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Alkaptonuria

Synonym: Alcaptonuria

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Summary

Clinical characteristics

Alkaptonuria is caused by deficiency of homogentisate 1,2-dioxygenase, an enzyme that converts homogentisic acid (HGA) to maleylacetoacetic acid in the tyrosine degradation pathway. The three major features of alkaptonuria are the presence of HGA in the urine, ochronosis (bluish-black pigmentation in connective tissue), and arthritis of the spine and larger joints. Oxidation of the HGA excreted in the urine produces a melanin-like product and causes the urine to turn dark on standing. Ochronosis occurs only after age 30 years; arthritis often begins in the third decade. Other manifestations include pigment deposition, aortic or mitral valve calcification or regurgitation and occasionally aortic dilatation, renal stones, and prostate stones.

Diagnosis/testing

The diagnosis of alkaptonuria is based on the detection of a significant amount of HGA in the urine by gas chromatography-mass spectrometry analysis. The amount of HGA excreted per day in individuals with alkaptonuria is usually between one and eight grams. Identification of biallelic pathogenic variants in *HGD* on molecular genetic testing confirms the diagnosis and allows family studies.

Management

Treatment of manifestations: Management of joint pain tailored to the individual; physical and occupational therapy to help maintain muscle strength and flexibility; knee, hip, and shoulder replacements when needed; surgical intervention for prostate stones and renal stones as needed; aortic stenosis may necessitate valve replacement.

Surveillance: In individuals older than age 40 years, echocardiography to detect aortic dilation, aortic or mitral valve calcification, and stenosis; CT to detect coronary artery calcification.

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Agents/circumstances to avoid: Physical stress to the spine and large joints, including heavy manual labor or high-impact sports, to try to reduce progression of severe arthritis.

Evaluation of relatives at risk: Testing for the presence of elevated urinary HGA in sibs of affected individuals allows for early diagnosis and intervention to prevent secondary complications.

Genetic counseling

Alkaptonuria is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if both *HGD* pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Alkaptonuria **should be suspected** in individuals with any of the following major features:

- **Dark urine or urine that turns dark on standing.** Oxidation of homogentisic acid (HGA) excreted in the urine produces a melanin-like product and causes the urine to turn dark on standing. Individuals with alkaptonuria usually have dark urine or urine that turns dark on standing or exposure to an alkaline agent. However, darkening may not occur for several hours after voiding and many individuals never observe any abnormal color to their urine.
- **Ochronosis(bluish-black pigmentation of connective tissue).** Accumulation of HGA and its oxidation products (e.g., benzoquinone acetic acid) in connective tissue leads to ochronosis (Figure 1).
  - Brown pigmentation of the sclera is observed midway between the cornea and the outer and inner canthi at the insertion of the recti muscles. Pigment deposition may also be seen in the conjunctiva and cornea. The pigmentation does not affect vision [Chévez Barrios & Font 2004].
  - Ear cartilage pigmentation is seen in the concha and antihelix. The cartilage is slate blue or gray and feels irregular or thickened. Calcification of the ear cartilage may be observed on radiographs.
  - Pigment also appears in cerumen and in perspiration, causing discoloration of clothing.
  - A deep purple or black discoloration may be seen on the skin of the hands, corresponding to the underlying tendons, or in the web between the thumb and index finger.
- **Arthritis,** often beginning in the spine and resembling ankylosing spondylitis in its large-joint distribution. Radiographs of the spine showing flattened and calcified intervertebral disks are pathognomonic (Figure 1). Findings include degeneration of the intervertebral disks followed by disk calcification and eventually fusion of the vertebral bodies. Osteophyte formation and calcification of the intervertebral ligaments also occur. Radiographs of the large joints may show joint space narrowing, subchondral cysts, and osteophyte formation. Enthesopathy can be seen at the muscle insertions [Mannoni et al 2004].

Establishing the Diagnosis

The diagnosis of alkaptonuria **is established** in a proband with the following:

Biochemical Findings

Elevated homogentisic acid (HGA) in the urine. The diagnosis of alkaptonuria is based on the detection of a significant amount of HGA in a urine sample by gas chromatography-mass spectrometry analysis. The amount of HGA excreted per day in individuals with alkaptonuria is usually between one and eight grams. A normal 24-hour urine sample contains 20-30 mg of HGA.

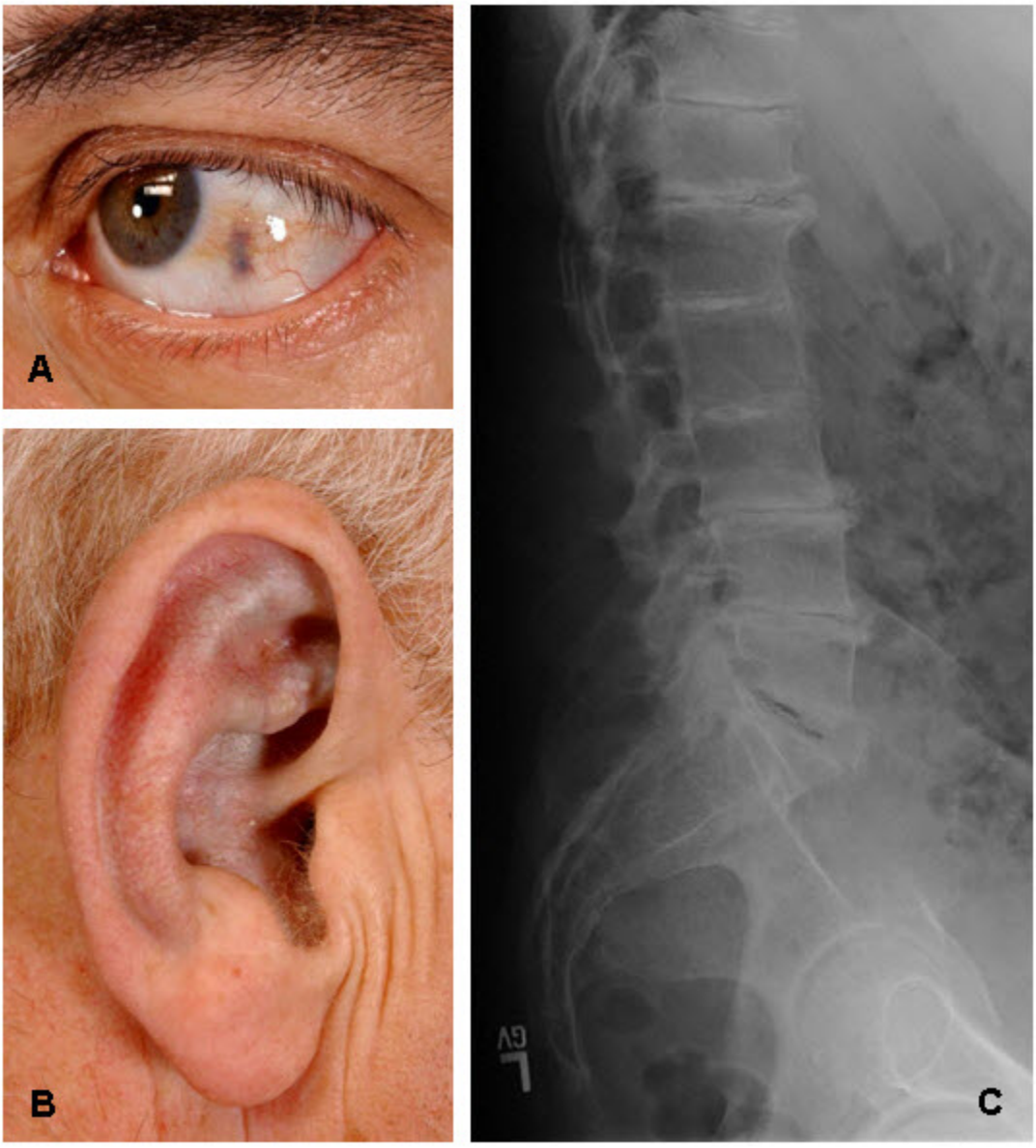

Figure 1. A. Ochronosis of the sclera of the eye

B. Ochronosis of the antihelix and concha

C. Classic radiographic findings of the lumbar spine with disc flattening, calcification, and osteophyte formation

Notes: (1) Elevated HGA can be detected on a random urine sample. (2) Biochemical testing cannot detect the carrier state.

Molecular Genetic Findings

Identification of biallelic pathogenic variants in *HGD* on molecular genetic testing (see Table 1) is not required to establish the diagnosis in a proband. However, molecular genetic testing is needed in order to provide carrier testing and prenatal test result interpretation for at-risk family members.

Molecular testing approaches can include **single-gene testing** and **genome sequencing.**

- **Single-gene testing.** Sequence analysis of *HGD* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

  Note: Targeted analysis for pathogenic variants may be performed first in individuals of Slovak ancestry. Pathogenic variants included in a panel may vary by laboratory.

- **Comprehensive genome sequencing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of alkaptonuria.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Alkaptonuria

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This Method
HGD	Sequence analysis [3]	90%
	Gene-targeted deletion/duplication analysis [4]	2 individuals [5]
	Targeted analysis for pathogenic variants	>80% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice-site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. To date, only two individuals with deletions involving *HGD* have been reported [Zouheir Habbal et al 2014, Nemethova et al 2016].
6. Four pathogenic variants (c.481G>A, c.457dup, c.808G>A, and c.1111dup) represent Slovak founder variants, accounting for 80% of all pathogenic variants found in the Slovak population. Six pathogenic variants c.688C>T, c.899T>G, c.174delA, c.16-1G>A, c.342+1G>A, and c.140C>T are common in other populations, but rare in the Slovak population.

Clinical Characteristics

Clinical Description

The clinical findings of alkaptonuria include darkening of urine on standing as a result of the presence of homogentisic acid (HGA) and its oxidation products, connective tissue ochronosis, and arthritis of the spine and larger joints. HGA excretion and disease severity can vary significantly within the same family. In some individuals, the diagnosis of alkaptonuria is identified only after the individual seeks medical attention for chronic joint pain or after black articular cartilage is noted during orthopedic surgery.

Alkaptonuria does not cause developmental delay or cognitive impairment and does not generally reduce the life span of affected individuals.

Urinary changes. Individuals with alkaptonuria usually have dark urine or urine that turns dark on standing or exposure to an alkaline agent. However, darkening may not occur for several hours after voiding and many individuals never observe any abnormal color to their urine.

Connective tissue. In general, pigmentary changes are observed after age 30 years. Tendon-related findings, including a thickened Achilles tendon, tendonitis, and rupture, have also been observed clinically [Phornphutkul et al 2002] and are demonstrable by MRI.

Joints. Ochronotic arthritis is a regular manifestation of longstanding alkaptonuria. Joint symptoms involving the spine usually appear in the third decade. In one large series, low back pain was observed prior to age 30 years in 49% of individuals and prior to age 40 years in 94% [Phornphutkul et al 2002].

Lumbar and thoracic spine symptoms precede cervical spine symptoms. The sacroiliac region is usually spared. Limitation of spine flexion directly correlates with degree of disability. Individuals with decreased forward flexion demonstrate impaired function and increased fatigue [Perry et al 2006].

Joint disease appears to start earlier and progress more rapidly in males than in females. Knees, hips, and shoulders are frequently affected. Fifty percent of individuals require at least one joint replacement by age 55 years [Phornphutkul et al 2002]. Small joint involvement is not significant.

Because the kidneys are responsible for secreting massive quantities of HGA, impaired renal function can accelerate the development of ochronosis and joint destruction [Introne et al 2002].

Other organ involvement

- **Heart.** Pigment deposition in the heart valves and blood vessels leads to aortic or mitral valve calcification with stenosis or regurgitation and occasionally aortic dilatation. Aortic valve stenosis occurs at a high frequency in the sixth and seventh decades of life. Unlike cardiac valve disease that occurs in the general population, there is no correlation with standard cardiovascular risk factors. Aortic stenosis may necessitate aortic valve replacement. Coronary artery calcification has been demonstrated on chest CT [Hannoush et al 2012].
- **Renal stones.** By age 64 years, 50% of individuals with alkaptonuria have a history of renal stones.
- **Prostate stones.** Black prostate stones occur relatively frequently in individuals with alkaptonuria. In one series, eight of 27 men age 31-60 years had prostate stones. Prostate stones may contribute to recurrent infection or urinary obstruction and require surgical removal.

Genotype-Phenotype Correlations

No correlation is observed between the type of *HGD* pathogenic variant and amount of HGA excreted or disease severity.

Penetrance

Elevated urinary HGA and ochronotic arthritis occur in all individuals who are homozygous or compound heterozygous for pathogenic variants in *HGD*.

Nomenclature

Occasionally alkaptonuria is referred to collectively (and incorrectly) as ochronosis.

Prevalence

At least 1000 affected individuals have been described in the literature; this is likely an underestimate. The incidence of alkaptonuria in the US is estimated at 1:250,000 to 1:1,000,000 live births.

Alkaptonuria occurs worldwide; a high prevalence has been observed in the Dominican Republic and in northwestern Slovakia, likely as the result of a founder effect. The prevalence of alkaptonuria in Slovakia is estimated at 1:19,000 [Zatkova et al 2003].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are associated with pathogenic variants in *HGD*.

Differential Diagnosis

Ochronosis. Ochronosis resulting from alkaptonuria may be confused with acquired, reversible pigmentary changes following prolonged use of carbolic acid dressings for chronic cutaneous ulcers [La Du 2001]. Chemically induced ochronosis has also been described following long-term use of either the antimalarial agent Atabrine® [Ludwig et al 1963], the skin-lightening agent hydroquinone, or the antibiotic minocycline [Suwannarat et al 2004].

In one individual with alkaptonuria, the ochronotic pigment in the eye was misdiagnosed as melanosarcoma, resulting in enucleation of the eye [Skinsnes 1948].

A thorough history combined with lack of excessive HGA excretion in the urine should eliminate false positive diagnoses.

Arthritis. The arthritis of alkaptonuria resembles ankylosing spondylitis in its damage to the spine and large joints, although it differs in sparing the sacroiliac joint and in its radiographic appearance. Radiographic findings of the spine also differentiate alkaptonuria from rheumatoid arthritis and osteoarthritis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with alkaptonuria, the following evaluations are recommended:

- Complete history and physical examination with particular attention to range of motion in the spine and large joints
- Physical medicine and rehabilitation evaluation if limited range of motion or joint pain occurs
- Electrocardiogram and echocardiogram in individuals older than age 40 years
- Renal ultrasound examination or helical abdominal CT to evaluate for the presence of renal calculi
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Joint pain is substantial in individuals with alkaptonuria, and close attention to pain control is necessary. Optimal pain management should be tailored to the individual with close follow up and long-term management.

Physical and occupational therapy are important to promote optimal muscle strength and flexibility.

Knee, hip, and shoulder replacement surgeries are options for managing significant arthritis. In general, the goal of joint replacement is pain relief rather than increased range of motion. Joint replacement in individuals with alkaptonuria is associated with prosthetic survival comparable to that found in individuals with osteoarthritis [Spencer et al 2004].

Aortic stenosis may necessitate valve replacement.

Treatment of prostate stones and renal stones may include surgical intervention.

Prevention of Primary Manifestations

Although several therapeutic modalities have been investigated, no preventive or curative treatment is available. See Therapies Under Investigation.

Prevention of Secondary Manifestations

Maintaining joint range of motion through moderate non-weight-bearing exercise such as swimming may have beneficial effects.

Younger individuals with alkaptonuria should be directed toward non-contact and lower-impact sports.

Surveillance

Cardiac. Surveillance for cardiac complications every one to two years is advisable after age 40 years and should include:

- Echocardiography to detect aortic dilation and aortic or mitral valve calcification and stenosis;
- Surveillance CT scans (according to the recommendation of a cardiologist) in affected individuals with coronary artery calcification.

Urology. Urologic complications become more prevalent after age 40 years:

- Routine surveillance is not recommended, but awareness of this potential complication is advised.
- Ochronotic prostate stones appear on radiography; kidney stones can be identified by ultrasonography and helical abdominal CT.

Agents/Circumstances to Avoid

Avoidance of physical stress to the spine and large joints, including heavy manual labor or high-impact sports, may reduce the progression of severe arthritis.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from preventive measures. Those found to have alkaptonuria should be counseled to avoid high-impact and contact sports. Career considerations include avoidance of occupations involving heavy physical labor. Instruction on joint strengthening and flexibility exercises, in conjunction with appropriate physical activity, can help preserve overall joint mobility and function.

Evaluations can include:

- Biochemical testing for the presence of elevated urinary homogentisic acid (HGA).
- Molecular genetic testing if the pathogenic variants in the family are known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Pharmacologic treatment of alkaptonuria with oral administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) or nitisinone has been proposed [Anikster et al 1998]. Nitisinone is a triketone herbicide that inhibits 4-hydroxyphenylpyruvate dioxygenase, the enzyme that produces HGA. Nitisinone is approved for the treatment of tyrosinemia type I.

Nitisinone reduced urinary HGA excretion by at least 69% in two individuals, but at the expense of an elevated plasma tyrosine concentration [Phornphutkul et al 2002], resulting in photophobia. The only other known side effect is (rarely) corneal crystals. Theoretically, neurologic complications associated with tyrosinemia type III may develop.

In a pilot study, low-dose nitisinone reduced urinary HGA by up to 95% in nine individuals with alkaptonuria. In the same study, seven individuals were treated for up to 15 weeks with nitisinone while receiving normal protein intake; all had elevated plasma tyrosine concentrations. No ophthalmic, neurologic, or severe dermatologic complications were observed. Two individuals had transient elevations in liver transaminase levels that returned to normal after stopping nitisinone [Suwannarat et al 2005].

In a three-year therapeutic trial, 2 mg of nitisinone daily reduced urine and plasma HGA by 95% throughout the study duration [Introne et al 2011]. Plasma tyrosine averaged 800µM without dietary restriction. Side effects were minimal. One affected individual developed corneal crystals that required discontinuation of nitisinone, and one affected individual had elevated liver transaminases. Statistically significant improvement in hip range of motion and measurements of musculoskeletal function were not observed in the treatment group compared to the control group; however there was a positive trend showing slowing of aortic stenosis. Additional trials are currently underway to establish clinical benefit.

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

No therapy is proven to prevent or correct the pigmentary changes of ochronosis.

- Dietary restriction of phenylalanine and tyrosine has been proposed to reduce the production of HGA, but severe restriction of these amino acids is not practical in the long term and may be dangerous.
- High-dose vitamin C decreases urinary benzoquinone acetic acid, a derivative of HGA, but has no effect on HGA excretion [Wolff et al 1989]. It has been hypothesized that high-dose ascorbic acid may prevent the deposition of ochronotic pigment, although it does not alter the basic metabolic defect [Wolff et al 1989]. No credible studies have demonstrated the clinical efficacy of ascorbic acid [La Du 2001].
- Oral bisphosphonate therapy has been suggested to halt the progressive bone loss; however, a prospective study of four affected individuals failed to demonstrate benefit [Aliberti et al 2007].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Alkaptonuria is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *HGD* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with alkaptonuria are obligate heterozygotes (carriers) for a pathogenic variant in *HGD*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *HGD* pathogenic variant.

Carrier (Heterozygote) Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *HGD* pathogenic variants in the family.

Biochemical testing. Biochemical genetic testing is not reliable as a method of carrier detection.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *HGD* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for alkaptonuria are possible.

Biochemical testing. In theory, homogentisic acid can be measured in amniotic fluid; however, no studies have been published to confirm the reliability of the test in an affected fetus.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Alkaptonuria Society**
  66 Devonshire Road
  Cambridge CB1 2BL

United Kingdom
Phone: +44 (0)1223 322897
akusociety.org

- **Alkaptonuria: A Fact Sheet for Patients**
  National Institutes of Health
  Phone: 800-411-1222 (toll-free)
  Email: prpl@cc.nih.gov
  Alkaptonuria: A Fact Sheet for Patients (PDF file)
- **Medline Plus**
  Alkaptonuria
- **My46 Trait Profile**
  Alkaptonuria
- **National Library of Medicine Genetics Home Reference**
  Alkaptonuria
- **Metabolic Support UK**
  5 Hilliards Court, Sandpiper Way
  Chester Business Park
  Chester CH4 9QP
  United Kingdom
  Phone: 0845 241 2173
  Email: contact@metabolicsupportuk.org
  www.metabolicsupportuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Alkaptonuria: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HGD	3q13.33	Homogentisate 1,2-dioxygenase	AKU database HGD mutation database HGD database	HGD	HGD

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Alkaptonuria (View All in OMIM)

203500	ALKAPTONURIA; AKU
607474	HOMOGENTISATE 1,2-DIOXYGENASE; HGD

Gene structure. *HGD* is 54.3 kb in length and has 14 exons coding for a 1715-bp transcript [Granadino et al 1997]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. At least 130 pathogenic variants in *HGD* have been reported and are found in different allelic combinations [HGD mutation database]. The pathogenic variants are distributed throughout the *HGD* sequence. The majority of pathogenic variants are missense; nonsense, frame shift, and splice-site variants also occur.

- p.Cys120Trp is a founder variant in the Dominican Republic [Goicoechea De Jorge et al 2002].
- In the Slovak population, evidence exists for mutational hot spots (e.g., c.342+1G>A [Zatková et al 2000]) and a founder effect (e.g., the frequent pathogenic variant p.Gly161Arg [Srsen et al 2002]).
- The most prevalent pathogenic variant in Europe (excluding the Slovak population) is c.1102A>G (p.Met368Val).
- No mutational hot spot or founder effect has been identified in the US [Phornphutkul et al 2002].

Table 2. Selected *HGD* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.140C>T	p.Ser47Leu	NM_000187.3 NP_000178.2
c.16-1G>A (IVS1-1G>A)	p.Tyr6_Gln29del	
c.174delA	p.Ser59AlafsTer52 (Ser59AlafsTer31) (R58fs)	
c.360T>G	p.Cys120Trp	
c.342+1G>A (IVS5+1G>A)	p.Leu95_Ser114del	
c.457dup	p.Asp153GlyfsTer26 (Gly152fs)	
c.481G>A	p.Gly161Arg	
c.688C>T	p.Pro230Ser	
c.808G>A	p.Gly270Arg	
c.899T>G	p.Val300Gly	
c.1102A>G	p.Met368Val	
c.1111dup (111_1112insC)	p.His371ProfsTer4 (Pro370fs)	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. The protein product of *HGD* is homogentisate 1,2-dioxygenase, an enzyme in the phenylalanine and tyrosine degradation pathway (see Figure 2). The enzyme is composed of 445 amino acids and is expressed predominantly in the liver and kidney, with some expression in the small intestine, colon, and prostate [Fernández-Cañón et al 1996]. Homogentisate 1,2-dioxygenase functions in the metabolism of HGA by catalyzing an oxidative cleavage of the benzene ring to yield maleylacetoacetic acid. It requires oxygen, ferrous iron, and sulfhydryl groups.

Abnormal gene product. Most mutated *HGD* alleles are predicted to result in complete loss of enzymatic activity.

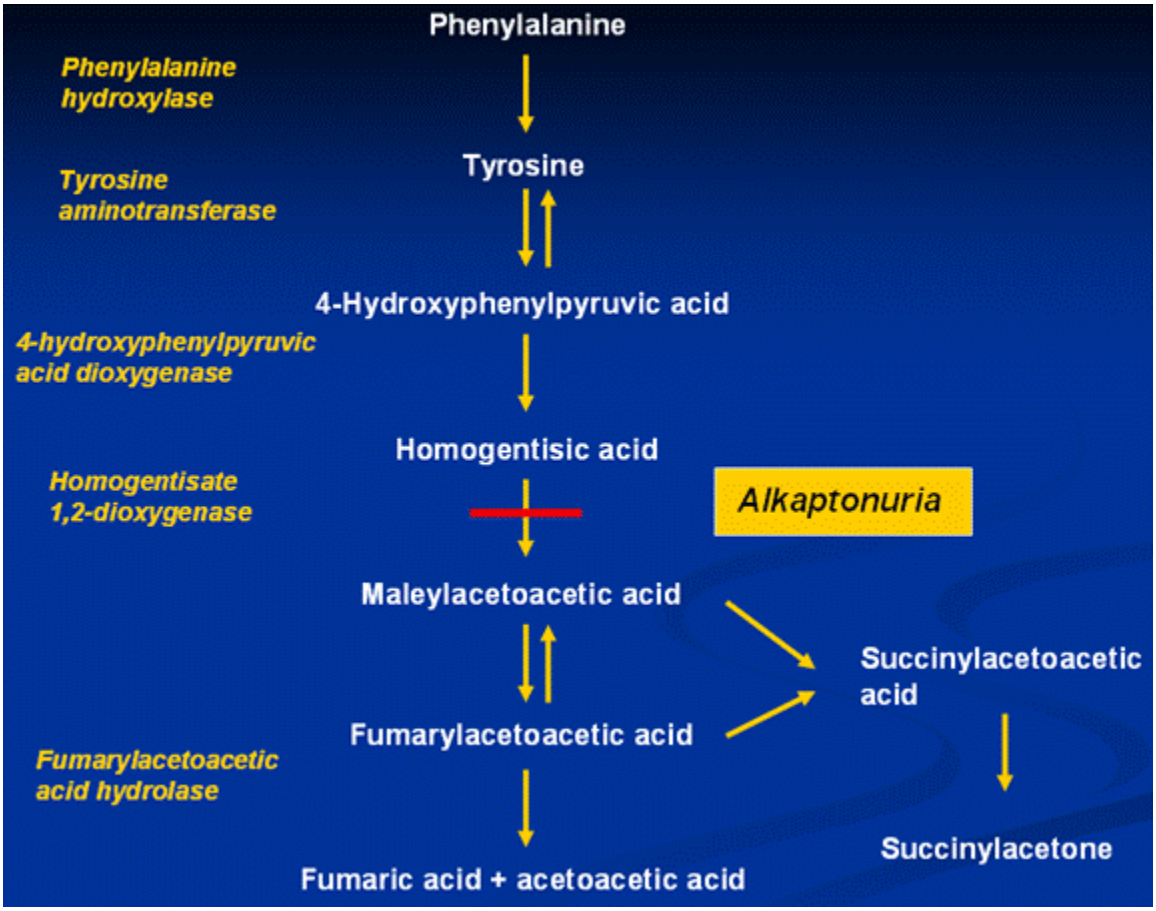

Figure 2. The tyrosine degradation pathway. Alkaptonuria is characterized by deficiency of homogentisate 1,2-dioxygenase, which converts homogentisic acid (HGA) to maleylacetoacetic acid.

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Chapter Notes

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- 2 July 2009 (cd) Revision: sequence analysis available clinically
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