrier of alkaptonuria.

Special considerations

Recently, a medication called nitisinone has been identified as a possible therapy for alkaptonuria. In research, nitisinone has decreased the amount of HGA in the blood in people with alkaptonuria. This may prevent the symptoms of the condition. The use of nitisinone to treat alkaptonuria is still under investigation and the drug has not yet been approved for sale in the US.

Resources

The AKU Society
http://www.akusociety.org/
Genetics Home Reference: Alkaptonuria
http://ghr.nlm.nih.gov/condition/alkaptonuria

References

Introne WJ, Gahl WA. (Updated 22 August 2013). Alkaptonuria. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK1454/. Accessed [11/10/2013].
Ranganath, LR. et al. (2013)."Recent advances in management of alkaptonuria." Journal of Clinical Pathology 66(5): 367-373.

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