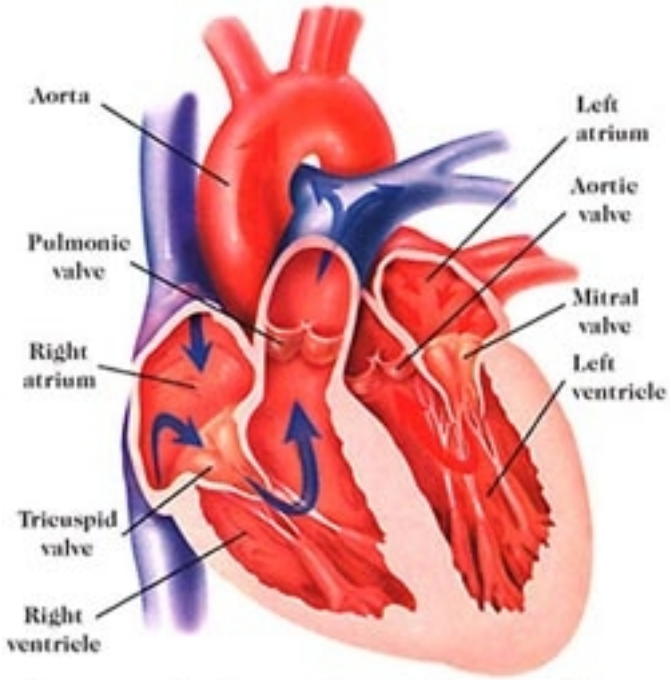
The Heart and Blood Vessels



Anatomy of the human heart. (Reproduced from the Department of Cardiothoracic Surgery, USC, with permission.)

Oxygen is vital to life as it provides fuel for all the body's functions. The heart's role is to pump oxygen-rich blood to every cell in the body. The blood vessels — a network of interconnecting arteries, arterioles, capillaries, venules, and veins — provide the pathway in which blood travels.

Arteries are the passageways through which the blood is delivered, the largest of which is the aorta. The aorta branches off the heart and divides into many smaller arteries, which have muscular walls that adjust their diameter to increase or decrease blood flow to a particular body area. Capillaries are thin walled, highly branched vessels that feed the tissues and collect wastes to be carried back to the lungs, liver, or kidney for elimination. Capillaries empty into the venules, which in turn drain into the veins that lead back to the heart. Veins carry deoxygenated blood to the lungs to pick up more oxygen, and then back to the heart once again.

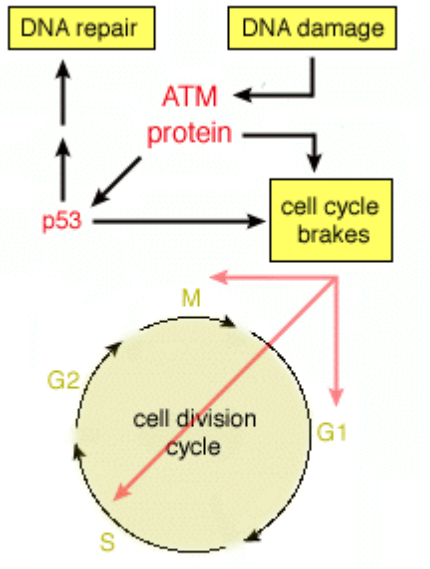
The four most common types of vascular disease are high blood pressure, coronary heart disease, stroke, and rheumatic heart disease. Other forms include arrhythmias, diseases of the arteries, arterioles and capillaries, congenital defects, valvular heart disease, diseases of pulmonary circulation; and diseases of veins and lymphatics. Some of these disorders are the result of the over production of blood vessel cells, while others occur from vascular malformations. Still others result from inflammation of the blood vessels or the build up of a fatty substance called plaque within the blood vessels.

Ataxia telangiectasia

The first signs of ataxia telangiectasia (A-T) usually appear in the second year of life as a lack of balance and slurred speech. It is a progressive, degenerative disease characterized by cerebellar degeneration, immunodeficiency, radiosensitivity (sensitivity to radiant energy, such as x-ray), and a predisposition to cancer.

Back in 1988 the gene responsible for A-T was mapped to chromosome 11. The subsequent identification of the gene proved difficult; it was 7 more years until the human ATM gene was cloned. The diverse symptoms seen in A-T reflect the main role of ATM, which is to induce several cellular responses to DNA damage. When the ATM gene is mutated, these signaling networks are impaired, and so the cell does not respond correctly to minimize the damage.

Some of the ATM-dependent signaling pathways are found in yeast. Because these pathways appear to be conserved throughout evolution, they are likely to be central to the DNA damage response. Research into finding an effective therapy for A-T sufferers is likely to be helped by harnessing the power of yeast genetics, which allows more rapid and systematic study of the pathways affected by an ATM mutation.



The ATM protein mediates responses to DNA damage, in particular those that control progression through the cell cycle.

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=ataxia%20telangiectasia&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4502267&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=208900] catalog of human genes and disorders

Websites

The A-T Children's Project [www.atcp.org/] support and research information

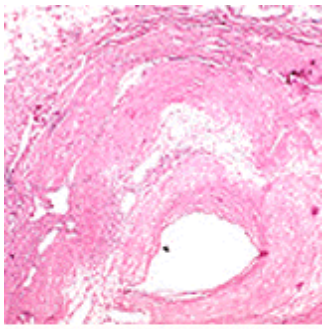
GeneClinics [www.geneclinics.org/profiles/ataxia-telangiectasia/] a medical genetics resource

Atherosclerosis

Atherosclerosis is a disease that can affect people at any age, although it usually doesn't pose a threat until people reach their forties or fifties. It is characterized by a narrowing of the arteries caused by cholesterol-rich plaques of immune system cells. Key risk factors for atherosclerosis, which can be genetic and/or environmental, include: elevated levels of cholesterol and triglyceride in the blood, high blood pressure, and cigarette smoke.

A protein called apolipoprotein E, which can exist in several different forms, is coded for by a gene found on chromosome 19. It is important for removing excess cholesterol from the blood, and does so by carrying cholesterol to receptors on the surface of liver cells. Defects in apolipoprotein E sometimes result in its inability to bind to the receptors, which leads to an increase a person's blood cholesterol and consequently their risk of atherosclerosis.

Currently, a debate is raging over how the various mutated forms of apolipoprotein E effect the body. As a result, many of the treatments proposed remain in their experimental phase. While mice are proving useful for modeling the human disease, a great deal of research is still required before we can fully understand the mechanisms that regulate the levels of lipoproteins—like apolipoprotein E—in the blood.



The size of the lumen of arteries can be significantly reduced by atherosclerotic plaques rich in cholesterol. [Image credit: Mark Boguski, NCBI, NIH, USA.]

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=APOE%20OR%20atherosclerosis&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557325&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=107741] catalog of human genes and disorders

Websites

National Heart, Blood and Lung Institute [www.nhlbi.nih.gov/health/public/heart/index.htm] cardiovascular information

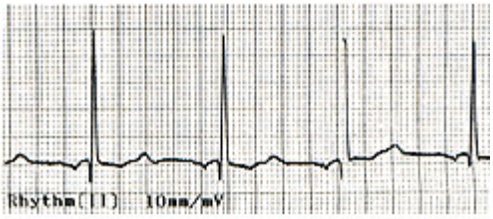
American Heart Association [amhrt.org/] information on heart disease and stroke

Long QT syndrome

Long QT syndrome (LQTS) results from structural abnormalities in the potassium channels of the heart, which predispose affected persons to an accelerated heart rhythm (arrhythmia). This can lead to sudden loss of consciousness and may cause sudden cardiac death in teenagers and young adults who are faced with stressors ranging from exercise to loud sounds.

LQTS is usually inherited as an autosomal dominant trait. In the case of LQT1, which has been mapped to chromosome 11, mutations lead to serious structural defects in the person's cardiac potassium channels that do not allow proper transmission of the electrical impulses throughout the heart. There also appear to be other genes, tentatively located on chromosomes 3, 6 and 11 whose mutated products may contribute to, or cause, LQT syndrome.

Beta blockers are used to treat the symptoms of the disease, and appear to be effective in some symptomatic patients. However, common sense therapies such as avoiding strenuous physical exercise and other stressors are also effective. Research on how the genes discussed above interact with each other should encourage the development of new treatments for long-QT syndrome.



Portion of an electrocardiogram (EKG) used to diagnose long-QT syndrome, an inherited cardiac arrythmia associated with mutations in an ion channel. [Image credit: John T. Cockerham, Georgetown University Medical Center, Washington DC, USA.

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=LQT1&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557689&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=192500] catalog of human genes and disorders

Websites

American Heart Association [amhrt.org] fighting heart disease and stroke

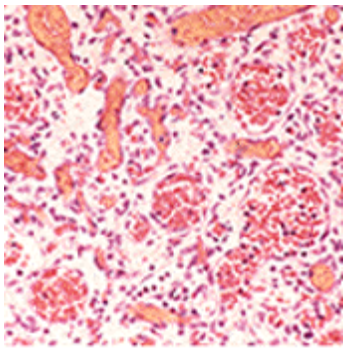
National Heart, Lung and Blood Institute, NIH [www.nhlbi.nih.gov/health/public/heart/other/arrhyth.htm] information on arrhythmias

Von Hippel-Lindau syndrome

Von Hippel-Lindau syndrome is an inherited multi-system disorder characterized by abnormal growth of blood vessels. While blood vessels normally grow like trees, in people with VHL little knots of blood capillaries sometimes occur. These knots are called angiomas or hemangioblastomas. Growths may develop in the retina, certain areas of the brain, the spinal cord, the adrenal glands and other parts of the body.

The gene for Von-Hippel Lindau disease (VHL) is found on chromosome 3, and is inherited in a dominant fashion. If one parent has a dominant gene, each child has a 50-50 chance of inheriting that gene. The VHL gene is a tumor suppressor gene. This means that its role in a normal cell is to stop uncontrolled growth and proliferation. If the gene is lost or mutated, then its inhibitory effect on cell growth is lost or diminished, which, in combination with defects in other regulatory proteins, can lead to cancerous growth. LIke the Rb tumor suppressor gene, VHL seems to act as a 'gatekeeper' to the multistep process of tumorigenesis.

Although unrelated to any other known family of human proteins, homologs to human VHL are found in mice and rats. Experiments using these animals as model organisms for the human disease are helping researchers discover the normal physiological role of VHL, which will shed light on its mechanism of pathogenesis. Initial results suggest that VHL may play a role in regulating exit form the cell cycle.



Microscopic section of hemangioblastoma, a tumor of the cerebellum characteriztically found in patients with von Hippel-Lindau disease. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=VHL&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507891&org=1] related sequences in different organisms

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=193300] catalog of human genes and disorders

Websites

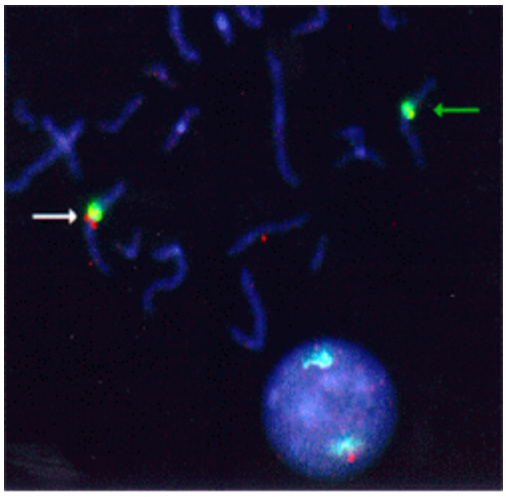
Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/vonhippe_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH

Williams syndrome

Williams syndrome is a rare congenital disorder characterized by physical and development problems. Common features include characteristic "elfin-like" facial features, heart and blood vessel problems, irritability during infancy, dental and kidney abnormalities, hyperacusis (sensitive hearing) and musculoskeletal problems. Although individuals with Williams syndrome may show competence in areas such as language, music and interpersonal relations, their IQs are usually low.

In Williams syndrome individuals, both the gene for elastin and an enzyme called LIM kinase are deleted. Both genes map to the same small area on chromosome 7. In normal cells, elastin is a key component of connective tissue, conferring its elastic properties. Mutation or deletion of elastin lead to the vascular disease observed in Williams syndrome. On the other hand, LIM kinase is strongly expressed in the brain, and deletion of LIM kinase is thought to account for the impaired visuospatial constructive cognition in Williams syndrome.

Williams syndrome is a contiguous disease, meaning that the deletion of this section of chromosome 7 may involve several more genes. Further study will be required to round up all the genes deleted in this disease. The remarkable musical and verbal abilities of individuals with Williams syndrome, and their tendency to be very sociable, has lead to the suggestion that children with Williams syndrome were an inspiration for folktales and legends, as the 'wee, magical people' were often musicians and storytellers.



Williams syndrome is caused by a deletion of part of chromosome 7 that includes the LIM kinase and elastin coding sequences. Above, this sequence (stained red) can no longer be seen in the chromosome with the deletion (green arrow). [Photograph kindly provided by L. G. Shaffer, Baylor College of Medicine.]

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=LIM%20kinase%20OR%20elastin&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5881413&org=1] related sequences in different organisms

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Websites

GeneClinics [www.geneclinics.org/profiles/williams/] a medical genetics resource