National Center for Biotechnology Information (US)

Genes and Disease

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Genes and Disease is a collection of articles that discuss genes and the diseases that they cause. These genetic disorders are organized by the parts of the body that they affect. As some diseases affect various body systems, they appear in more than one chapter.

With each genetic disorder, the underlying mutation(s) is discussed, along with clinical features and links to key websites.

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Introduction to Genes and Disease

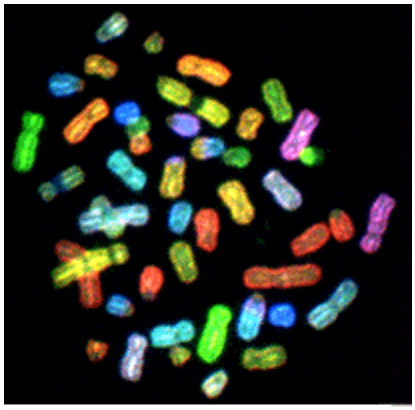
Genes and Disease is a collection of articles that discuss genes and the diseases that they cause. These genetic disorders are organized by the parts of the body that they affect. As some diseases affect various body systems, they appear in more than one chapter.

With each genetic disorder, the underlying mutation(s) is discussed, along with clinical features and links to key websites. You can browse through the articles online, and you can also download a printable file (PDF) of each chapter.

From *Genes and Disease* you can delve into many online related resources with free and full access. For example, you can visit the human genome to see the location of the genes implicated in each disorder. You can also find related gene sequences in different organisms. And for the very latest information, you can search for complete research articles, and look in other books in the NCBI Bookshelf.

Currently over 80 genetic disorders have been summarized, and the content of *Genes and Disease* is continually growing. Your ideas and suggestions are welcome. You can contact us at: info@ncbi.nlm.nih.gov.

Preface



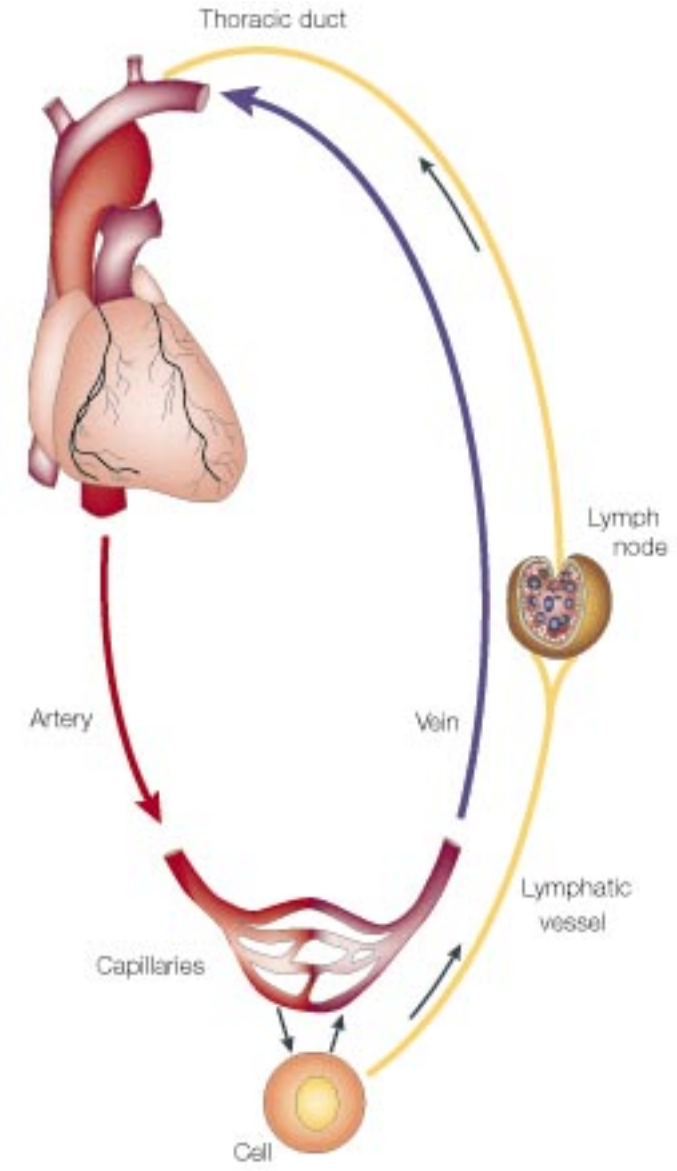
This photograph shows a complete set of chromosomes from an acute promyelocytic leukemia (APL) patient. A new technique called chromosome painting allows visual distinction between chromsomes and can be used to show the chromosome translocations that frequently occur in human cancers. In the case of APL, chromosome 13 is lost, there is a translocation between chromosomes 7 and 15, translocation between chromosomes 11, 15, 17, and between chromosomes 9 and 18. (Look for chromosomes painted with more than one color.) With thanks to Thomas Ried, National Human Genome Research Institute, NIH, for supplying the picture.

The sequence of the human genome is providing us with the first holistic view of our genetic heritage. While not yet complete, continued refinement of the data bring us ever closer to a complete human genome reference sequence. This will be a fundamental resource in future biomedical research.

The 46 human chromosomes (22 pairs of autosomal chromosomes and 2 sex chromosomes) between them house almost 3 billion base pairs of DNA that contains about 30,000 - 40,000 protein-coding genes. The coding regions make up less than 5% of the genome (the function of the remaining DNA is not clear) and some chromosomes have a higher density of genes than others.

Most of the genetic disorders featured on this web site are the direct result of a mutation in one gene. However, one of the most difficult problems ahead is to find out how genes contribute to diseases that have a complex pattern of inheritance, such as in the cases of diabetes, asthma, cancer and mental illness. In all these cases, no one gene has the yes/no power to say whether a person has a disease or not. It is likely that more than one mutation is required before the disease is manifest, and a number of genes may each make a subtle contribution to a person's susceptibility to a disease; genes may also affect how a person reacts to environmental factors. Unraveling these networks of events will undoubtedly be a challenge for some time to come, and will be amply assisted by the availability of the sequence of the human genome.

Blood and Lymph Diseases



The cardiovascular system consists of the heart as well as blood vessels (arteries, veins and capillaries) and lymphatic vessels. Arteries deliver oxygenated blood (red) to the capillaries where bidirectional exchange occurs between blood and tissues. Veins collect deoxygenated blood (blue) from the microvascular bed and carry it back to the heart. Lymphatic vessels (yellow) collect extravasated tissue fluid, filter it through lymph nodes and return it to the circulation through the thoracic and lymphatic ducts and the lymphaticovenous anastomoses (not shown). The lymphatic vascular system is not continuous like the blood vascular system. (Figure and legend reproduced from: Jones, N., et al. (2001) Tie receptors: new modulators of angiogenic and lymphangiogenic responses. *Nat. Rev. Mol. Cell Biol.* 2; 257-267, with permission.)

As most of the cells in the human body are not in direct contact with the external environment, the circulatory system acts as a transport system for these cells. Two distinct fluids move through the circulatory system: blood and lymph. Blood carries oxygen and nutrients to the body's cells, and carries waste materials away. Blood also carries hormones, which control body processes, and antibodies, to fight invading germs. The heart is the pump that keeps this transport system moving. Together, the blood, heart, and blood vessels form the circulatory system.

The lymphatic system (lymph, lymph nodes and lymph vessels) supports the circulatory system by draining excess fluids and proteins from tissues back into the bloodstream, thereby preventing tissue swelling. It also serves as a defense system for the body, filtering out organisms that cause disease, producing white blood cells, and generating antibodies.

The biochemical make up of lymph — the fluid found in the lymphatic vessels — varies with the site of origin. For example, lymph from bone marrow, spleen, and thymus have high concentrations of white blood cells for fighting infection, while lymph from intestines is high in fat that has been absorbed during digestion. Damage to the lymphatic and circulatory systems leaves the body more susceptible to sickness and infection, as well as to serious conditions such as cancer.

Diseases

Anemia, sickle cell

Burkitt lymphoma

Gaucher disease

Hemophilia A

Leukemia, chronic myeloid

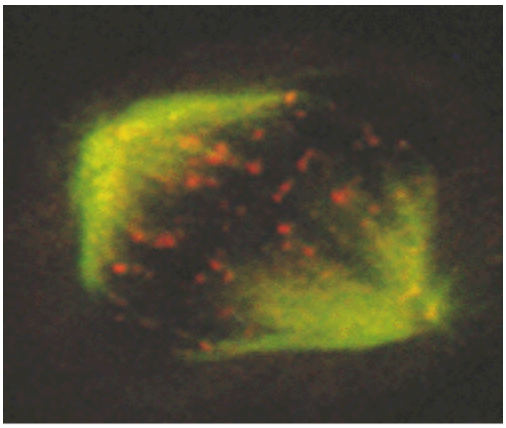
Niemann-Pick disease

Paroxysmal nocturnal hemoglobinuria

Porphyria

Thalassemia

Cancers



An immortal HeLa cell, originally derived from a human tumor, undergoing cell division. It is stained with anti-tubulin (green) and anti-CENP-E (red) antibodies. CENP-E, a kinesin, is associated with the centromeres of paired sister chromatids during metaphase. [Photograph by Tim Yen and colleagues, Fox Chase Cancer Center, PA, USA. Reproduced from Endow, SE (1993) Trends Genet. 9, 52-55, with permission.]

Cancer occurs when cell division gets out of control. Usually, the timing of cell division is under strict constraint, involving a network of signals that work together to say when a cell can divide, how often it should happen and how errors can be fixed. Mutations in one or more of the nodes in this network can trigger cancer, be it through exposure to some environmental factor (e.g. tobacco smoke) or because of a genetic predisposition, or both. Usually, several cancer-promoting factors have to add up before a person will develop a malignant growth: with some exceptions, no one risk alone is sufficient.

The predominant mechanisms for the cancers featured here are (i) impairment of a DNA repair pathway (ii) the transformation of a normal gene into an oncogene and (iii) the malfunction of a tumor supressor gene.

Diseases

Breast and ovarian cancer

Burkitt lymphoma

Colon cancer

Leukemia, chronic myeloid

Lung carcinoma, small cell

Malignant melanoma

Multiple endocrine neoplasia

Neurofibromatosis

The p53 tumor suppressor protein

Pancreatic cancer

Polycystic kidney disease

Prostate cancer

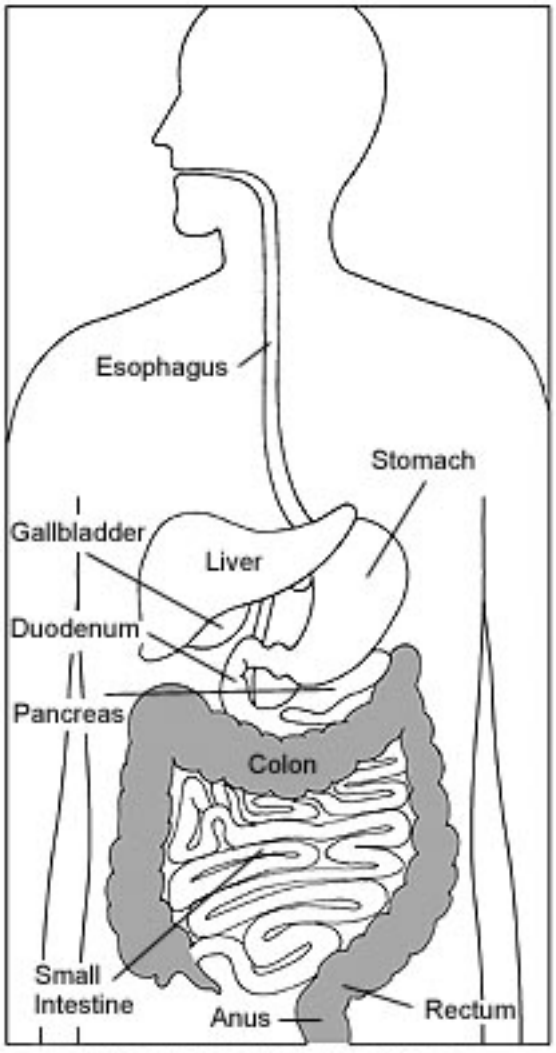
Harvey Ras oncogene

Retinoblastoma

Tuberous sclerosis

Von Hippel-Lindau syndrome

The Digestive System



The human digestive system.

Digestion is the process of turning food into fuel for energy, and for maintenance of the body structure. The digestive tract is a series of hollow organs joined in a long, twisting tube from the mouth to the anus. Inside this tube is a lining called the mucosa. In the mouth, stomach, and small intestine, the mucosa contains tiny glands that produce enzymes to help digest food. There are also two solid digestive organs, the liver and the pancreas, which produce enzymes that reach the intestine through small tubes.

During the digestive process, food passes down the throat, through the esophagus, and into the stomach, where food continues to be broken down. The partially digested food passes into a short tube called the duodenum — the first part of the small intestine. The jejunum and ileum are also part of the small intestine. The liver, the gallbladder, and the pancreas produce enzymes and substances to help with digestion in the small intestine. After the digestive process is complete, the resulting waste travels downstream to the colon. The colon and rectum are parts of the body's digestive system, which removes nutrients from food and stores waste until it passes out of the body. Together, the colon and rectum form a long, muscular tube called the large intestine.

The health of your digestive system has a lot to do with lifestyle — the food you eat, the amount of exercise you get, and the pace and stress level of your day. However, some digestive diseases, such as those discussed here, are thought to be hereditary or stem from an infection. For others, there is no known cause.

Diseases

Colon cancer

Crohn's disease

Cystic fibrosis

Diabetes, type 1

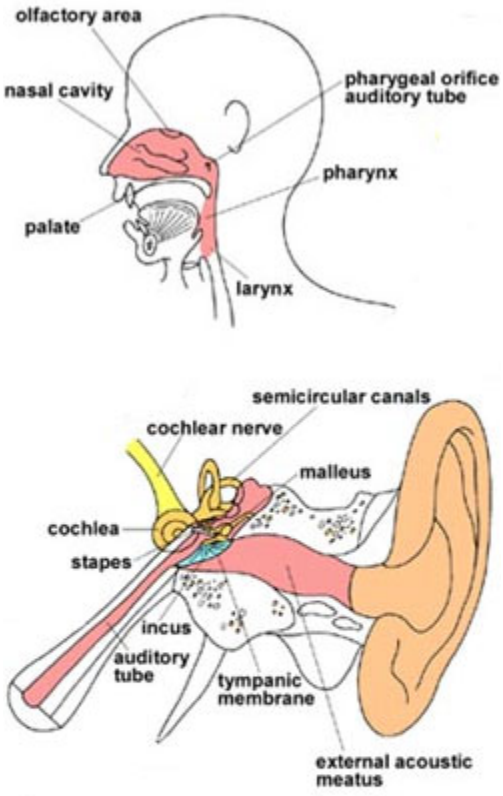
Glucose galactose malabsorption

Pancreatic cancer

Wilson's disease

Zellweger syndrome

Ear, Nose, and Throat



The human ear, nose and throat are related in their functions, and thus often in the disorders that affect them . The ear is connected with the nose and throat by the auditory (or Eustachian) tube, which leads to the pharynx.

[Reproduced from University of Maryland Medical School, Otolaryngology Health guide, with permission]

Within the structures of the ear, nose and throat are complex and interrelated mechanisms that allow a person to make sound, hear, maintain balance, smell, breathe, and swallow. Traditionally, treatment of the ear — otology — was associated with that of the eye in medical practice. With the development of laryngology — the study of the throat — in the late 19th century, the connection between the ear and throat became known. Thus the birth of a discipline called otolaryngology.

Many people associate otolaryngologists with the treatment of ear infections, hearing loss and sinus problems. Otolaryngology actually encompasses the treatment of many diverse conditions, including: dizziness, facial plastic and reconstructive surgery, head and neck cancer, hearing loss, problems of the larynx and sinus, difficulties swallowing, tumors of the auditory nerve, and voice production.

When diagnosing ear, nose, and throat disorders, it is important to differentiate genetic disorders from those due to environmental influences. This is often difficult as similar clinical features may be produced by different environmental factors or by different genes or groups of genes.

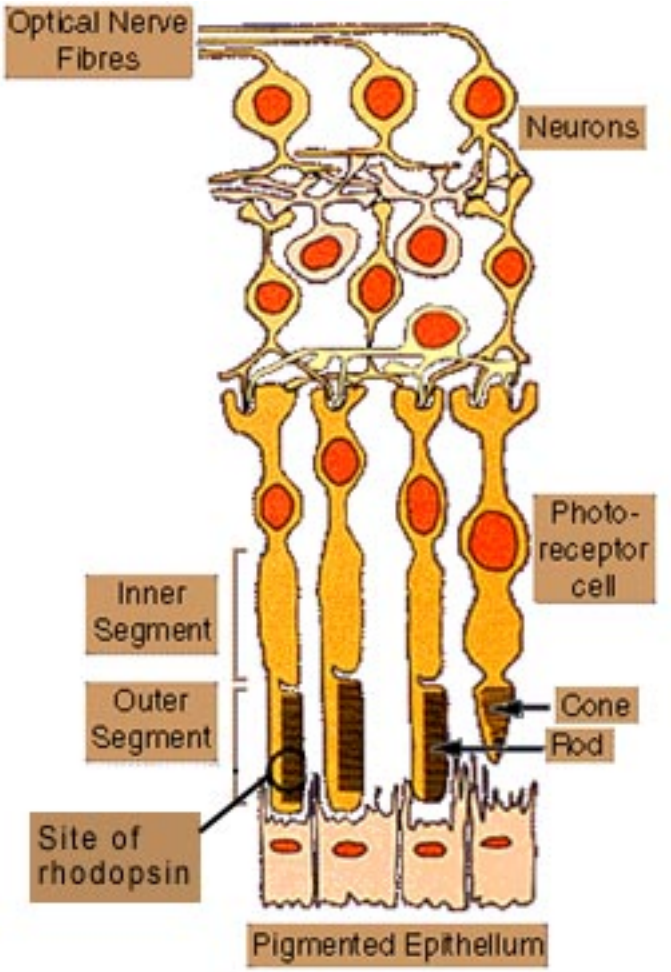
Diseases

Deafness

Neurofibromatosis

Pendred syndrome

Diseases of the Eye



In the eye, light enters the pupil, is focused and inverted by the cornea and lens, and then is projected onto the retina at the back of the eye. The retina consists of several layers of cells, shown above. The only light-sensitive step during vision takes place in the outer segment of photoreceptor cells, and is catalysed by the molecule rhodopsin. Light causes rhodopsin to change shape, which then triggers a signal to be sent through the layers of cells that make up the retina, resulting in a neural signal to the brain. (Adapted from Gebhard Schertler's web page, MRC-LMB, Cambridge, UK, with permission.)

The function of our eyes is to allow us to see the objects in our surroundings at variable distances and under various conditions of lights. This function is achieved by a very complex arrangement of layers and structures found in the eye. In addition, two pockets of transparent fluid — the aqueous and vitreous humors — nourish eye tissues and help maintain constant eye shape.

The eye is comprised of three layers: an outer protective white coating called the sclera; a middle layer (choroid) containing blood vessels which nourish the eye; and an inner layer (retina) which contains the nerves that bear information to the brain for processing.

The cornea is the clear portion found at the front of the eye and serves to bend light rays. The iris, an extension of the choroid, is the colored portion of the eye and is made up of a spongy tissue. The pupil (black) is an opening in the iris that allows light into the eye. The lens then helps focus the light rays onto photoreceptors,

which absorb and convert the light into electrical signals that carry information. The optic nerve contains fibers that transmit these signals to the brain for interpretation of the objects seen.

With the recent advances in molecular genetic techniques, new genes that cause eye disease are rapidly being identified, such as for those diseases discussed here. In many instances, these findings allow researchers to develop innovative strategies for preventing or slowing the progress of genetic eye diseases.

Diseases

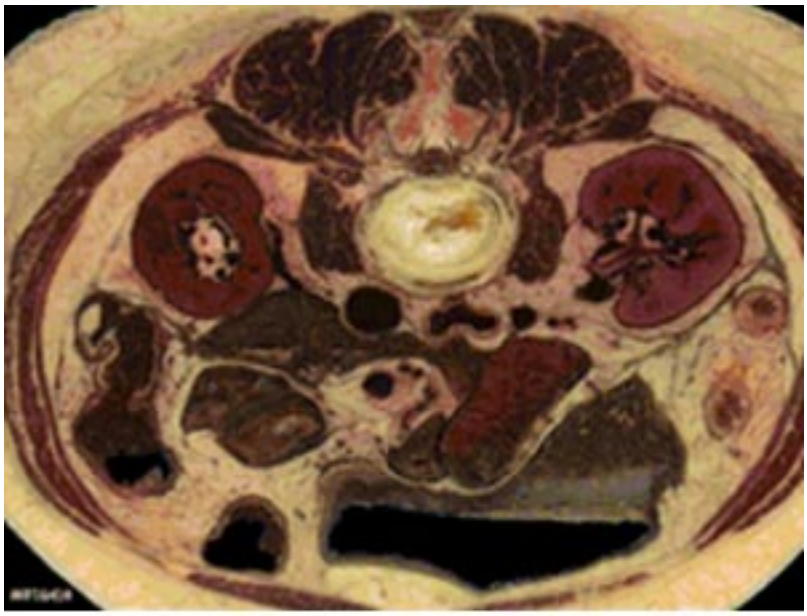
Best disease

Glaucoma

Gyrate atrophy of the choroid and retina

Retinoblastoma

Female-Specific Diseases



Axial view of visible woman. (From the Visible Human Project, National Library of Medicine.)

Biomedical research has demonstrated biological differences between females and males in virtually every organ and system of the body. Research has also revealed the genetic and molecular basis of a number of gender-based differences in health and disease, some of which are related to genotype — XX in the female and XY in the male.

These findings suggest that there are multiple differences in the basic cellular biochemistry of males and females that can affect an individual's health. Many of these differences do not arise from differences in the hormonal regime to which males and females are exposed, but are a direct result of the genetic differences between the two sexes.

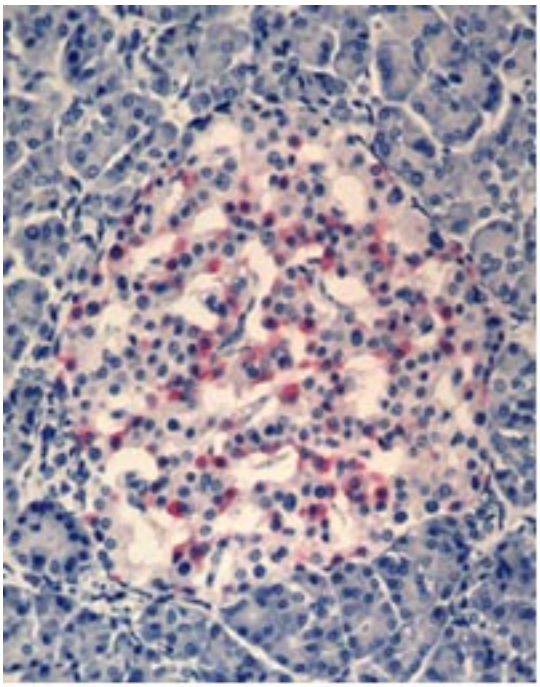
Further studies on the relative roles of the sex chromosome genes is likely to illuminate the reasons for expression of some diseases within and between the sexes. Understanding the bases of these gender-based differences is also important for the development of new approaches to disease prevention, diagnosis, and treatment.

Diseases

Breast and ovarian cancer

Rett syndrome

Glands and Hormones



The pancreas produces the hormones insulin, glucagon, and somatostatin. These are made in groups of cells known as the islets of Langerhans. One such islet is shown above. The average human pancreas has about one million islets, which are each composed of four cell types. In particular, alpha cells produce glucagon and beta cells produce insulin, which together are responsible for controling sugar metabolism; delta cells produce somatostatin, which inhibits growth hormone, insulin, glucagon and other physiologically important compounds. (Repoduced from Brown Medical School Slide Collection, with permission.)

The endocrine system is a complex collection of hormone-producing glands that control basic body functions such as metabolism, growth and sexual development. The endocrine glands consist of: pineal; pituitary; thyroid and parathyroids; thymus; adrenals; pancreas; ovaries (female); and testes (male).

Hormones are the chemical signaling molecules produced by the endocrine glands and secreted directly into the bloodstream. They travel through the blood to distant tissues and organs, where they can bind to specific cell sites called receptors. By binding to receptors, hormones trigger various responses in the tissues containing the receptors.

In addition to the classical endocrine organs, many other cells in the body secrete hormones. Myocytes in the atria of the heart and scattered epithelial cells in the stomach and small intestine are examples of what is sometimes called the "diffuse" endocrine system. If the term hormone is defined broadly to include all secreted chemical messengers, then virtually all cells can be considered part of the endocrine system.

Advances in molecular genetics have led to a greatly strengthened understanding of the mechanisms of certain of the hereditary endocrine disorders. This section of genes and disease focuses on disorders for which the primary gene defect has been characterized or recently identified.

Diseases

Adrenal hyperplasia, congenital

Adrenoleukodystrophy

Autoimmune polyglandular syndrome

Breast and ovarian cancer

Cockayne syndrome

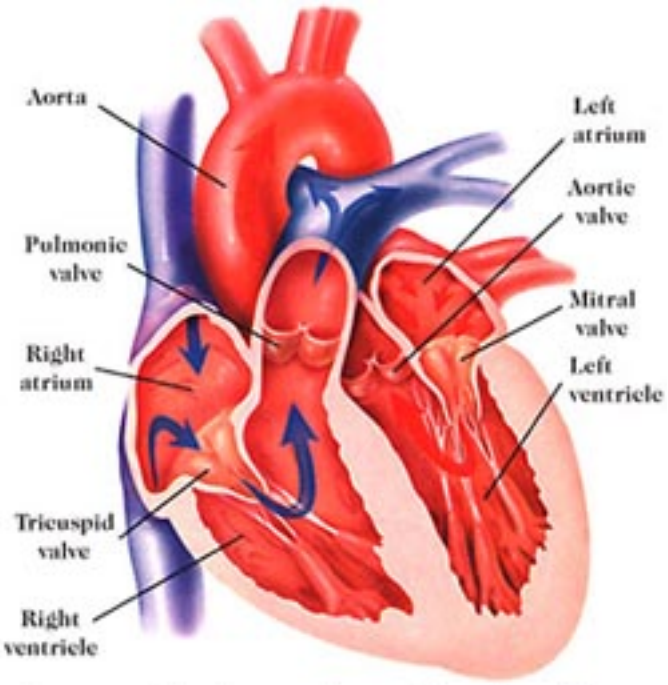
Diabetes, type 1

Diastrophic dysplasia

Multiple endocrine neoplasia

Pendred syndrome

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.

Diseases

Ataxia telangiectasia

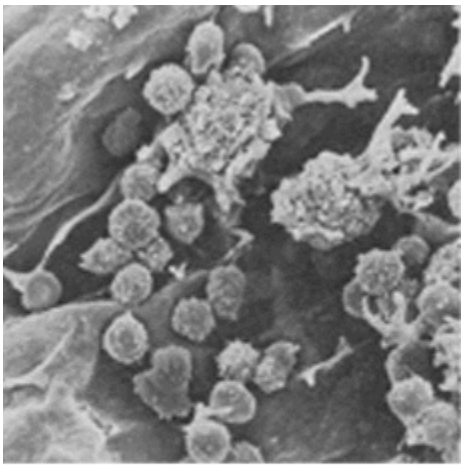
Atherosclerosis

Long QT syndrome

Von Hippel-Lindau syndrome

Williams syndrome

Diseases of the Immune System



Scanning electron micrograph of a lymph node. The large cells with multiple protrusions are macrophages; the smaller round cells are lymphocytes. A biconcave red blood cell can be seen on the left. (Micrograph by Willem van Ewijk, Dept Immunology, Erasmus University of Rotterdam, The Netherlands.)

The immune system is a complex and highly developed system, yet its mission is simple: to seek and kill invaders. If a person is born with a severely defective immune system, death from infection by a virus, bacterium, fungus or parasite will occur. In severe combined immunodeficiency, lack of an enzyme means that toxic waste builds up inside immune system cells, killing them and thus devastating the immune system. A lack of immune system cells is also the basis for DiGeorge syndrome: improper development of the thymus gland means that T cell production is diminished.

Most other immune disorders result from either an excessive immune response or an 'autoimmune attack'. Asthma, familial Mediterranean fever and Crohn's disease (inflammatory bowel disease) all result from an over-reaction of the immune system, while autoimmune polyglandular syndrome and some facets of diabetes are due to the immune system attacking 'self' cells and molecules. A key part of the immune system's role is to differentiate between invaders and the body's own cells - when it fails to make this distinction, a reaction against 'self' cells and molecules causes autoimmune disease.

Diseases

Asthma

Ataxia telangiectasia

Autoimmune polyglandular syndrome

Burkitt lymphoma

Diabetes, type 1

DiGeorge syndrome

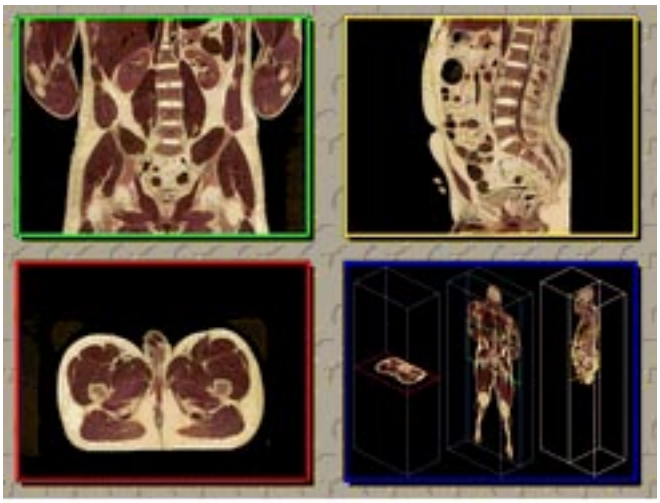
Familial Mediterranean fever

Immunodeficiency with hyper-IgM

Leukemia, chronic myeloid

Severe combined immunodeficiency

Male-Specific Diseases



Main Screen of Visible Human Explorer (Visible Man), Visible Human Project, National Library of Medicine.

What kind of biological mechanisms lie behind the formation of the different genders? Some scientists now conclude that cells from male and female organisms differ in ways that result from chromosomes, not hormones, and believe that every organ in the body — not just those related to reproduction — has the capability to respond differently on the basis of sex. For example, unique or gender-specific features of human biology have been found in skin, bone, heart and brain, to name just a few. In addition, many diseases are expressed differently in men and women.

Researchers are working to identify and understand differences related to the cause, prevention, treatment and impact of diseases and conditions which primarily affect men or women, or which affect men and women differently — with particular emphasis on gender and sex as key variables. Such differences can have a significant impact on the prevention, diagnosis and treatment of disease in both sexes.

Diseases

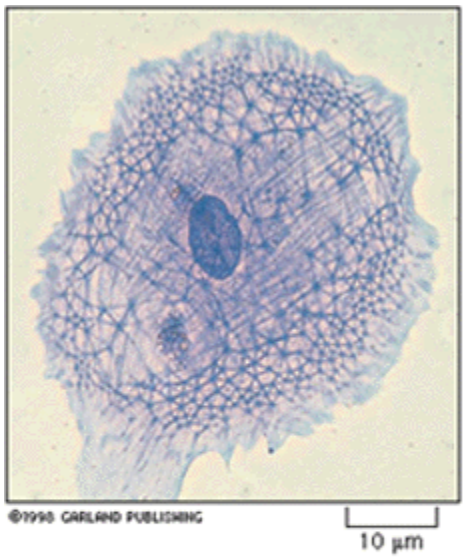
Alport syndrome

Male pattern baldness

Prostate cancer

SRY: Sex determination

Muscle and Bone



A cultured fibroblast (connective tissue cell) stained with Coomassie blue, a general stain for proteins. Many filamentous structures, which together make up the cytoskeleton, can be seen. The blue central oval is the nucleus. [Reproduced from Alberts et al. (1998) Essential Cell Biology, Garland Publishing Inc., with permission.]

The skeleton provides an anchor point against which muscles, attached via tendons, can exert force. There are a number of diseases that are caused by defects in genes important for the formation and function of muscles, and connective tissues. (Connective tissue is a broad term that includes bones, cartilage and tendons.)

Defects in fibrillin - a connective tissue proteins that is important in making the tissue strong yet flexible - cause Marfan syndrome, while diastrophic dysplasia is caused by a defect in a sulfate transporter found in cartilage.

Two diseases that originate through a defect in the muscle cells themselves are Duchenne muscular dystrophy (DMD) and myotonic dystrophy (DM). DM is another 'dynamic mutation' disease, similar to Huntington disease, that involves the expansion of a nucleotide repeat, this time in a muscle protein kinase gene. DMD involves a defect in the cytoskeletal protein, dystrophin, which is important for maintaining cell structure.

While the gene for Ellis-van Creveld syndrome has been mapped, we await the function of the protein to understand the molecular basis for this disease.

Diseases

Achondroplasia

Amyotrophic lateral sclerosis

Charcot-Marie-Tooth syndrome

Cockayne syndrome

Diastrophic dysplasia

Duchenne muscular dystrophy

Ellis-van Creveld syndrome

Fibrodysplasia ossificans progressiva

Marfan syndrome

Myotonic dystrophy

Neonatal Diseases

The human genome is often referred to as a "blueprint" and contains all of the information and instructions necessary for defining a human being. The term genome refers collectively to the DNA and associated protein molecules contained in an organism or a cell. The human genome consists of 23 pairs of chromosomes — threadlike packages of genes and other DNA — with each parent contributing one chromosome to each pair.

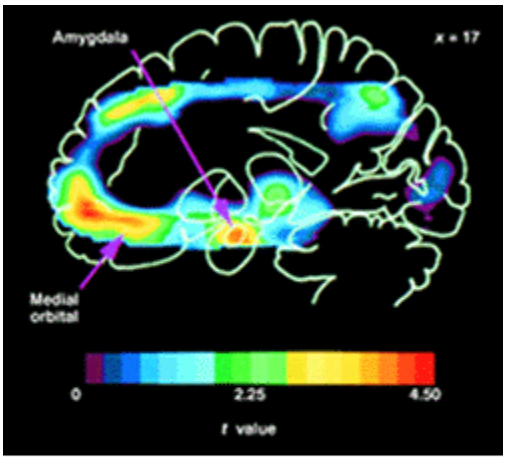
A gene is a specific sequence of DNA and is actually the functional unit of inheritance. Most genes contain the information needed to make a protein, or molecules that carry out all of a cell's vital activities. Therefore, slight variations in genes lead to slight changes in a protein. Although some human diseases are explained by alterations in a single gene or of a single chromosome, most are complex and may involve multiple genes and protein pathways.

A myriad of genes, as well as environmental factors, are believed to control the complex and integrated processes necessary for fetal development. When one or more of these processes goes awry, it can result in the birth of an individual with a genetic alteration. Scientific studies, often those that use other organisms as a model, will provide information about biological and regulatory processes involved in human development and will identify critical pathways in which genetic changes result in disease. This information will come not only from human studies, but also from other model organisms — such as mouse or yeast — that can provide insights into how key genes operate in complex systems.

Diseases

- Achondroplasia
- Angelman syndrome
- Cockayne syndrome
- Cystic fibrosis
- DiGeorge syndrome
- Fragile X syndrome
- Marfan syndrome
- Prader-Willi syndrome
- Severe combined immunodeficiency
- Waardenburg syndrome
- Werner syndrome
- Williams syndrome
- Zellweger syndrome

The Nervous System



One of the major areas in which molecular genetics will play an important role in the future is in complex disorders like schizophrenia and depression. The figure shows areas of increased bloodflow (red hotspots) in the left amygdala and the medial orbital cortex of a person with familial, major depressive order. The molecular basis for this observation, and others like it, remain a challenge for the future. [Reproduced from Andreasen, NC (1997) Science 275, 1586-1593, with permission.]

The brain and nervous system form an intricate network of electrical signals that are responsible for coordinating muscles, the senses, speech, memories, thought and emotion.

Several diseases that directly affect the nervous system have a genetic component: some are due to a mutation in a single gene, others are proving to have a more complex mode of inheritance. As our understanding of the pathogenesis of neurodegenerative disorders deepens, common themes begin to emerge: Alzheimer brain plaques and the inclusion bodies found in Parkinson disease contain at least one common component, while Huntington disease, fragile X syndrome and spinocerebellar atrophy are all 'dynamic mutation' diseases in which there is an expansion of a DNA repeat sequence. Apoptosis is emerging as one of the molecular mechanisms invoked in several neurodegenerative diseases, as are other, specific, intracellular signaling events. The biosynthesis of myelin and the regulation of cholesterol traffic also figure in Charcot-Marie-Tooth and Neimann-Pick disease, respectively.

Diseases

Adrenoleukodystrophy

Alzheimer disease

Amyotrophic lateral sclerosis

Angelman syndrome

Ataxia telangiectasia

Charcot-Marie-Tooth syndrome

Cockayne syndrome

Deafness

Duchenne muscular dystrophy

Epilepsy

Essential tremor

Fragile X syndrome

Friedreich's ataxia

Gaucher disease

Huntington disease

Lesch-Nyhan syndrome

Maple syrup urine disease

Menkes syndrome

Myotonic dystrophy

Narcolepsy

Neurofibromatosis

Niemann-Pick disease

Parkinson disease

Phenylketonuria

Prader-Willi syndrome

Refsum disease

Rett syndrome

Spinal muscular atrophy

Spinocerebellar ataxia

Tangier disease

Tay-Sachs disease

Tuberous sclerosis

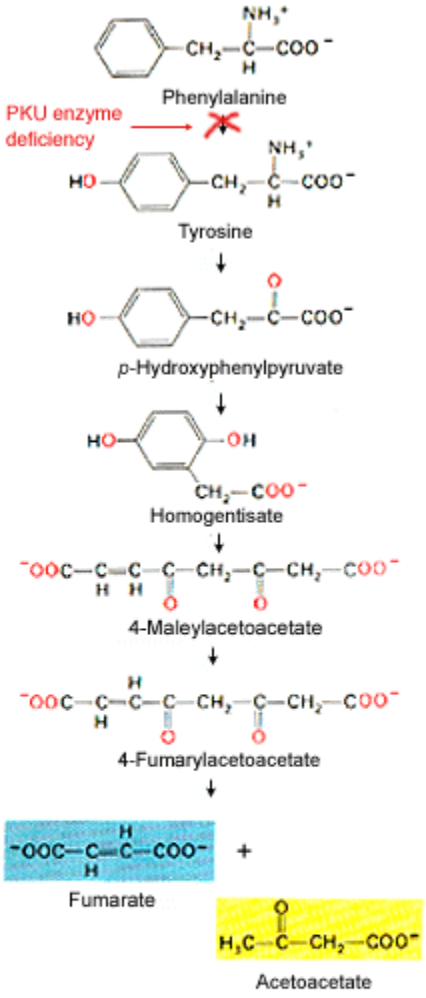
Von Hippel-Lindau syndrome

Williams syndrome

Wilson's disease

Zellweger syndrome

Nutritional and Metabolic Diseases



Surplus amino acids are broken down to make metabolic energy. The first step in the degradation pathway of phenylalanine and tyrosine requres the enzyme phenylalanine hydroxylase. Individuals lacking this enzyme suffer from phenylketonuria (PKU), an inborn error of metabolism. [Modified from Stryer, L. (1988) Biochemistry 3rd edn, W.H. Freeman and Co., with permission.]

Metabolism is the means by which the body derives energy and synthesizes the other molecules it needs from the fats, carbohydrates and proteins we eat as food, by enzymatic reactions helped by minerals and vitamins.

This global statement masks the complicated network of enzyme- catalyzed reactions that occurs in cells. Although this page is devoted to diseases caused by errors in metabolic processes, there is actually a significant level of tolerance of errors in the system: often, a mutation in one enzyme does not mean that the individual will suffer from a disease. A number of different enzymes may compete to modify the same molecule, and there may be more than one way to achieve the same end result for a variety of metabolic intermediates. Disease will only occur if a critical enzyme is disabled, or if a control mechanism for a metabolic pathway is affected.

Here, we highlight the diseases of metabolism for which a gene has been identified, cloned and mapped. Many of these are inborn errors of metabolism: inherited traits that are due to a mutation in a metabolic enzyme; others involve mutations in regulatory proteins and in transport mechanisms.

Diseases

Adrenoleukodystrophy

Diabetes, type 1

Gaucher disease

Glucose galactose malabsorption

Hereditary hemochromatosis

Lesch-Nyhan syndrome

Maple syrup urine disease

Menkes syndrome

Niemann-Pick disease

Obesity

Pancreatic cancer

Phenylketonuria

Prader-Willi syndrome

Porphyria

Refsum disease

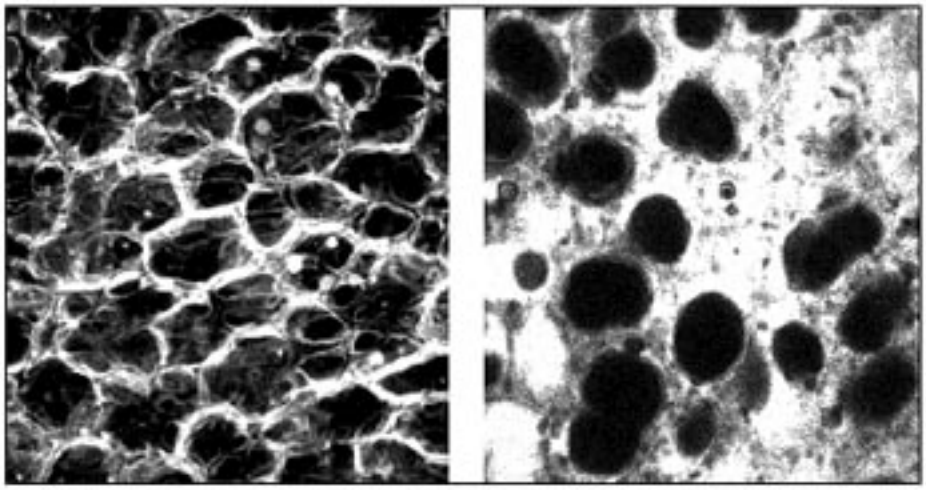
Tangier disease

Tay-Sachs disease

Wilson's disease

Zellweger syndrome

Respiratory Diseases



Laser confocal images of subpleural alveoli of a normal (left) and an edematous, or flooded (right) rat lung. The edema fluid appears white, the alveolar walls gray and airpockets are black. (Gajic and Lee, unpublished). (Reproduced from the web site of Rolf D Hubmayr, M.D., Mayo Clinic and Foundation, Rochester, MN, with permission.)

The respiratory system plays a vital role in delivering oxygen to the body — fuel for all the body's functions. It also removes carbon dioxide waste, eliminates toxic waste, regulates temperature, and stabilizes blood acid-alkaline balance (pH).

The lungs are the largest part of the respiratory system and have both "respiratory" and "non-respiratory" functions. The respiratory function involves gas exchange — the transfer of oxygen from the air into the blood and the removal of carbon dioxide from the blood. Non-respiratory lung functions are mechanical, biochemical, and physiological. The lungs provide a defense against bacterial, viral and other infectious agents; remove various metabolic waste products; control the flow of water, ions, and large proteins across its cellular structures; and manufacture a variety of essential hormones and chemical agents that have important biological roles.

Respiratory diseases can arise from a number of causes, including inhalation of toxic agents, accidents, and harmful lifestyles, such as smoking. Infections, genetic factors, and anything else that affects lung development, either directly or indirectly, can cause respiratory symptoms.

Diseases

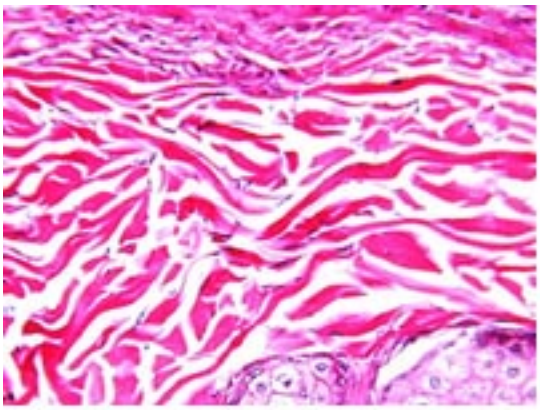
Alpha-1-antitrypsin deficiency

Asthma

Cystic fibrosis

Lung carcinoma, small cell

Skin and Connective Tissue



The dermis, shown above, is a layer of cells - mostly fibroblasts - that lies below the epidermis. Together these two layers make up the skin. The dermis is responsible for thermoregulation and the supply of nutrients to the epidermis. The fibroblasts secrete substances such as collagen and elastin, which supports and confers elasticity to the skin. The dermis is the tough connective tissue from which leather is made. (Reproduced from the website of David Hawkins, Ph.D, Exercise Biology Program, UC Davis, with permission.)

The skin is the largest organ in the body — both in weight and in surface area — and separates the body's internal environment from the external environment. The skin has many diverse roles. It acts as a channel of communication with the outside world; protects the body from water loss; uses specialized pigment cells, called melanocytes, to protect the body from ultraviolet radiation; participates in calcium homeostasis by contributing to the body's supply of vitamin D; and helps regulate body temperature and metabolism.

Elastic tissues such as the skin require a strong and resilient structural framework. This framework is called the extracellular matrix, or connective tissue. The orientation of the connective tissues — adipose (fat cells), cartilage, bone, tendons, and ligaments — found beneath the skin are also key for tissue appearance and function. All connective tissue is composed of three major classes of biomolecules: structural proteins (collagen and elastin), specialized proteins (fibrillin, fibronectin, and laminin), and proteoglycans.

Some skin and connective tissue diseases, such as those discussed in this section of genes and disease, are due strictly to genetic inheritance, while others do not have specific gene abnormalities as their sole cause. Many features of skin and connective tissue disorders overlap with each other, and with other disorders, even though they have unique genetic causes.

Diseases

Male pattern baldness

Diastrophic dysplasia

Ellis-van Creveld syndrome

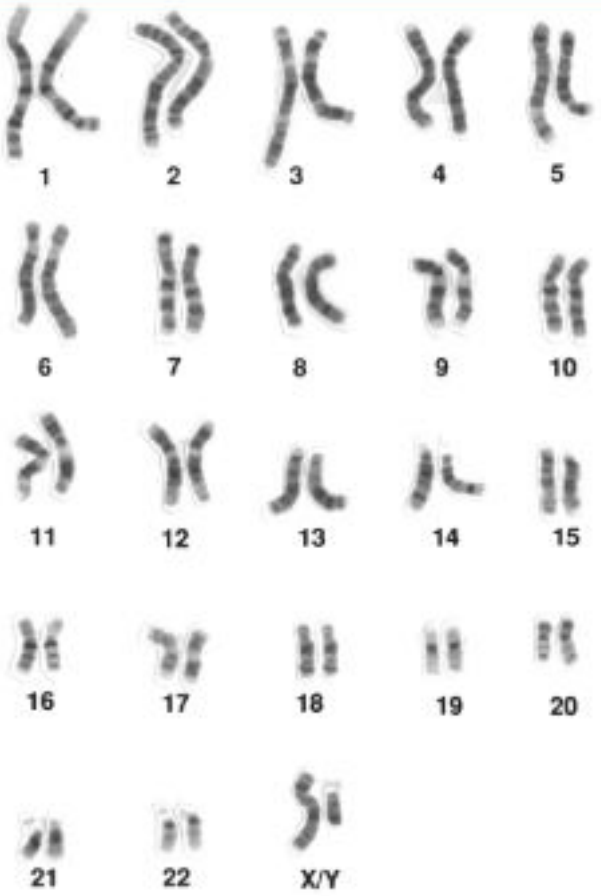
Marfan syndrome

Malignant melanoma

Menkes syndrome

Porphyria

Chromosome Map



Karyogram of a human male.
This is a photo of human chromosomes. They have been stained and arranged in order of decreasing size. The presence of the Y chromosome in the last pair of chromosomes tells us that these chromosomes are from a man.

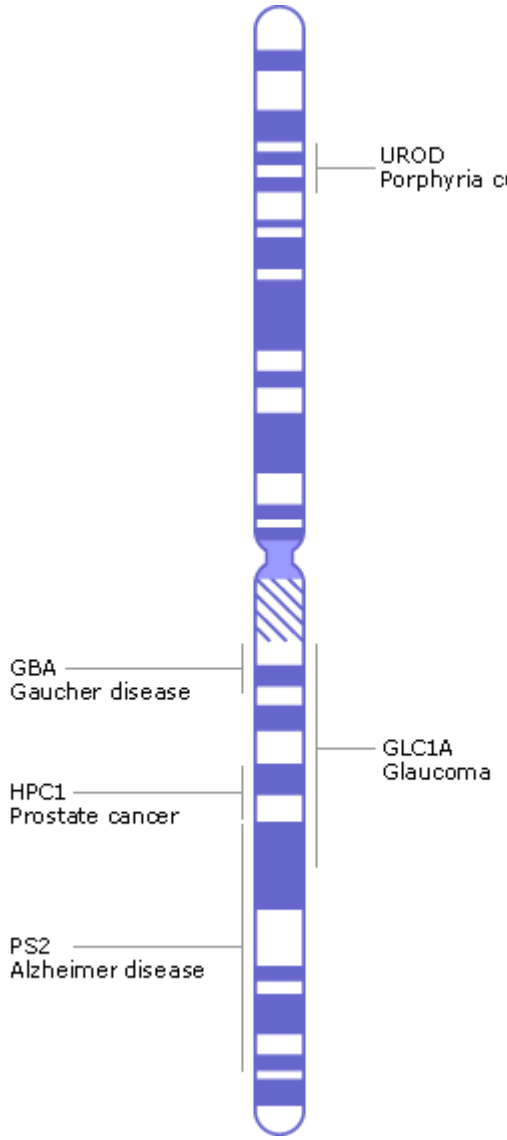
Our genetic information is stored in 23 pairs of chromosomes that vary widely in size and shape. Chromosome 1 is the largest and is over three times bigger than chromosome 22. The 23rd pair of chromosomes are two special chromosomes, X and Y, that determine our sex. Females have a pair of X chromosomes (46, XX), whereas males have one X and one Y chromosomes (46, XY). Chromosomes are made of DNA, and genes are special units of chromosomal DNA. Each chromosome is a very long molecule, so it needs to be wrapped tightly around proteins for efficient packaging.

Near the center of each chromosome is its centromere, a narrow region that divides the chromosome into a long arm (q) and a short arm (p). We can further divide the chromosomes using special stains that produce stripes known as a banding pattern. Each chromosome has a distinct banding pattern, and each band is numbered to help identify a particular region of a chromosome. This method of mapping a gene to a particular band of the chromosome is called cytogenetic mapping. For example, the hemoglobin beta gene (*HBB*) is found on chromosome 11p15.4. This means that the *HBB* gene lies on the short arm (p) of chromosome 11 and is found at the band labeled 15.4.

With the advent of new techniques in DNA analysis, we are able to look at the chromosome in much greater detail. Whereas cytogenetic mapping gives a bird's eye view of the chromosome, more modern methods show DNA at a much higher resolution. The Human Genome Project aims to identify and sequence the ~30,000 genes in human DNA.

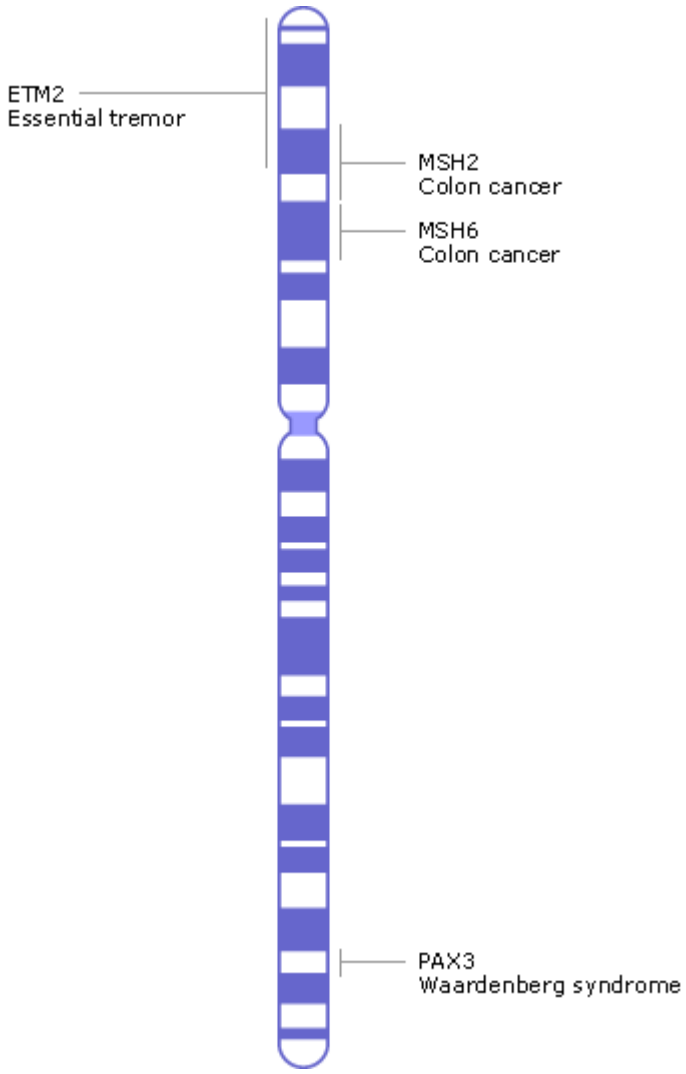
Chromosome 1

- Contains over 3000 genes
- Contains over 240 million base pairs, of which ~90% have been determined
- See the diseases associated with chromosome 1 in the NCBI Genome Data Viewer.



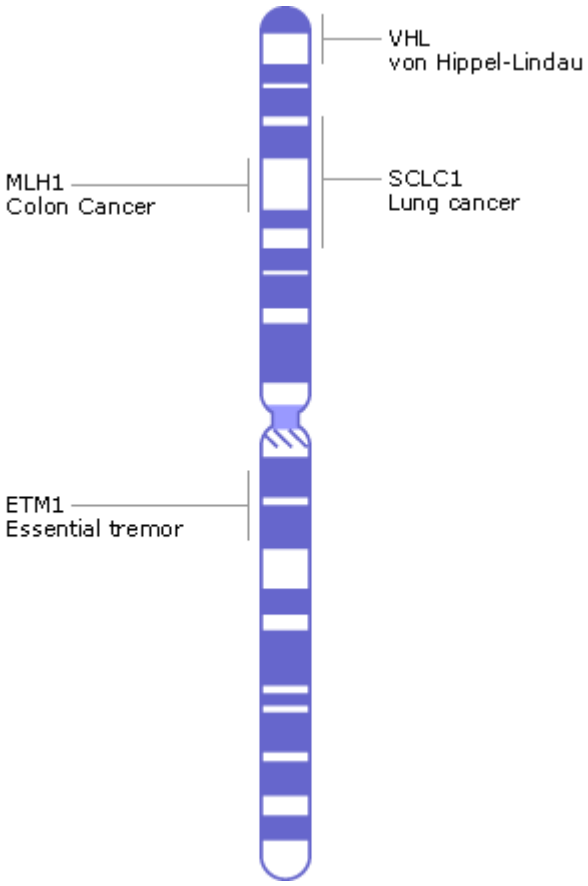
Chromosome 2

- Contains over 2500 genes
- Contains over 240 million base pairs, of which ~95% have been determined
- See the diseases associated with chromosome 2 in the NCBI Genome Data Viewer.



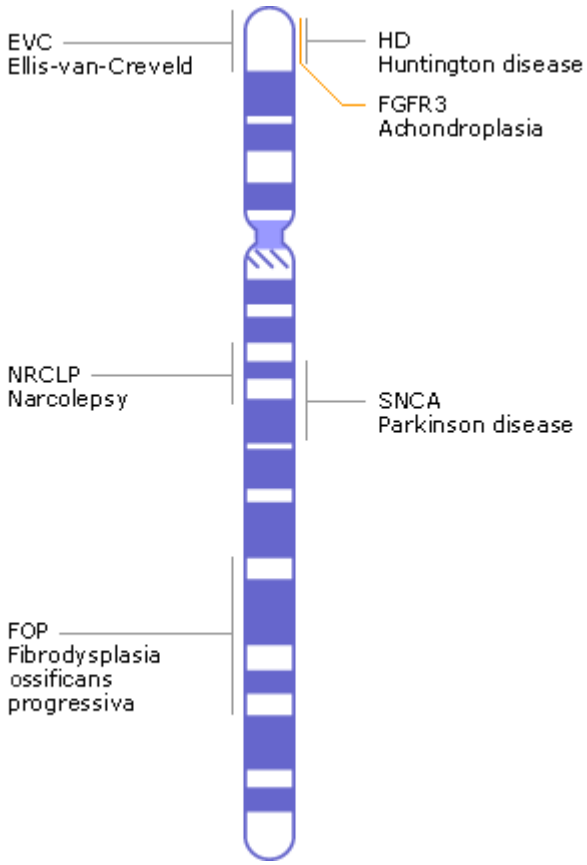
Chromosome 3

- Contains approximately 1900 genes
- Contains approximately 200 million base pairs, of which ~95% have been determined
- See the diseases associated with chromosome 3 in the NCBI Genome Data Viewer.



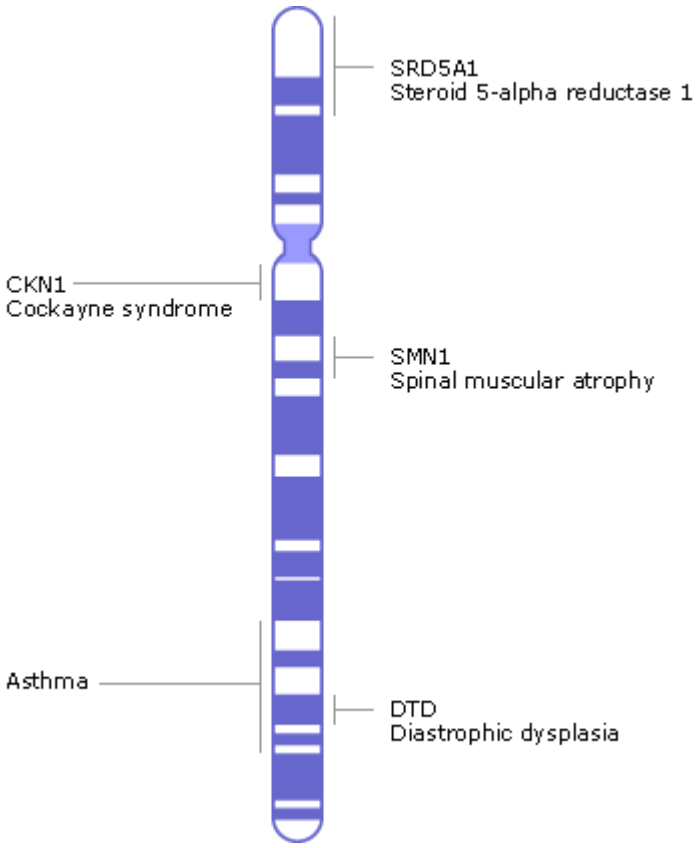
Chromosome 4

- Contains approximately 1600 genes
- Contains approximately 190 million base pairs, of which ~95% have been determined
- See the diseases associated with chromosome 4 in the NCBI Genome Data Viewer.



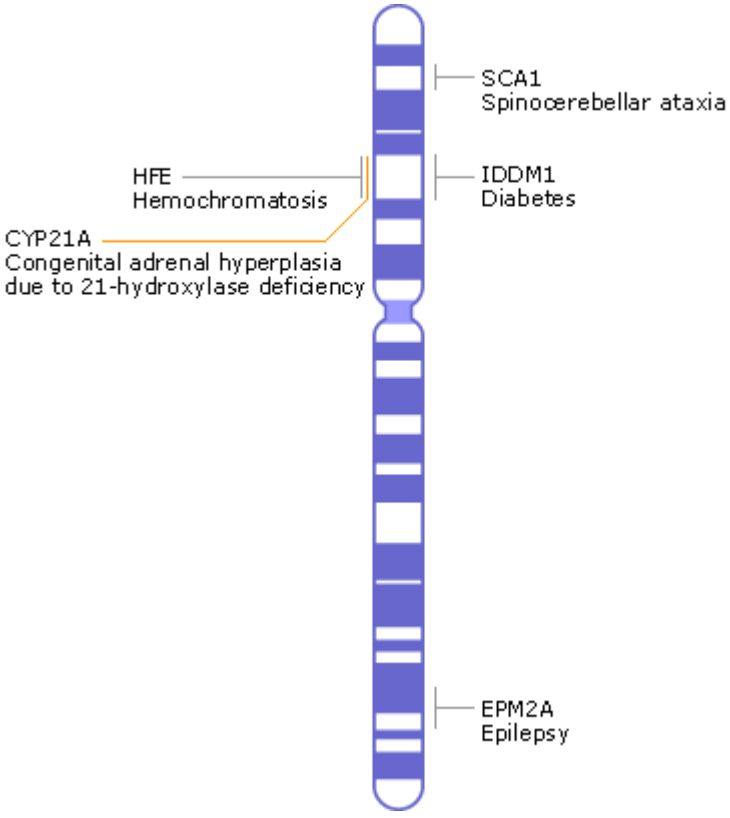
Chromosome 5

- Contains approximately 1700 genes
- Contains approximately 180 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 5 in the NCBI Genome Data Viewer.



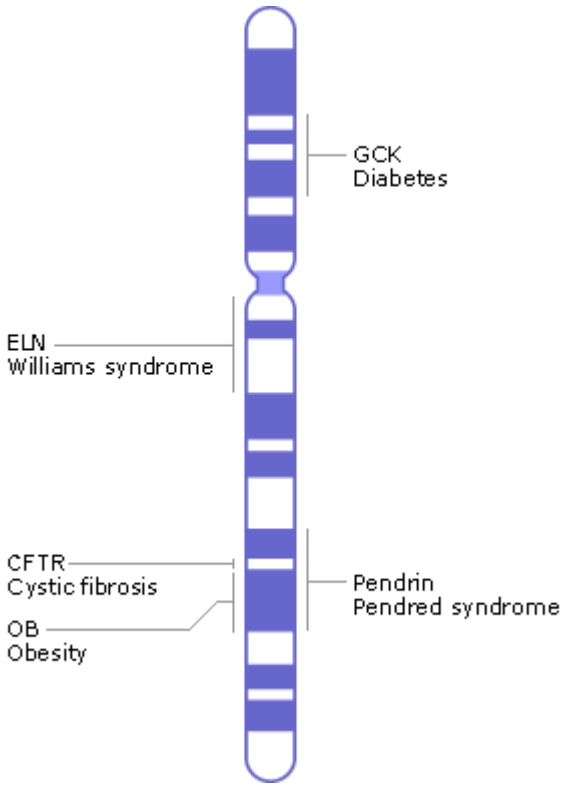
Chromosome 6

- Contains approximately 1900 genes
- Contains approximately 170 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 6 in the NCBI Genome Data Viewer.



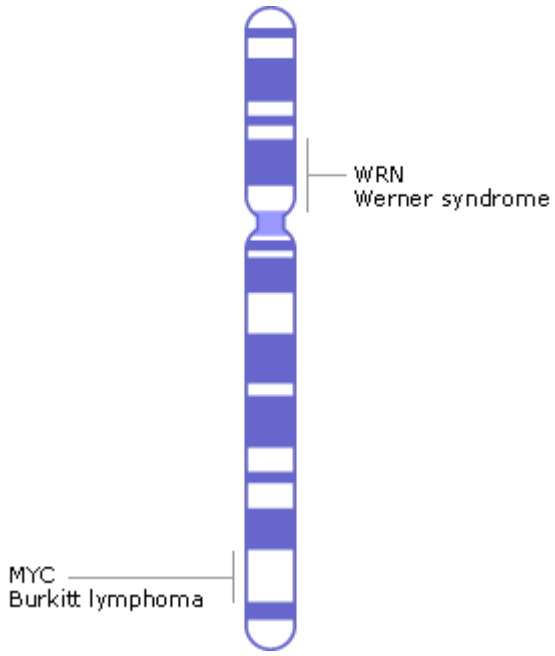
Chromosome 7

- Contains approximately 1800 genes
- Contains over 150 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 7 in the NCBI Genome Data Viewer.



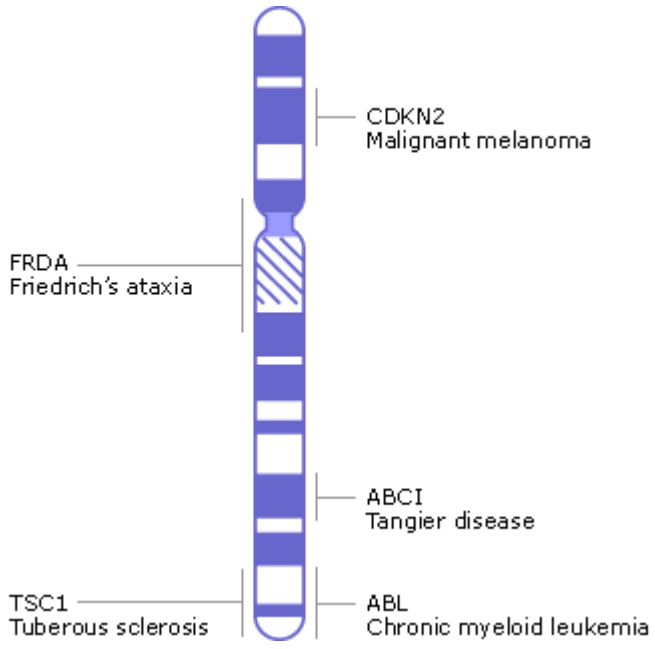
Chromosome 8

- Contains over 1400 genes
- Contains over 140 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 8 in the NCBI Genome Data Viewer.



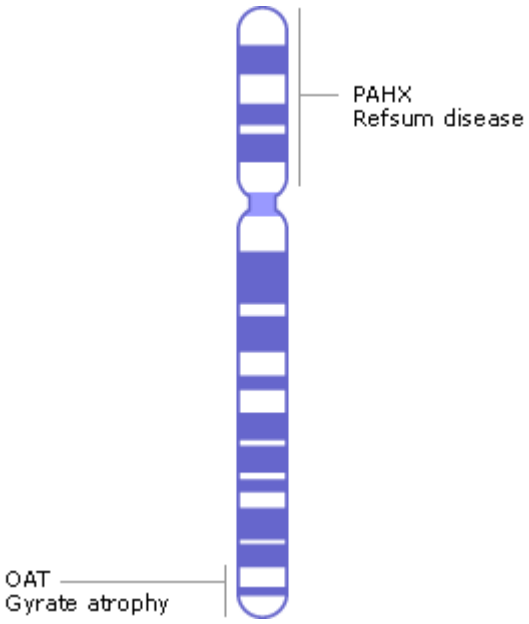
Chromosome 9

- Contains over 1400 genes
- Contains over 130 million base pairs, of which over 85% have been determined
- See the diseases associated with chromosome 9 in the NCBI Genome Data Viewer.



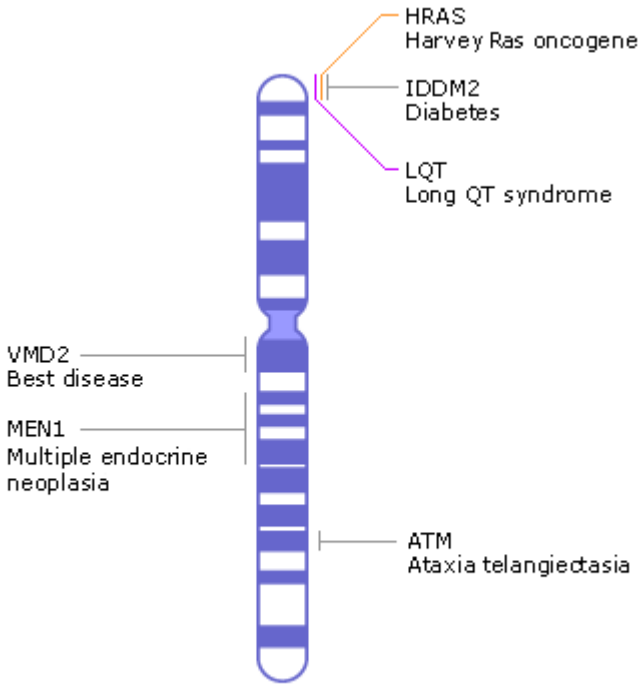
Chromosome 10

- Contains over 1400 genes
- Contains over 130 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 10 in the NCBI Genome Data Viewer.



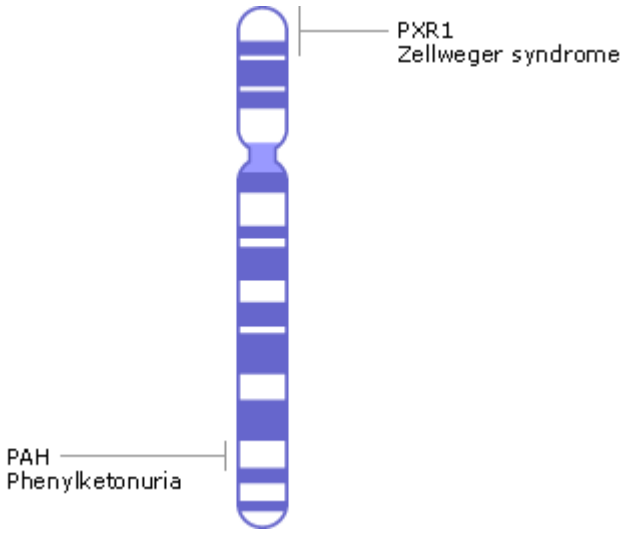
Chromosome 11

- Contains approximately 2000 genes
- Contains over 130 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 11 in the NCBI Genome Data Viewer.



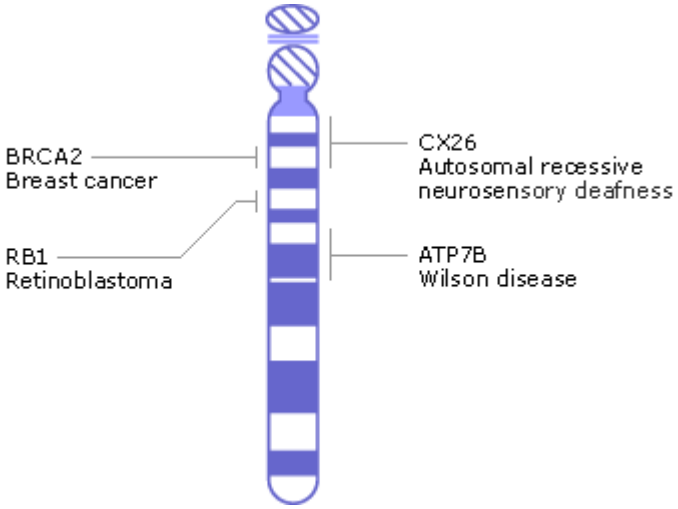
Chromosome 12

- Contains over 1600 genes
- Contains over 130 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 12 in the NCBI Genome Data Viewer.



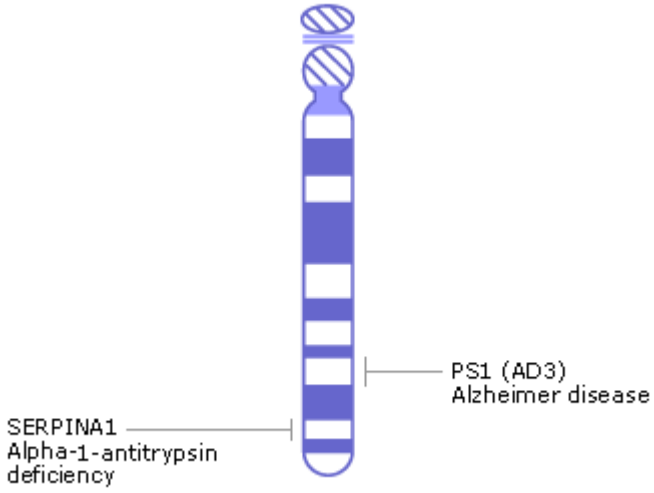
Chromosome 13

- Contains approximately 800 genes
- Contains over 110 million base pairs, of which over 80% have been determined
- See the diseases associated with chromosome 13 in the NCBI Genome Data Viewer.



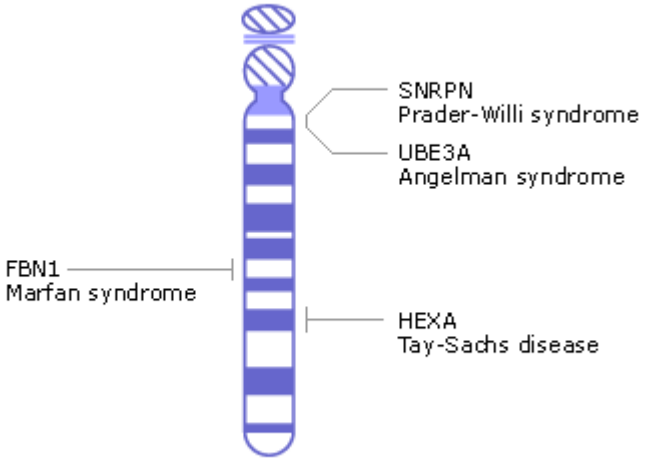
Chromosome 14

- Contains approximately 1200 genes
- Contains over 100 million base pairs, of which over 80% have been determined
- See the diseases associated with chromosome 14 in the NCBI Genome Data Viewer.



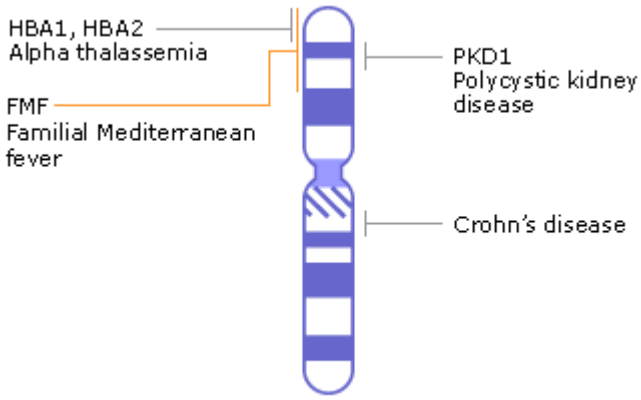
Chromosome 15

- Contains approximately 1200 genes
- Contains approximately 100 million base pairs, of which over 80% have been determined
- See the diseases associated with chromosome 15 in the NCBI Genome Data Viewer.



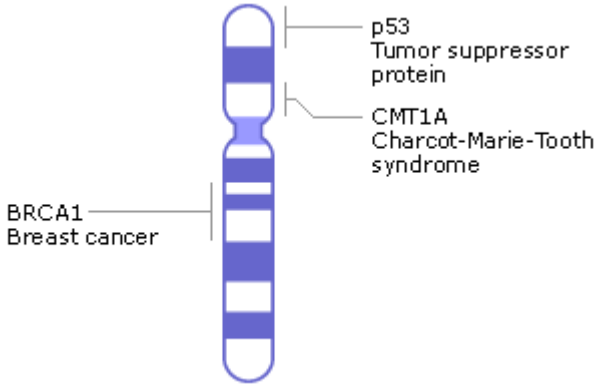
Chromosome 16

- Contains approximately 1300 genes
- Contains approximately 90 million base pairs, of which over 85% have been determined
- See the diseases associated with chromosome 16 in the NCBI Genome Data Viewer.



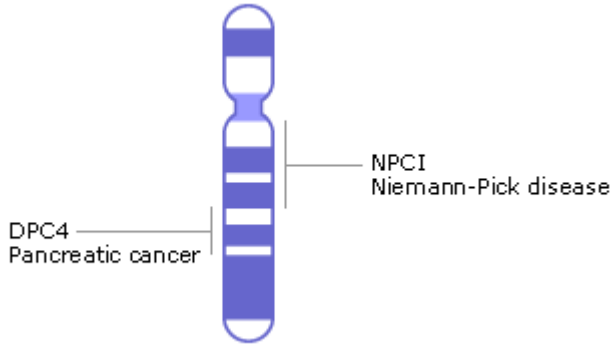
Chromosome 17

- Contains over 1600 genes
- Contains approximately 80 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 17 in the NCBI Genome Data Viewer.



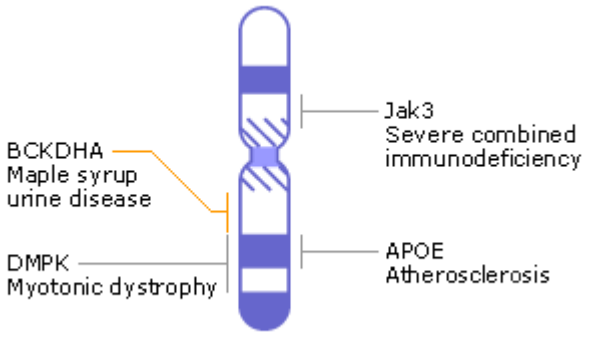
Chromosome 18

- Contains over 600 genes
- Contains over 70 million base pairs, of which over 95% have been determined
- See the diseases associated with chromosome 18 in the NCBI Genome Data Viewer.



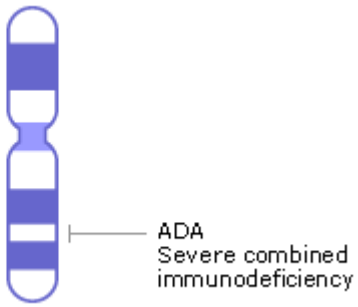
Chromosome 19

- Contains over 1700 genes
- Contains over 60 million base pairs, of which over 85% have been determined
- See the diseases associated with chromosome 19 in the NCBI Genome Data Viewer.



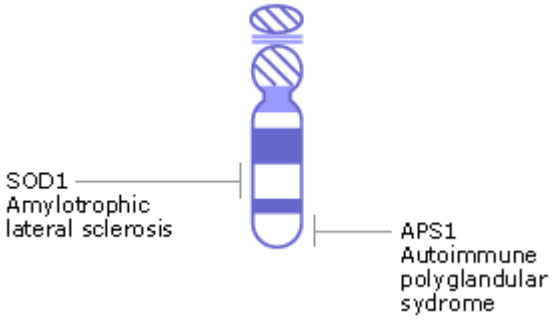
Chromosome 20

- Contains over 900 genes
- Contains over 60 million base pairs, of which over 90% have been determined
- See the diseases associated with chromosome 20 in the NCBI Genome Data Viewer.



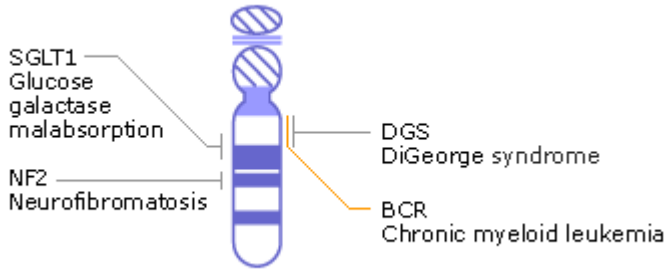
Chromosome 21

- Contains over 400 genes
- Contains over 40 million base pairs, of which over 70% have been determined
- See the diseases associated with chromosome 21 in the NCBI Genome Data Viewer.



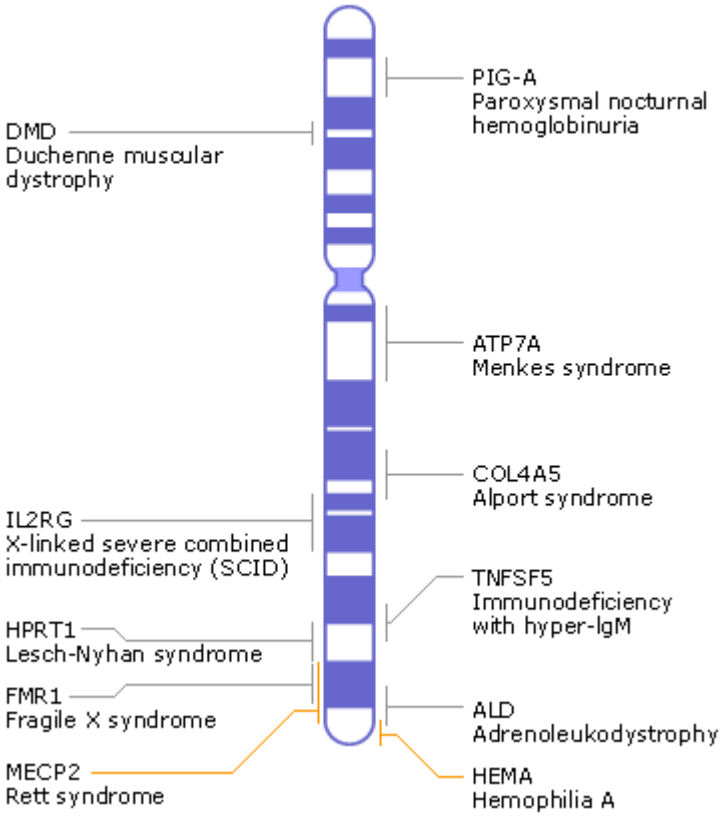
Chromosome 22

- Contains over 800 genes
- Contains over 40 million base pairs, of which approximately 70% have been determined
- See the diseases associated with chromosome 22 in the NCBI Genome Data Viewer.



Chromosome X

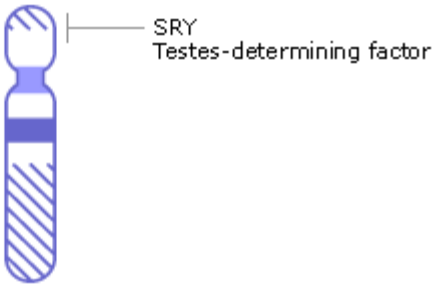
- Contains over 1400 genes
- Contains over 150 million base pairs, of which approximately 95% have been determined
- See the diseases associated with chromosome X in the NCBI Genome Data Viewer.



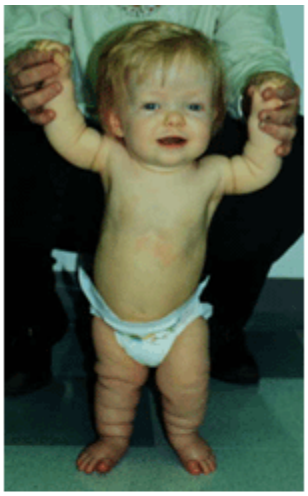
Chromosome Y

- Contains over 200 genes

- Contains over 50 million base pairs, of which approximately 50% have been determined
- See the diseases associated with chromosome Y in the NCBI Genome Data Viewer.



Achondroplasia



Achondroplasia. This girl has disproportionate shortening of the limbs that is more marked in the upper arms and upper legs (rhizomelic shortening). She also has a prominent forehead (frontal bossing) and depressed nasal bridge.

[Image credit: Jorde, Carey, Bamshad, White; Medical Genetics 2nd Edition © 1999, with permission from Elsevier.]

Achondroplasia is a Greek word meaning "without cartilage formation" and is one of the most common causes of dwarfism. The appearance is of short stature with disproportionately short arms and legs and a large head. The characteristic facial features include a prominent forehead and a flattened bridge of the nose.

Although this condition can be inherited in an autosomal dominant manner, 80% of cases are due to new, sporadic mutations. Mutations involve the gene encoding fibroblast growth factor receptor 3 (FGFR3), situated on chromosome 4. Most commonly, a point mutation causes the substitution of arginine for glycine (G380R) in the transmembrane region of the receptor.

There is growing evidence that mutations of FGF3R confer a "gain of function". It is proposed that the normal function of FGFR3 is to slow down the formation of bone by inhibiting the proliferation of chondrocytes, the cells that produce cartilage. The mutation increases the activity of FGFR3, severely limiting bone growth.

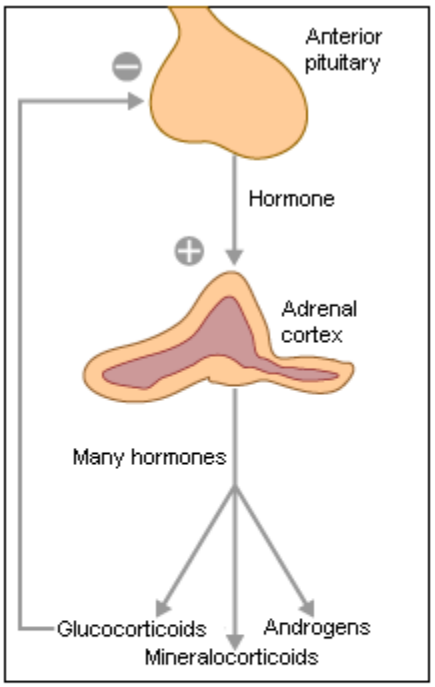
This theory is supported by the knock-out mouse model in which the receptor is absent, and so the negative regulation of bone formation is lost. The result is a mouse with excessively long bones and elongated vertebrae, resulting in a long tail. Achondroplastic mouse models are useful tools in developing potential treatments.

Related diseases

See other Muscle and Bone Diseases

See other Neonatal Diseases

Adrenal hyperplasia, congenital



The adrenal cortex is stimulated (+) to produce many hormones that have a wide range of effects on the body. One effect of the glucocorticoid cortisol is to regulate this production. If levels of hormones are adequate, cortisol feeds back this information to the anterior pituitary and inhibits (-) any further stimulation of the adrenal gland.

Click here for further information

Congenital adrenal hyperplasia (CAH) is a genetic disease that affects the adrenal glands. The production of several important hormones is blocked.

One adrenal gland sits on top of each kidney. The outer cortex of the gland secretes three types of hormones that may be missing in CAH:

- Corticosteroids, such as cortisol, are important in the body's response to illness or injury.
- Mineralocorticoids, such as aldosterone, regulate the levels of salt and water in the body.
- Androgens, such as testosterone, are the sex hormones.

The most common cause of CAH is a deficiency of the enzyme 21-hydroxylase. The gene for this enzyme lies on chromosome 6. There are two copies of the gene because of a duplication that occurred hundreds of thousands of years ago. One gene is called CYP21 and is the active gene; the other is called CYP21P and is inactive. The 21-hydroxylase deficiency is unique because most mutations result from the transfer of genetic information between inactive and active genes.

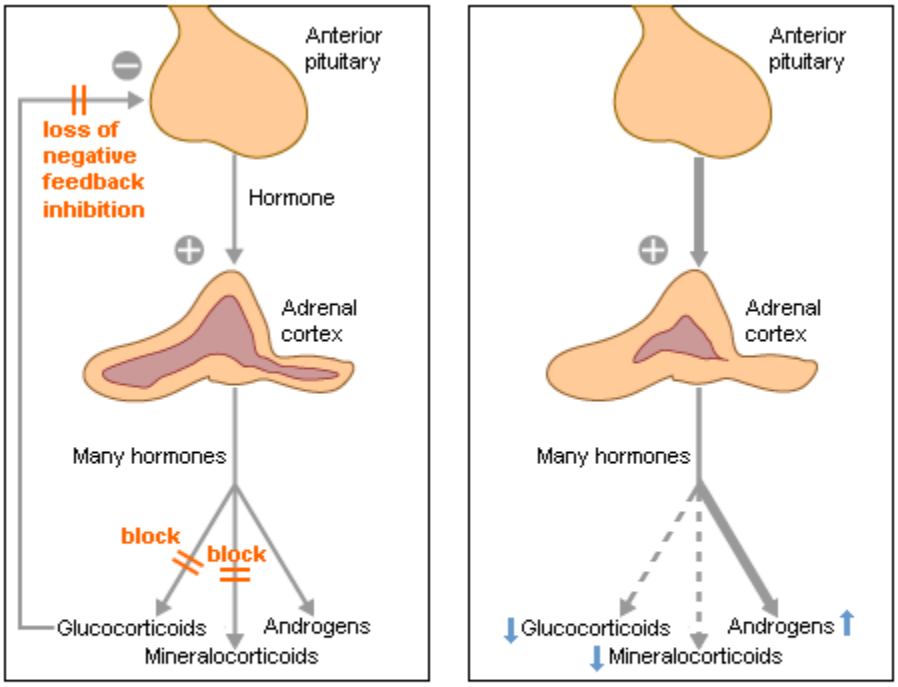
Various mutations of the 21-hydroxylase gene result in various levels of enzyme. As a consequence, there is a spectrum of effects.

In the absence of 21-hydroxylase, affected individuals are unable to make cortisol and aldosterone. The adrenal gland responds by trying to increase production of all its hormones. The number of cells increases, a phenomenon called adrenal hyperplasia. Other hormones such as androgens are pathologically overproduced.

But because of the missing enzyme, cortisol and aldosterone levels still do not rise. Cortisol deficiency causes low levels of sugar in the blood. Aldosterone deficiency can cause a "salt wasting crisis" where the body loses too much salt and, eventually, water.

The effects of CAH can begin in the womb. An affected fetus can produce high levels of androgens. This may result in girls being born with masculine-appearing external genitals. In boys, it may result in early sexual development.

CAH cannot be cured, but it can be treated by replacing the missing hormones. In particular, it is essential to give more cortisol in times of stress. A mouse deficient in 21-hydroxylase is proving to be a useful model in which to test new types of treatment.



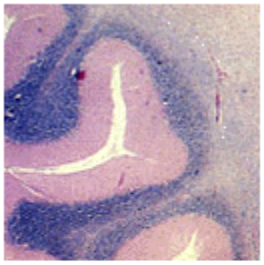
Loss of the enzyme 21-hydroxylase blocks the production of glucocorticoids and mineralocorticoids. Levels of cortisol are low, and the anterior pituitary is no longer inhibited.

As a result, the anterior pituitary produces more hormone to stimulate the adrenal cortex. The cortex becomes thickened (hypertrophied). The cortex is only able to produce androgens, which it produces in high amounts.

Related diseases

See other Glands and Hormones Diseases

Adrenoleukodystrophy



Myelin-stained section of brain in adrenoleukodystrophy, showing build-up of long-chain fatty acids [With thanks to Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA, for supplying the image.]

Adrenoleukodystrophy (ALD) is a rare, inherited metabolic disorder that afflicts the young boy Lorenzo Odone, whose story is told in the 1993 film "Lorenzo's oil." In this disease, the fatty covering (myelin sheath) on nerve fibers in the brain is lost, and the adrenal gland degenerates, leading to progressive neurological disability and death.

People with ALD accumulate high levels of saturated, very long chain fatty acids in their brain and adrenal cortex because the fatty acids are not broken down by an enzyme in the normal manner. So, when the *ALD* gene was discovered in 1993, it was a surprise that the corresponding protein was in fact a member of a family of transporter proteins, not an enzyme. It is still a mystery as to how the transporter affects the function the fatty acid enzyme and, for that matter, how high levels of very long chain fatty acids cause the loss of myelin on nerve fibers.

More recently, all the transporters related to ALD protein have been found in the yeast *Saccharomyces cerevisiae*, and a mouse model for the human disease has been developed. These and other molecular biology approaches should further our understanding of ALD and hasten our progress toward effective therapies.

Related diseases

See other Glands and Hormones Diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Alpha-1-antitrypsin deficiency

Updated: January 31, 2011.

Alpha-1-antitrypsin (AAT) is a protein that protects the body from damage by its immune cells. Deficiency of this protein leaves the lung, and occasionally the liver, vulnerable to injury.

The lung contains many tiny air sacs called alveoli. Oxygen travels across their walls into the bloodstream.

White blood cells release elastase, a powerful enzyme that can fight infections. But it can also attack normal tissues. If uncontrolled elastase is released around alveoli, it would destroy their walls and surrounding tissue, leaving areas of trapped air. This abnormal accumulation of air in the lungs is called emphysema and causes shortness of breath.

AAT inhibits elastase around normal tissue. Deficiency is caused by mutations in the SERPINA1 gene, located on chromosome 14. This gene has many different versions (alleles) that produce different amounts of AAT. The M allele produces normal levels of the AAT protein, the S allele produces moderately low levels, and the Z allele produces very low levels.

The alleles are expressed in a codominant manner — that means that a person with MZ has levels of AAT that are between the levels of those people who have alleles MM or ZZ.

Individuals who have at least one normal allele (MZ or MS) or two copies of S (SS) usually produce enough AAT to protect the lungs but do have an increased risk of lung disease. The risk is particularly high if they smoke. Individuals who inherit the Z allele from each parent (ZZ) have very low AAT and are at a higher risk of developing emphysema and liver disease.

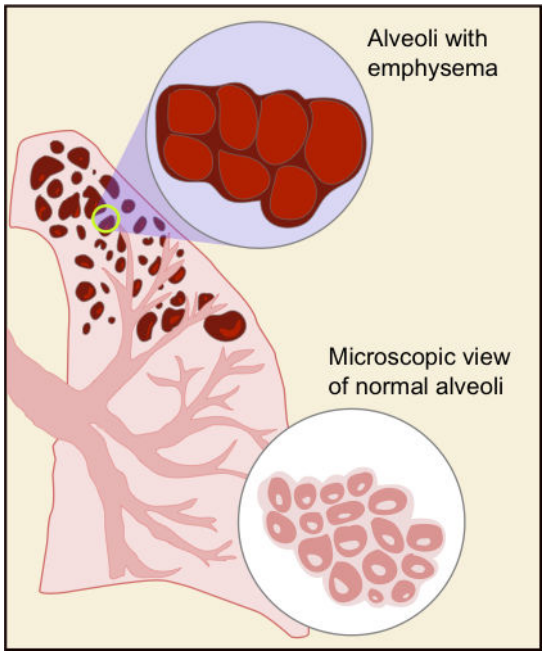
There are over 70 known mutations that occur at the SERPINA1 gene. A common mutation that creates the Z allele involves a switch in amino acids — glutamic acid is replaced by lysine at position 342 (Glu342Lys). The resulting AAT protein cannot fold properly. This hinders its secretion from the liver (which makes AAT) into the bloodstream (which transports AAT to the lungs). The accumulation of AAT complexes can damage the liver, whereas the lack of AAT fails to stop the destruction of lung tissue.

Treatment of AAT deficiency includes the standard treatment of emphysema (bronchodilators, early use of antibiotics in infections) as well as the more experimental therapies of correcting AAT levels by replacing the protein. Gene therapy to replace the defective SERPINA1 gene with a functional copy is currently being investigated.

However, the most important part of treatment of AAT deficiency is to avoid smoking. Affected individuals are far less likely to develop emphysema if they do not smoke. Not only is smoking a lung irritant, which attracts white blood cells (and therefore neutrophil elastase) to the lungs, it also prevents any AAT that is present in the lungs from working properly.

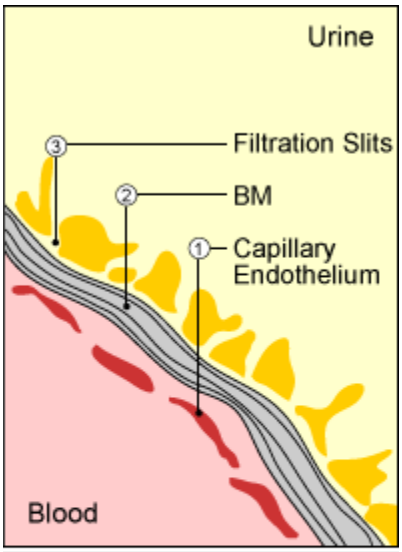
Related diseases

See other Respiratory Diseases



Lung alveoli. In AAT deficiency, the walls of the lung tissue (alveoli) are broken down. The result is a trapping of air known as emphysema. The damaged lung tissue can no longer transfer oxygen to the bloodstream.

Alport syndrome



Filtration barrier in the kidney. To enter urine, waste molecules pass through: 1, gaps between the lining of the blood vessel; 2, the BM; and 3, slits between epithelial cells. In AS, the BM deteriorates, allowing proteins and red blood cells to enter the urine.

Alport syndrome (AS) is a genetic disease in which a collagen mutation affects the kidneys, the ears, and the eyes. The syndrome was named for Dr. Alport who in 1927 described a British family in which many members developed renal disease as well as deafness. He noted that affected men in the family died as a result of their kidney problems, whereas females were less affected and lived until old age.

It is now known that most cases of AS are caused by a mutation in the collagen gene *COL4A5*. This gene encodes for the alpha-5 chain of collagen type IV and is located on the X chromosome. Because women have two X chromosomes (XX), affected women usually have one normal copy and one abnormal copy of the gene. Men only have one copy of the X chromosome (XY). If they inherit the *COL4A5* mutation, this abnormal copy of the gene is the only copy they have and the effects are more severe.

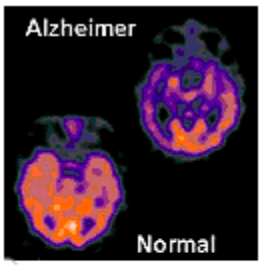
Type IV collagen is found in basement membranes (BM), which are selective barriers between cells. In the kidney, the glomerular BM filters waste products into the urine while keeping useful molecules within the blood stream. In AS, the abnormal collagen disrupts this filter, leading to the loss of proteins and red blood cells into the urine. Blood in the urine (hematuria) is a sign common to all types of AS. In the ear, abnormal collagen in the cochlea results in a progressive deafness in which the ability to hear high tones is lost first. Abnormal collagen can also affect the lens of the eye.

Currently, renal failure due to AS is treated by dialysis or, for some, renal transplantation. However, gene therapy may one day be able to provide a cure for AS by replacing the faulty *COL4A5* gene.

Related diseases

See other Male-Specific Diseases

Alzheimer disease



Brain scans of a healthy elderly person and a patient with Alzheimer's disease. [Image supplied Keith Johnson, Bringham and Women's Hospital, Boston, MA, USA.]

Alzheimer disease (AD) is the fourth leading cause of death in adults. The incidence of the disease rises steeply with age. AD is twice as common in women than in men, although former president Ronald Reagan is a well known disease sufferer. Some of the most frequently observed symptoms of the disease include a progressive inability to remember facts and events and, later, to recognize friends and family.

AD tends to run in families; currently, mutations in four genes, situated on chromosomes 1, 14, 19, and 21, are believed to play a role in the disease. The best-characterized of these are PS1 (or AD3) on chromosome 14 and PS2 (or AD4) on chromosome 1. The formation of lesions made of fragmented brain cells surrounded by amyloid-family proteins are characteristic of the disease. Interestingly, these lesions and their associated proteins are closely related to similar structures found in Down Syndrome. Tangles of filaments largely made up of a protein associated with the cytoskeleton have also been observed in samples taken from Alzheimer brain tissue.

Currently, scientists are studying the interrelationship between the various gene loci (particularly the mutation on chromosome 21) and how environmental factors could effect a person's susceptibility to AD. Recently, use of a mouse model of the disease identified an enzyme that may be responsible for the increase in amyloid production characteristic of AD. If a way to regulate this enzyme could be found, then AD may be slowed or halted in some people.

Related diseases

See other Diseases of the Nervous System

Amyotrophic lateral sclerosis

Lou Gerhig, who played baseball for the New York Yankees 1925 to 1939. His career was cut short by the disease amylotrophic lateral sclerosis.

Amyotrophic lateral sclerosis (ALS) is a neurological disorder characterized by progressive degeneration of motor neuron cells in the spinal cord and brain, which ultimately results in paralysis and death. The disease takes its less-scientific name from Lou Gehrig, a baseball player with the New York Yankees in the late 1920s and 1930s, who was forced to retire in 1939 as a result of the loss of motor control caused by the disease.

In 1991, a team of researchers linked familial ALS to chromosome 21. Two years later, the SOD1 gene was identified as being associated with many cases of familial ALS. The enzyme coded for by SOD1 carries out a very important function in cells: it removes dangerous superoxide radicals by converting them into non-harmful substances. Defects in the action of this enzyme mean that the superoxide radicals attack cells from the inside, causing their death. Several different mutations in this enzyme all result in ALS, making the exact molecular cause of the disease difficult to ascertain.

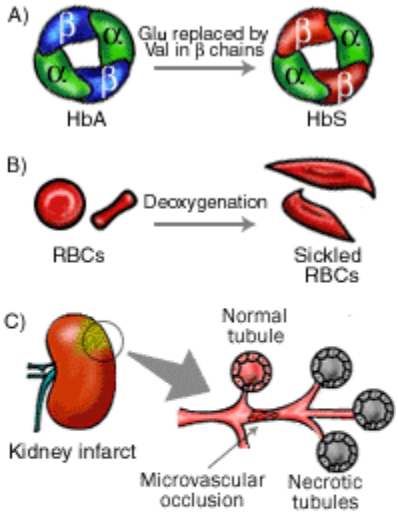
Recent research has suggested that treatment with drugs called antioxidants may benefit ALS patients. However, since the molecular genetics of the disease are still unclear, a significant amount of research is still required to design other promising treatments for ALS.

Related diseases

See other Muscle and Bone Diseases

See other Diseases of the Nervous System

Anemia, sickle cell



A) Hemoglobin is made up of 4 chains: 2 α and 2 β. In SCA, a point mutation causes the amino acid glutamic acid (Glu) to be replaced by valine (Val) in the β chains of HbA, resulting in the abnormal HbS. **B)** Under certain conditions, such as low oxygen levels, RBCs with HbS distort into sickled shapes. **C)** These sickled cells can block small vessels producing microvascular occlusions which may cause necrosis (death) of the tissue.

Sickle cell anemia is the most common inherited blood disorder in the United States, affecting about 72,000 Americans or 1 in 500 African Americans. SCA is characterized by episodes of pain, chronic hemolytic anemia and severe infections, usually beginning in early childhood.

SCA is an autosomal recessive disease caused by a point mutation in the *hemoglobin beta gene* (*HBB*) found on chromosome 11p15.5. Carrier frequency of *HBB* varies significantly around the world, with high rates associated with zones of high malaria incidence, since carriers are somewhat protected against malaria. About 8% of the African American population are carriers. A mutation in *HBB* results in the production of a structurally abnormal hemoglobin (Hb), called HbS. Hb is an oxygen carrying protein that gives red blood cells (RBC) their characteristic color. Under certain conditions, like low oxygen levels or high hemoglobin concentrations, in individuals who are homozygous for HbS, the abnormal HbS clusters together, distorting the RBCs into sickled shapes. These deformed and rigid RBCs become trapped within small blood vessels and block them, producing pain and eventually damaging organs.

Though, as yet, there is no cure for SCA, a combination of fluids, painkillers, antibiotics and transfusions are used to treat symptoms and complications. Hydroxyurea, an antitumor drug, has been shown to be effective in preventing painful crises. Hydroxyurea induces the formation of fetal Hb (HbF)—a Hb normally found in the fetus or newborn—which, when present in individuals with SCA, prevents sickling. A mouse model of SCA has been developed and is being used to evaluate the effectiveness of potential new therapies for SCA.

Related diseases

See other Blood and Lymph Diseases

Angelman syndrome

Updated: January 31, 2011.

Angelman syndrome (AS) is an uncommon neurogenetic disorder characterized by mental retardation, abnormal gait, speech impairment, seizures, and an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. The uncoordinated gait and laughter have caused some people to refer to this disorder as the "happy puppet" syndrome.

The genetic basis of AS is very complex, but the majority of cases are due to a deletion of segment 15q11-q13 on the maternally derived chromosome 15. When this same region is missing from the paternally derived chromosome, an entirely different disorder, Prader-Willi syndrome, results. This phenomenon—when the expression of genetic material depends on whether it has been inherited from the mother or the father—is termed genomic imprinting.

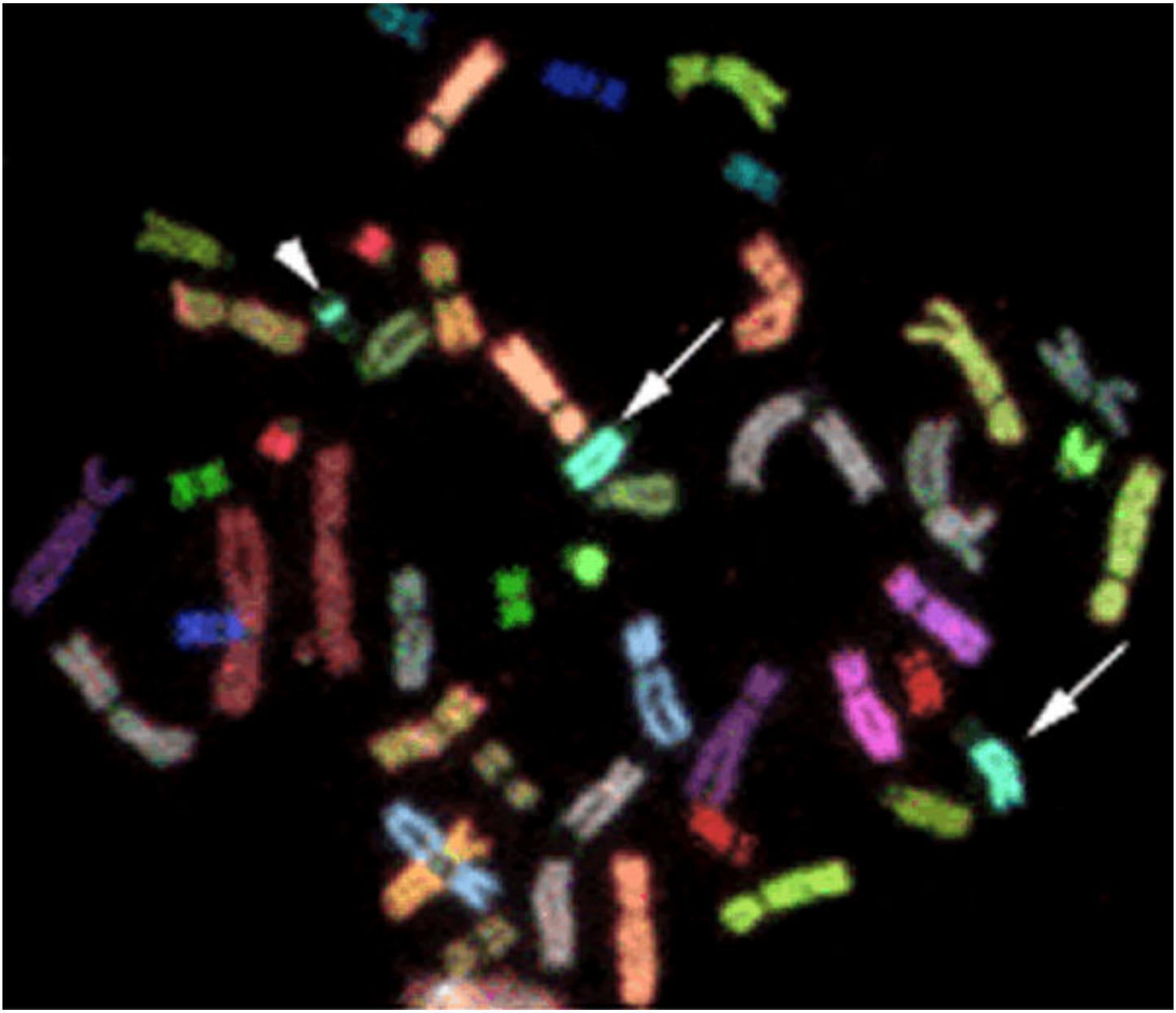
The ubiquitin ligase gene (UBE3A) is found in the AS chromosomal region. It codes for an enzyme that is a key part of a cellular protein degradation system. AS is thought to occur when mutations in UBE3A disrupt protein break down during brain development.

In a mouse model of AS, affected animals had much less maternally inherited UBE3A than their unaffected litter mates. However, this difference in UBE3A levels was only found in the hippocampus and the cerebellum, and not all of the brain. This animal model and other molecular techniques are helping us learn more about the disparate maternal and paternal expression of the UBE3A gene.

Related diseases

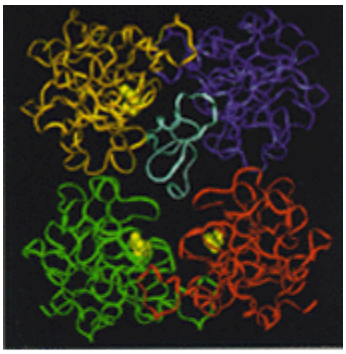
See other Neonatal Diseases

See other Diseases of the Nervous System



Chromosome painting. Chromosome painting techniques such as M-FISH tint each pair of the 24 human chromosomes a different color. This allows the fragment (arrow head) to be identified as an extra piece of chromosome, since it is the same aqua color as the two normal copies of chromosome 15 (arrows). This technique may help in the diagnosis of genetic disorders that arise from chromosomal changes too subtle for conventional techniques.

Asthma



Tryptase is an enzyme found specifically in mast cells, a type of white blood cells important for fighting infection. It may have a role in casuing asthma and other inflammatory disorders. [Reproduced from Pereira, P.J.B. et al. (1998) Nature 392, 30-311, with permission.]

Asthma affects more than 5% of the population of the US, including children. It is a chronic inflammatory disorder of the airways characterized by coughing, shortness of breath, and chest tightness. A variety of "triggers" may initiate or worsen an asthma attack, including viral respiratory infections, exercise, and exposure to irritants such as tobacco smoke. The physiological symptoms of asthma are a narrowing of the airways caused by edema (fluid in the intracellular tissue space) and the influx of inflammatory cells into the walls of the airways.

Asthma is a what is known as a "complex" heritable disease. This means that there are a number of genes that contribute toward a person's susceptibility to a disease, and in the case of asthma, chromosomes 5, 6, 11, 14, and 12 have all been implicated. The relative roles of these genes in asthma predisposition are not clear, but one of the most promising sites for investigation is on chromosome 5. Although a gene for asthma from this site has not yet been specifically identified, it is known that this region is rich in genes coding for key molecules in the inflammatory response seen in asthma, including cytokines, growth factors, and growth factor receptors.

The search for specific asthma genes is ongoing. Assisting in this international human effort are model organisms such as mice, which have similar chromosomal architecture to our chromosome 5 site on their chromosomes 11, 13, and 18. Further study of the genes in these areas (and others) of the human genome will implicate specific genes involved in asthma and perhaps also suggest related biological pathways that play a role in the pathogenesis of asthma.

Related diseases

See other Diseases of the Immune System

See other Respiratory Diseases

Ataxia telangiectasia

Updated: January 31, 2011.

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.

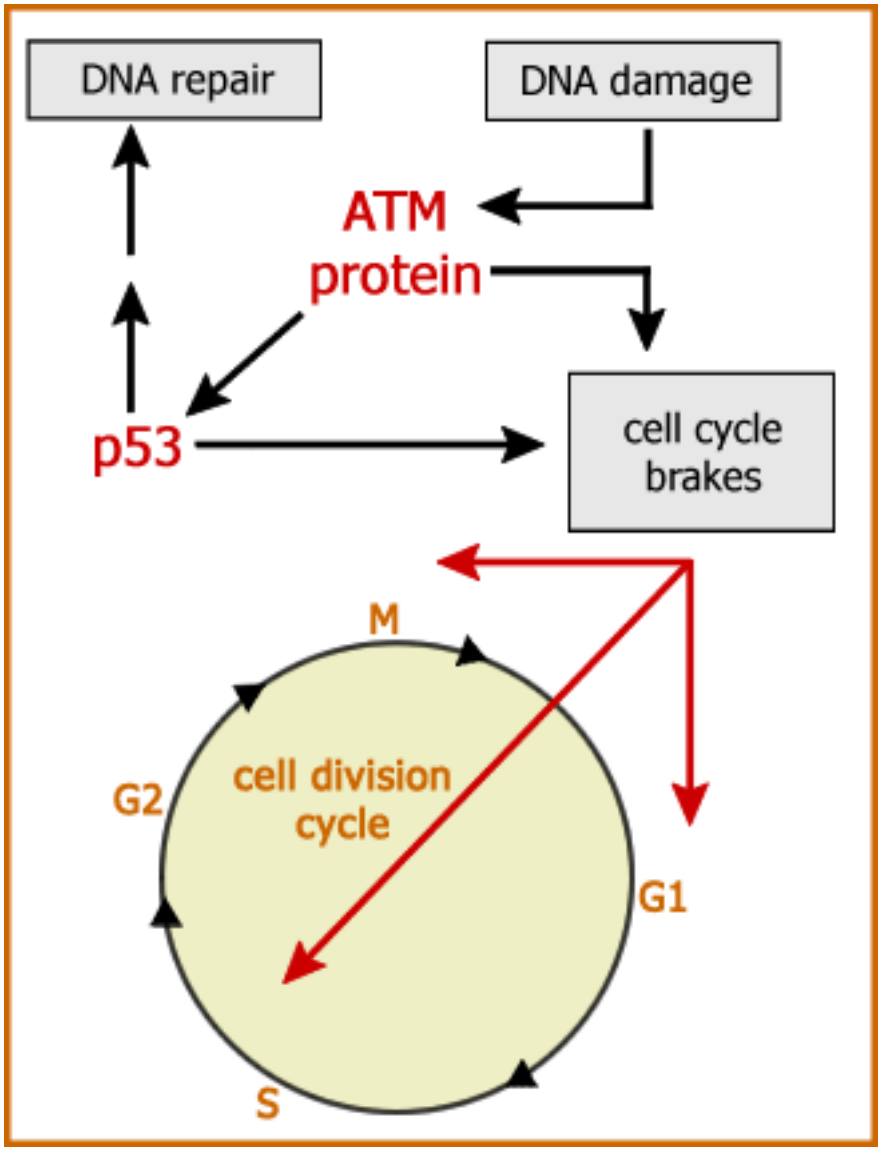
Some of the ATM-dependent signaling pathways are found in yeast. Because these pathways appear to be conserved throughout evolution, they are likely to be central to the DNA damage response. Research into finding an effective therapy for A-T sufferers is likely to be helped by harnessing the power of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

Related diseases

See other Diseases of the Heart and Blood Vessels

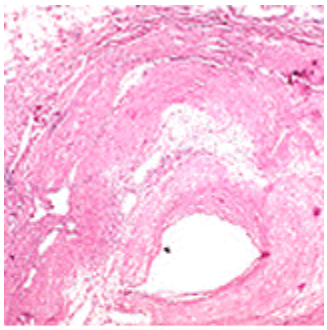
See other Diseases of the Immune System

See other Diseases of the Nervous System



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

Atherosclerosis



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

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 affect 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.

Related diseases

See other Diseases of the Heart and Blood Vessels

Autoimmune polyglandular syndrome

The endocrine system is responsible for the release of hormones into the blood or lymph. Deficiencies in the endocrine system can be caused by infection, infarction, or a tumor destroying all or a large part of the gland. However, the activity of an endocrine organ is most often depressed as a result of an autoimmune reaction that ultimately results in partial or complete destruction of the gland. Autoimmune disease affecting one organ is frequently followed by the impairment of other glands, resulting in multiple endocrine failure.

Autoimmune polyglandular syndrome type I (APS1, also called APECED) is a rare autosomal recessive disorder that maps to human chromosome 21. At the end of 1997, researchers reported that they isolated a novel gene, which they called AIRE (autoimmune regulator). Database searches revealed that the protein product of this gene is a transcription factor—a protein that plays a role in the regulation of gene expression. The researchers showed that mutations in this gene are responsible for the pathogenesis of APS1.

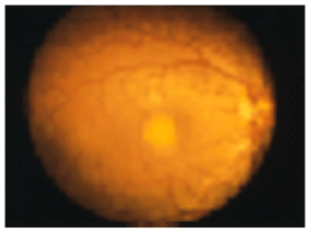
The identification of the gene defective in APS1 is the first step toward developing tests that will be able to genetically diagnose the disease. Further investigations of the gene and its function should also facilitate finding a potential treatment for the disease as well as increasing our general understanding of the mechanisms underlying other autoimmune diseases.

Related diseases

See other Glands and Hormones Diseases

See other Diseases of the Immune System

Best disease



Photograph of an eye from a patient with Best disease. Note the mass of lipid-like material in the macular region.

[Reproduced from Marquardt, A. *et al.* (1988) *Human Molecular Genetics* 7(9): 1517-25, with permission.

Best disease, also known as Vitelliform Macular Dystrophy type 2 (VMD2), is a heritable disorder occurring primarily in European Caucasians. Individuals with Best disease generally show a gradual loss of visual acuity starting in their teenage years, although the frequency with which an affected individual may show symptoms and the severity of those symptoms are highly variable.

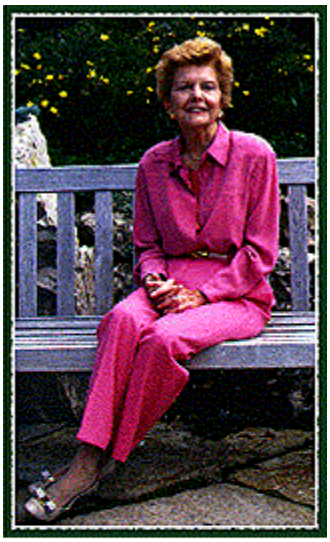
Best disease is autosomal dominant; in other words, a mutation in only one copy of the VMD2 gene located on chromosome 11 may result in development of the disease. Prior to their vision loss, individuals with Best disease accumulate a mass of fat-like material that resembles an egg yolk (vitelline is a word that means yolk-like) in the area of the retina responsible for central vision. Surprisingly, it is the breakup of this mass rather than its formation that is associated with the gradual vision loss characteristic of Best disease.

Little is known about the protein product of the VMD2 gene, although its function seems to be restricted to an area of the eye known as the retinal pigment epithelium. There is speculation that the protein encoded by VMD2 may be involved in the removal and/or processing of photoreceptor components. Determination of the VMD2 protein function and development of an animal model will be the next crucial steps toward a better understanding of Best disease.

Related diseases

See other Diseases of the Eye

Breast and ovarian cancer



"While we all work toward a cure, education, research and increased access to treatment remain our best allies in the fight against breast cancer."

Betty Ford, former breast cancer patient and now an activist on behalf of expanded breast cancer research and education.

Breast cancer is the second major cause of cancer death in American women, with an estimated 44,190 lives lost (290 men and 43,900 women) in the United States in 1997. Although ovarian cancer accounts for fewer deaths than breast cancer, ovarian cancer still represents 4% of all female cancers. For some of the cases of both types of cancer, there is also a clear genetic link.

In 1994, two breast cancer susceptibility genes were identified: *BRCA1* on chromosome 17 and *BRCA2* on chromosome 13. When individuals carry a mutation in either *BRCA1* or *BRCA2*, they are at an increased risk of being diagnosed with breast or ovarian cancer at some point in their lives. Until recently, it was not clear what the function of these genes was, until studies on a related protein in yeast revealed their normal role: they participate in repairing radiation-induced breaks in double-stranded DNA. It is thought that mutations in *BRCA1* or *BRCA2* might disable this mechanism, leading to more errors in DNA replication and ultimately to cancerous growth.

Thus far, the best opportunity to reduce mortality is through early detection (general screening of the population for *BRCA1* and *BRCA2* is not yet recommended). However, new strategies to find anticancer drugs are constantly being developed. The latest strategy, called "synthetic lethal screening", looks for new drug targets in organisms such as yeast and fruit flies. In the same way that studies in yeast recently helped to identify the functions of BRCA1 and BRCA2, it is thought that drugs that work in more primitive organisms will also be applicable to humans.

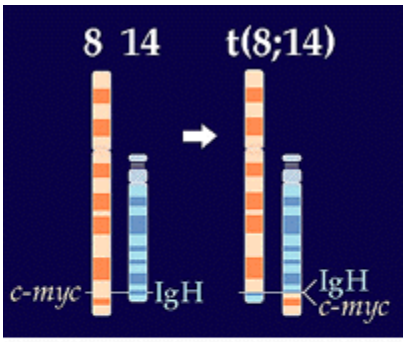
Related diseases

See other Cancers

See other Female-Specific Diseases

See other Glands and Hormones Diseases

Burkitt lymphoma



In Burkitt lymphoma, Myc, which is normally found on chromosome 8, is transferred to chromosome 14. This is known as chromosome translocation and can be characteristic of a cancer type. [image credit: Gregory Schuler, NCBI, NLM, NIH.]

Burkitt lymphoma is a rare form of cancer predominantly affecting young children in Central Africa, but the disease has also been reported in other areas. The form seen in Africa seems to be associated with infection by the Epstein-Barr virus, although the pathogenic mechanism is unclear.

Burkitt lymphoma results from chromosome translocations that involve the *Myc* gene. A chromosome translocation means that a chromosome is broken, which allows it to associate with parts of other chromosomes. The classic chromosome translocation in Burkitt lymophoma involves chromosome 8, the site of the *Myc* gene. This changes the pattern of *Myc*'s expression, thereby disrupting its usual function in controlling cell growth and proliferation.

We are still not sure what causes chromosome translocation. However, research in model organisms such as mice is leading us toward a better understanding of how translocations occur and, hopefully, how this process contributes to Burkitt lymphoma and other cancers such as leukemia.

Related diseases

See other Blood and Lymph Diseases

See other Cancers

See other Diseases of the Immune System

Charcot-Marie-Tooth syndrome

Charcot-Marie-Tooth disease (CMT) is named after its three discoverers, who first noted the disease around the turn of the century. It is the most common inherited peripheral neuropathy in the world, characterized by a slowly progressive degeneration of the muscles in the foot, lower leg, hand, and forearm and a mild loss of sensation in the limbs, fingers, and toes. Full expression of CMT's clinical symptoms generally occurs by age 30. CMT is not a fatal disease, however, and the disorder does not affect normal life expectancy.

CMT is a genetically heterogeneous disorder in which mutations in different genes can produce the same clinical symptoms. In CMT there are not only different genes but different patterns of inheritance. One of the most common forms of CMT is Type 1A. The gene for Type 1A CMT maps to chromosome 17 and is thought to code for a protein (PMP22) involved in coating peripheral nerves with myelin, a fatty sheath that is important for their conductance. Other types of CMT include Type 1B, autosomal-recessive, and X-linked.

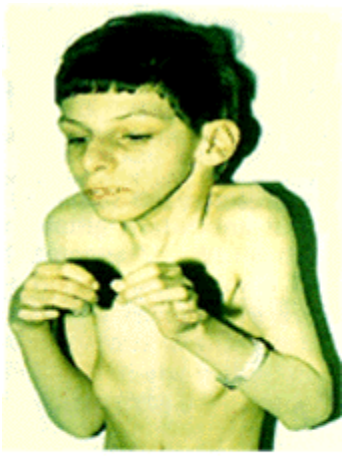
The same proteins involved in the Type 1A and Type 1B CMT are also involved in a disease called Dejerine-Sottas Syndrome (DSS), in which similar clinical symptoms are presented, but they are more severe. Research into understanding the pathogenesis of CMT, through the use of animal models for the disease, should also give insight into DSS and may lead to therapies for both diseases.

Related diseases

See other Muscle and Bone Diseases

See other Diseases of the Nervous System

Cockayne syndrome



Cockayne syndrome sufferers have multi-systemic disorders due to a defect in the ability of cells to repair DNA that is being transcribed. [Photograph by D. Atherton. Reproduced from Lehmann, A.R. (1995) Trends Biochem. Sci. 20, 402-405, with permission.]

Edward Alfred Cockayne (1880-1956), after whom this disease is named, was a London physician who concentrated particularly on hereditary diseases of children. Cockayne syndrome is a rare inherited disorder in which people are sensitive to sunlight, have short stature, and have the appearance of premature aging. In the classical form of Cockayne syndrome (Type I), the symptoms are progressive and typically become apparent after the age of 1 year. An early onset or congenital form of Cockayne syndrome (Type II) is apparent at birth. Interestingly, unlike other DNA repair diseases, Cockayne syndrome is not linked to cancer.

After exposure to UV radiation (found in sunlight), people with Cockayne syndrome can no longer perform a certain type of DNA repair, known as "transcription-coupled repair." This type of DNA repair occurs "on the fly" right as the DNA that codes for proteins is being replicated. Two genes defective in Cockayne syndrome, CSA and CSB, have been identified so far. The CSA gene is found on chromosome 5. Both genes code for proteins that interacts with components of the transcriptional machinery and with DNA repair proteins.

Escherichia coli, a bacterium, also undergoes transcription-coupled repair, and a yeast counterpart of the CSB gene has also recently been discovered. These similar mechanisms to the one found in humans are invaluable for studying the molecular processes involved in transcription-coupled repair because powerful molecular genetics techniques can be used. A better understanding of the mechanisms involved will help unravel the pathogenesis of disease and may identify potential drug targets.

Related diseases

See other Glands and Hormones Diseases

See other Muscle and Bone Diseases

See other Neonatal Diseases

See other Diseases of the Nervous System

Colon cancer

The human genes mutated in some colon cancers are homologous to enzymes in the DNA mismatch repair pathway in the E. coli bacterium (above) as well as yeast and mice.

The American Cancer Society estimates that there will be 93,800 new cases of colon cancer diagnosed in the US in 2000, with 47,700 resulting deaths. All kinds of cancer occur when cell division, normally a very highly regulated process, gets out of control. While environmental factors can certainly contribute to a person's risk of cancer (e.g. smoking, diet, and exercise), most cancers have a genetic basis too. Literally hundreds of genes and proteins are involved in monitoring the process of cell division and DNA replication; a mutation in one or more of these genes or proteins can sometimes lead to uncontrolled cancerous growth.

Colon cancer is one of the most common inherited cancer syndromes known. Among the genes found to be involved in colorectal cancer are: *MSH2* and *MSH6* both on chromosome 2 and *MLH1*, on chromosome 3. Normally, the protein products of these genes help to repair mistakes made in DNA replication. If the MSH2, MSH6, and MLH1 proteins are mutated and therefore don't work properly, the replication mistakes are not repaired, leading to damaged DNA and, in this case, colon cancer.

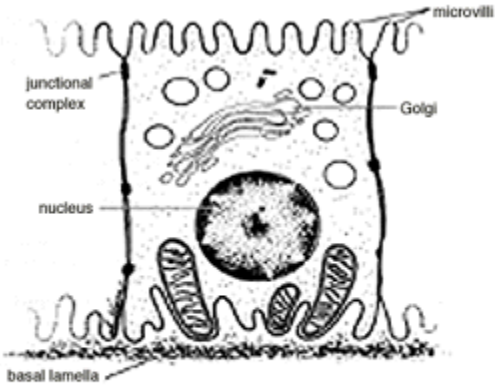
It is not clear why mutations in genes that are essential in all tissues preferentially cause cancer in the colon. However, studies on the equivalent genes in mice and brewer's yeast are helping to further our understanding of the mechanisms of DNA repair and the role that environmental factors might play in colon cancer incidence.

Related diseases

See other Cancers

See other Diseases of the Digestive System

Crohn's disease



Epithelial cells line the intestine and are one of several cell types in the lining of the intestine to be affected in ulcerative colitis or Crohn's disease.

Inflammatory bowel disease (IBD) is a group of chronic disorders that causes inflammation or ulceration in the small and large intestines. Most often, IBD is classified either as ulcerative colitis or Crohn's disease. While ulcerative colitis affects the inner lining of the colon and rectum, Crohn's disease extends into the deeper layers of the intestinal wall. It is a chronic condition and may recur at various times over a lifetime.

About 20% of cases of Crohn's disease appear to run in families. It is a "complex trait," which means that several genes at different locations in the genome may contribute to the disease. A susceptibility locus for the disease was recently mapped to chromosome 16. Candidate genes found in this region include several involved in the inflamatory response, including: CD19, involved in B-lymphocyte function; sialophorin, involved in leukocyte adhesion; the CD11 integrin cluster, involved in microbacterial cell adhesion; and the interleukin-4 receptor, which is interesting, as IL-4-mediated functions are altered in IBDs.

Because some of the genetic factors involved in Crohn's disease may also contribute to ulcerative colitis susceptibility, research into Crohn's disease may assist in further understanding both types of IBD.

Related diseases

See other Diseases of the Digestive System

Cystic fibrosis

Updated: January 31, 2011.

Cystic fibrosis (CF) is the most common fatal genetic disease in the United States today. It causes the body to produce a thick, sticky mucus that clogs the lungs, leading to infection, and blocks the pancreas, stopping digestive enzymes from reaching the intestines where they are required to digest food.

CF is caused by a defective gene, which codes for a chloride transporter found on the surface of the epithelial cells that line the lungs and other organs. Several hundred mutations have been found in this gene, all of which result in defective transport of chloride, and secondarily sodium, by epithelial cells. As a result, the amount of sodium chloride (salt) is increased in bodily secretions. The severity of the disease symptoms of CF is directly related to the characteristic effects of the particular mutation(s) that have been inherited by the sufferer.

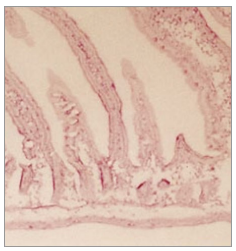
CF research has accelerated sharply since the discovery of CFTR in 1989. In 1990, scientists successfully cloned the normal gene and added it to CF cells in the laboratory, which corrected the defective chloride transport mechanism. This technique—gene therapy—was then tried on a limited number of CF patients. However, this treatment may not be as successful as originally hoped. Further research will be required before gene therapy, and other experimental treatments, prove useful in combating CF.

Related diseases

See other Diseases of the Digestive System

See other Neonatal Diseases

See other Respiratory Diseases



Building mouse models of human disease. Expression of a human cystic fibrosis (CFTR) gene in the gut of a mouse. A human antisense probe was used to show human CFTR expressed in the mouse duodenum.

Image reproduced with permission from Manson, A.L et al. (1997) EMBO J. 16, 4238-4249.

Deafness

Updated: January 31, 2011.

Hearing loss is extremely common and can present at any time from infancy to old age. About 1 in 1000 infants has profound hearing impairment, with half thought to be of genetic origin. Many deafness genes exist, but the most common cause of hearing loss in American and European populations is a mutation in the *connexin 26* (*Cx26*) gene. *Cx26* has a carrier rate of 3%, similar to that for cystic fibrosis, and it causes about 20% of childhood deafness.

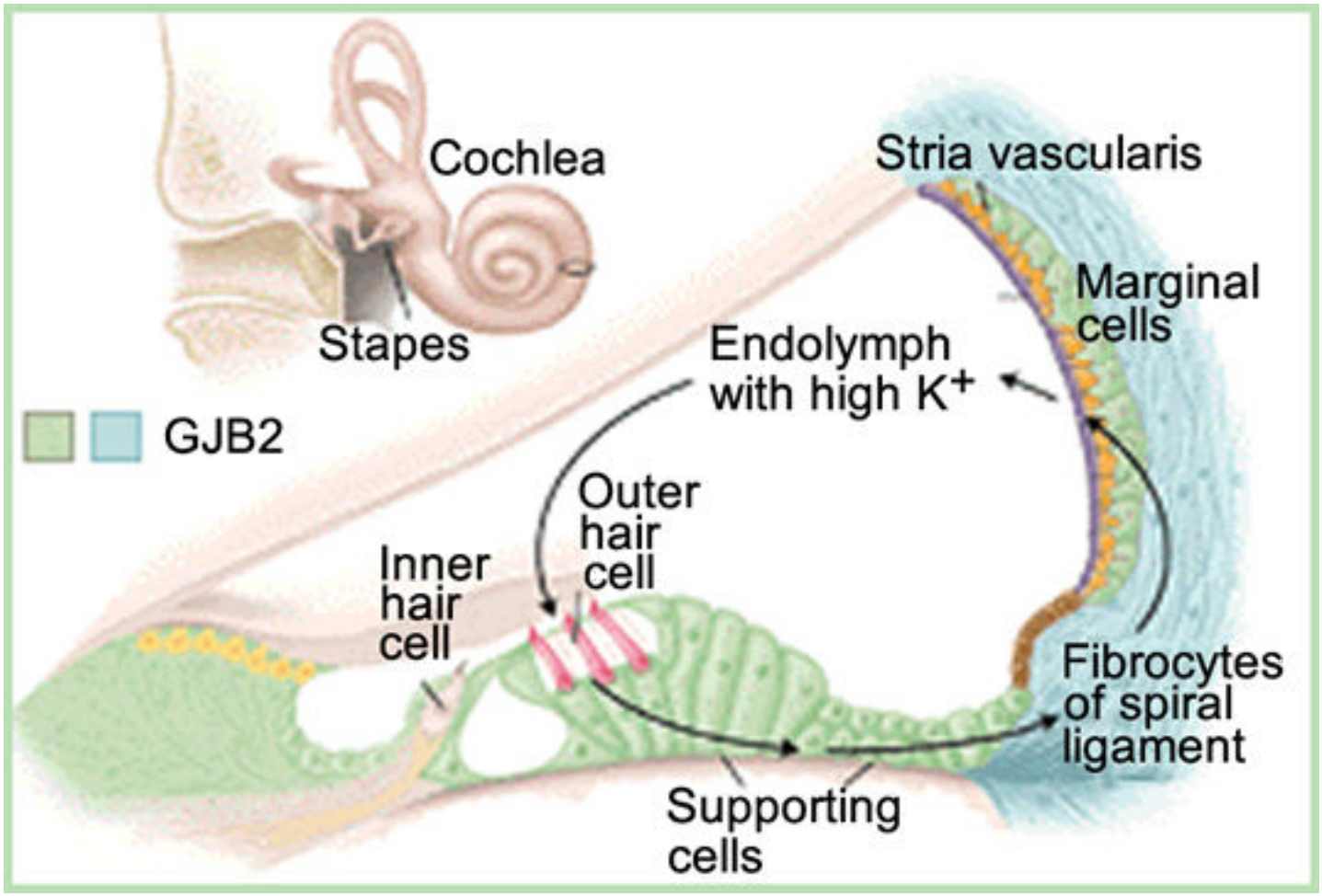
Mutations in *Cx26* cause congenital syndromic and nonsyndromic deafness—that is, the deafness is not accompanied by other symptoms, such as blindness. *Cx26* is located on chromosome 13q11-12 and codes for a gap junction protein called connexin 26. Gap junctions are plasma membrane channels that allow the movement of small molecules and ions between adjacent cells. Gap junctions of the inner ear may play a role in maintaining potassium homeostasis, which is important for inner-ear function and, thus, hearing. It has been proposed that mutations in *Cx26* may disrupt potassium circulation and result in deafness.

The discovery that *Cx26* mutations are a cause of congenital hearing loss can help in the early diagnosis of hearing impairment. Early identification and management of deafness is important for the development of language and social skills.

Related diseases

See other Ear, Nose, and Throat Diseases

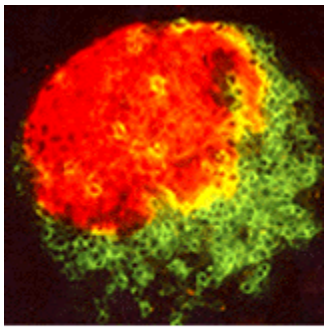
See other Diseases of the Nervous System



Connexin 26. Connexin 26 (GJB2) is one of the main proteins involved in potassium (K+) homeostasis in the cochlea of the inner ear. It is found in the supporting cells, fibrocytes of the spiral ligament and in cells of the spiral limbus

Adapted from Steel, K.P. (1999) *Science* 285, 1363-1364, with permission.

Diabetes, type 1



T lymphocytes attacking insulin-producing pancreatic islet cells.[Image credit: A. Cooke and John Todd, Wellcome Trust Center for Human Genetics, Oxford, UK.]

Diabetes is a chronic metabolic disorder that adversely affects the body's ability to manufacture and use insulin, a hormone necessary for the conversion of food into energy. The disease greatly increases the risk of blindness, heart disease, kidney failure, neurological disease, and other conditions for the approximately 16 million Americans who are affected by it. Type 1, or juvenile onset diabetes, is the more severe form of the illness.

Type 1 diabetes is what is known as a 'complex trait', which means that mutations in several genes likely contribute to the disease. For example, it is now known that the insulin-dependent diabetes mellitus (IDDM1) locus on chromosome 6 may harbor at least one susceptibility gene for Type 1 diabetes. Exactly how a mutation at this locus adds to patient risk is not clear, although a gene maps to the region of chromosome 6 that also has genes for antigens (the molecules that normally tell the immune system not to attack itself). In Type 1 diabetes, the body's immune system mounts an immunological assault on its own insulin and the pancreatic cells that manufacture it. However, the mechanism of how this happens is not yet understood.

About 10 loci in the human genome have now been found that seem to confer susceptibility to Type 1 diabetes. Among these are 1) a gene at the locus IDDM2 on chromosome 11 and 2) the gene for glucokinase (GCK), an enzyme that is key to glucose metabolism which helps modulate insulin secretion, on chromosome 7.

Conscientious patient care and daily insulin dosages can keep patients comparatively healthy. But in order to prevent the immunoresponses that often cause diabetes, we will need to experiment further with mouse models of the disease and advance our understanding of how genes on other chromosomes might add to a patient's risk of diabetes.

Related diseases

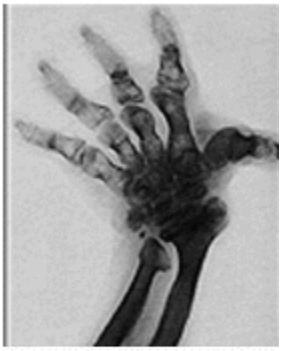
See other Diseases of the Digestive System

See other Glands and Hormones Diseases

See other Diseases of the Immune System

See other Nutritional and Metabolic Diseases

Diastrophic dysplasia



Radiograph of the hand of a patient with diastrophic dysplasia. [Image credit: Eric Lander, Whitehead Institute, MIT, USA.]

Diastrophic dysplasia (DTD) is a rare growth disorder in which patients are usually short, have club feet, and have malformed handsmand joints. Although found in all populations, it is particularly prevalent in Finland.

The gene whose mutation results in DTD maps to chromosome 5 and encodes a novel sulfate transporter. This ties in with the observation of unusual concentrations of sulfate in various tissues of DTD patients. Sulfate is important for skeletal joints because cartilage—the shock-absorber of joints—requires sulfur during its manufacture. Adding sulfur increases the negative charge within cartilage, which contributes to its shock-absorbing properties.

A great deal of further research must be done before this condition is fully understood and effective therapies are developed.

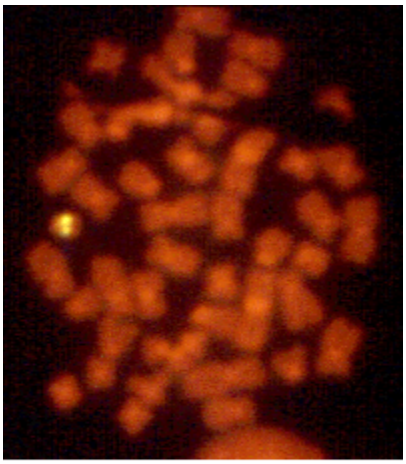
Related diseases

See other Glands and Hormones Diseases

See other Muscle and Bone Diseases

See other Skin and Connective Tissue Diseases

DiGeorge syndrome



Deletion of genes in DiGeorge syndrome can be visualized by a fluorescent signal on only one of the two copies of chromosome 22.[Image credit: David Ian Wilson, University of Newcastle upon Tyne, UK.]

DiGeorge syndrome is a rare congenital (i.e. present at birth) disease whose symptoms vary greatly between individuals but commonly include a history of recurrent infection, heart defects, and characteristic facial features.

DiGeorge syndrome is caused by a large deletion from chromosome 22, produced by an error in recombination at meiosis (the process that creates germ cells and ensures genetic variation in the offspring). This deletion means that several genes from this region are not present in DiGeorge syndrome patients. It appears that the variation in the symptoms of the disease is related to the amount of genetic material lost in the chromosomal deletion.

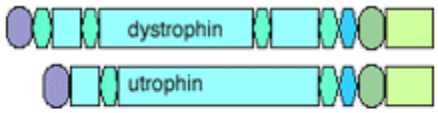
Although researchers now know that the DGS gene is required for the normal development of the thymus and related glands, counteracting the loss of DGS is difficult. Some effects, for example the cardiac problems and some of the speech impairments, can be treated either surgically or therapeutically, but the loss of immune system T-cells (produced by the thymus) is more challenging and requires further research on recombination and immune function.

Related diseases

See other Diseases of the Immune System

See other Neonatal Diseases

Duchenne muscular dystrophy



Dystrophin and utrophin are a similar size and have comparable modular architecture. This similarity means that utrophin can sometimes substitute for dystrophin, so providing a potential route for therapy for muscular dystrophy sufferers.

Duchenne muscular dystrophy (DMD) is one of a group of muscular dystrophies characterized by the enlargement of muscles. DMD is one of the most prevalent types of muscular dystrophy and is characterized by rapid progression of muscle degeneration that occurs early in life. All are X-linked and affect mainly males—an estimated 1 in 3500 boys worldwide.

The gene for DMD, found on the X chromosome, encodes a large protein—dystrophin. Dystrophin is required inside muscle cells for structural support; it is thought to strengthen muscle cells by anchoring elements of the internal cytoskeleton to the surface membrane. Without it, the cell membrane becomes permeable, so that extracellular components enter the cell, increasing the internal pressure until the muscle cell "explodes" and dies. The subsequent immune response can add to the damage.

A mouse model for DMD exists and is proving useful for furthering our understanding on both the normal function of dystrophin and the pathology of the disease. In particular, initial experiments that increase the production of utrophin, a dystrophin relative, in order to compensate for the loss of dystrophin in the mouse are promising and may lead to the development of effective therapies for this devastating disease.

Related diseases

See other Muscle and Bone Diseases

See other Diseases of the Nervous System

Ellis-van Creveld syndrome

Ellis-van Creveld syndrome. The search for a molecular basis for the disease is on-going. Image credit: Clement D. Erhardt, Jr., Baltimore, MD, USA.

Ellis-van Creveld syndrome, also known as "chondroectodermal dysplasia," is a rare genetic disorder characterized by short-limb dwarfism, polydactyly (additional fingers or toes), malformation of the bones of the wrist, dystrophy of the fingernails, partial hare-lip, cardiac malformation, and often prenatal eruption of the teeth.

The gene causing Ellis-van Creveld syndrome, EVC, has been mapped to the short arm of chromosome 4. As yet, the function of a healthy EVC gene is not known; this is one of the most important questions that must be answered about the disease, since it would give an indication as to the molecular mechanism of the disease.

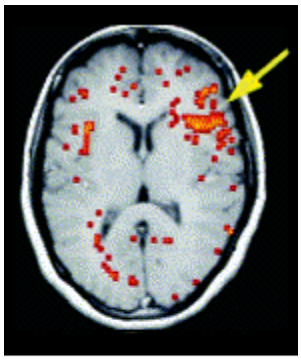
Ellis-van Creveld syndrome is often seen among the Old Order Amish community in Lancaster County, Pennsylvania. Because this group of people is small and isolated, it affords a rare opportunity to observe the passage of this particular disorder from generation to generation. A pattern of inheritance can be observed that has indicated the disease is autosomal-recessive (i.e. a mutated gene form both parents is required before the effects of the disease to become apparent).

Related diseases

See other Muscle and Bone Diseases

See other Skin and Connective Tissue Diseases

Epilepsy



Brain scan of a person with frontal lobe epilepsy. Arrow points to the focus of seizure activity. [Image reproduced with permission from Seeck et al. (1998) Electroenceph. Clin. Neurophys. 106, 508-512.]

Epilepsy affects approximately 1% of the population making it one of the most common neurological diseases. Epilepsy can strike at any time of life—from infancy to old age. While epilepsy varies widely in type and severity, all forms of this disorder are characterized by recurring seizures resulting from abnormal cell firing in the brain. In approximately 30% of cases, epilepsy is caused by such events as head trauma, tumor, stroke, or infection. In those cases for which there is no known cause, recent evidence suggests there may be genetic predisposition to developing the disease.

There are many forms of epilepsy—most are rare. But to date, at least twelve forms of epilepsy have been demonstrated to possess some genetic basis. For example, LaFora Disease (progressive myoclonic, type 2), a particularly aggressive epilepsy, is characterized in part by the presence of glycogen-like Lafora bodies in the brain. It is an autosomal recessive disorder that has been linked to mutation of the gene *EPM2A*, found on chromosome 6. This gene produces a phosphatase called laforin. The regulatory function of the phosphatase may be disrupted by mutation, leading to LaFora Disease. Some recent work suggests that laforin may be found in similar parts of the cell as glycogen synthase, a glycogen processing enzyme, and that the mutations may misplace laforin within the cell, leading indirectly to a loss of EPM2A function.

Much progress has been made in narrowing down regions of chromosomes associated with different forms of epilepsy. With this effort, scientists continue to expand the list of genes involved in seizure disorders. Animal models of epilepsy also contribute to our understanding of electrical brain disturbances. By focussing on the genetic basis for epilepsy, scientists hope to develop more effective anticonvulsive treatments and, possibly, gene replacement therapies for seizure disorders such as LaFora Disease.

Related diseases

See other Diseases of the Nervous System

Essential tremor

Tremor, or uncontrollable shaking, is a common symptom of neurological disorders such as Parkinson disease, head trauma, and stroke. However, many people with tremor have what is called idiopathic or essential tremor. In these cases, which number 3-4 million people in the US, the tremor itself is the only symptom of the disorder. While essential tremor may involve other parts of the body, the hands and head are most often affected.

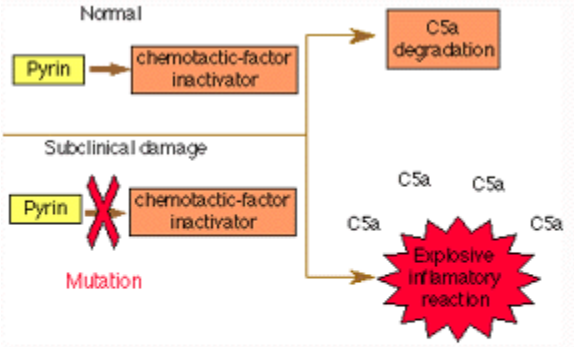
In more than half of the cases, essential tremor is inherited as an autosomal dominant trait, which means that children of an affected individual will have a 50% chance of also developing the disorder. In 1997, the ETM1 gene (also called FET1) was mapped to chromosome 3 in a study of Icelandic families, while another gene, called ETM2, was mapped to chromosome 2 in a large American family of Czech descent. That two genes for essential tremor have been found on two different chromosomes demonstrates that mutations in a variety of genes may lead to essential tremor.

While the mainstays of treatment are drugs such as propranolol and primidone, alternative drugs and surgical treatments are also available. Further understanding of the molecular mechanism behind the disease awaits the discovery and cloning of an essential tremor gene.

Related diseases

See other Diseases of the Nervous System

Familial Mediterranean fever



Pyrin, or marenostrin, the product of the gene for familial Mediterranean fever, is thought to activate the biosynthesis of a chemotactic-factor inactivator. Without functional pyrin, no inactivator is produced, leading to attacks of familial Mediterranean fever. [Adapted from Fig. 1, Babior, B.M. and Matzner, Y. (1997) New Engl. J. Med., 377, 1548-1549.]

Familial Mediterranean fever (FMF) occurs most commonly in people of non-Ashkenazi Jewish, Armenian, Arab, and Turkish background. As many as 1 in 200 people in these populations have the disease, with as many as 1 in 5 acting as a disease carrier. FMF is an inherited disorder usually characterized by recurrent episodes of fever and peritonitis (inflammation of the abdominal membrane).

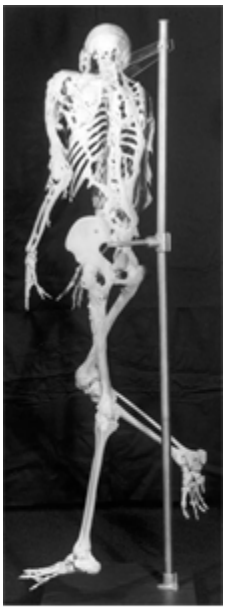
In 1997, researchers identified the gene for FMF and found several different gene mutations that cause this inherited rheumatic disease. The gene, found on chromosome 16, codes for a protein that is found almost exclusively in granulocytes—white blood cells important in the immune response. The protein is likely to normally assist in keeping inflammation under control by deactivating the immune response—without this "brake," an inappropriate full-blown inflammatory reaction occurs: an attack of FMF.

Discovery of the gene mutations will allow the development of a simple diagnostic blood test for FMF. With identification of the mutant protein, it may be easier to recognize environmental triggers that lead to attacks and may lead to new treatments for not only FMF but also other inflammatory diseases.

Related diseases

See other Diseases of the Immune System

Fibrodysplasia ossificans progressiva



Skeleton of Harry Eastlack, who had FOP. Connective tissue on the back has turned into bone.

Courtesty of Muller Museum, College of Physicians of Philadelphia.

Fibrodysplasia Ossificans Progressiva (FOP) is an extremely rare genetic disease that causes muscle to be turned into bone. The condition was first reported in the 17th century by Patin, a French physician, who described a woman who "turned into wood". The wood he described was actually the formation of new bone.

FOP is an autosomal dominant condition, but most cases are sporadic. FOP patients have a genetic fault, which means that their bodies cannot switch off the mechanism that grows the skeleton in the womb. Any small injury to connective tissue (muscles, ligaments, and tendons) can result in the formation of hard bone around the damaged site. Children are born with a characteristic malformation of the great toes and begin to develop heterotopic (extra) bone formation during early childhood. Eventually, a second skeleton begins to form that severely restricts mobility.

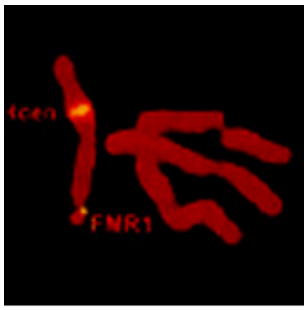
FOP affects 1 of 2 million people. Because of the very small numbers of patients, identifying the mutation(s) causing FOP is difficult. There are several genes that have been implicated in the disease process. For example, when the *Noggin* gene (*NOG*) is deleted in mice, the mice are unable to stop the deposition of bone, causing an FOP-like disease. Another gene of interest is the Bone Morphogenic Protein gene (*BMP*), which Noggin regulates. Proteins encoded by *BMP* induce bone formation, and one of their roles is to stimulate the formation of the fetal skeleton. In FOP, lymphocytes deliver BMP4 to areas of damaged muscle, and so initiate bone growth rather than aid tissue repair.

It is hoped that future studies will pinpoint the mutation(s) occurring in FOP and lead to a better understanding of the disease's mechanism.

Related diseases

See other Muscle and Bone Diseases

Fragile X syndrome



An unstable nucleotide repeat is associated with the most common form of mental retardation known as Fragile X syndrome. [Image credit: Steve Warren, Emory University School of Medicine, Atlanta, GA, USA.]

Fragile X syndrome is the most common inherited form of mental retardation currently known. Fragile X syndrome is a defect in the X chromosome and its effects are seen more frequently, and with greater severity, in males than females.

In normal individuals, the FMR1 gene is transmitted stably from parent to child. However, in Fragile X individuals, there is a mutation in one end of the gene (the 5' untranslated region), consisting of an amplification of a CGG repeat. Patients with fragile X syndrome have 200 or more copies of the CGG motif. The huge expansion of this repeat means that the FMR1 gene is not expressed, so no FMR1 protein is made. Although the exact function of FMR1 protein in the cell is unclear, it is known that it binds RNA.

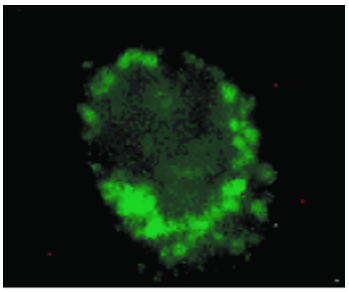
A similar nucleotide repeat expansion is seen in other diseases, such as Huntington disease. Research in mice has proven helpful in elucidating some of the mechanisms that cause the instability of this gene. Our methods for identifying carriers of Fragile X syndrome have also improved, and further research will help people carrying "premutations" to avoid having children who have a larger expansion (i.e. more CGG repeats) in FMR1, and therefore suffer from Fragile X syndrome.

Related diseases

See other Neonatal Diseases

See other Diseases of the Nervous System

Friedreich's ataxia



Mitochondrial localization of human frataxin in live mammalian cells. [Reproduced from Babcock, M. et al. (1997) Regulation of Science 276: 1709-1712, with permission.]

Friedreich's ataxia (FRDA) is a rare inherited disease characterized by the progressive loss of voluntary muscular coordination (ataxia) and heart enlargement. It is named after the German doctor, Nikolaus Friedreich, who first described the disease in 1863. FRDA is generally diagnosed in childhood and affects both males and females.

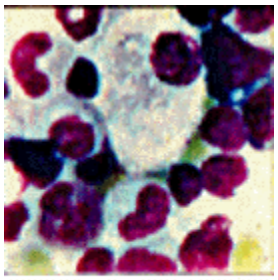
FRDA is an autosomal recessive disease caused by a mutation of a gene called frataxin, which is located on chromosome 9. This mutation means that there are many extra copies of a DNA segment, the trinucleotide GAA. A normal individual has 8 to 30 copies of this trinucleotide, while FRDA patients have as many as 1000. The larger the number of GAA copies, the earlier the onset of the disease and the quicker the decline of the patient.

Although we know that frataxin is found in the mitochondria of humans, we do not yet know its function. However, there is a very similar protein in yeast, YFH1, which we know more about. YFH1 is involved in controlling iron levels and respiratory function. Since frataxin and YFH1 are so similar, studying YFH1 may help us understand the role of frataxin in FRDA.

Related diseases

See other Diseases of the Nervous System

Gaucher disease



Gaucher cells. [Image credit: E. Beutler, Scripps Research Institute, La Jolla, CA, USA.]

Gaucher (pronounced "go-SHAY") disease is an inherited illness caused by a gene mutation. Normally, this gene is responsible for an enzyme called glucocerebrosidase that the body needs to break down a particular kind of fat called glucocerebroside. In people with Gaucher disease, the body is not able to properly produce this enzyme, and the fat can not be broken down. It then accumulates, mostly in the liver, spleen, and bone marrow. Gaucher disease can result in pain, fatigue, jaundice, bone damage, anemia, and even death.

Gaucher disease is considerably more common in the descendants of Jewish people from Eastern Europe (Ashkenazi), although individuals from any ethnic group may be affected. Among the Ashkenazi Jewish population, Gaucher disease is the most common genetic disorder, with an incidence of approximately 1 in 450 persons. In the general public, Gaucher disease affects approximately 1 in 100,000 persons. According to the National Gaucher Foundation, 2500 Americans suffer from Gaucher disease.

In 1991, enzyme replacement therapy became available as the first effective treatment for Gaucher disease. The treatment consists of a modified form of the glucocerebrosidase enzyme given intravenously. Performed on an outpatient basis, the treatment takes about 1-2 h and is given every 2 weeks. Enzyme replacement therapy can stop and often reverse the symptoms of Gaucher disease, allowing patients to enjoy a better quality of life.

Related diseases

See other Blood and Lymph Diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Glaucoma

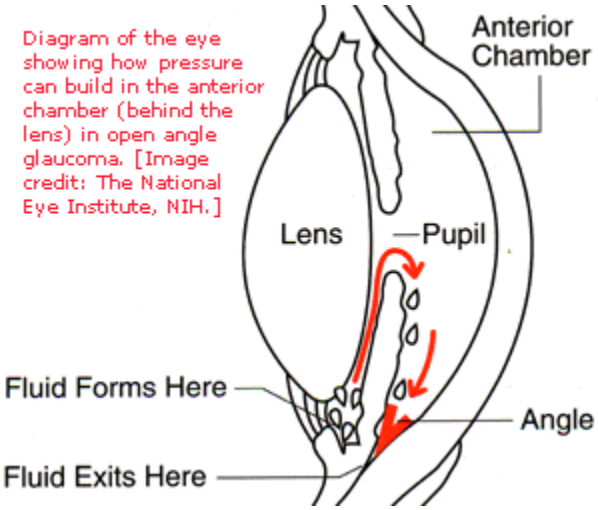


Diagram of the eye showing how pressure can build in the anterior chamber (behind the lens) in open angle glaucoma. [Image credit: The National Eye Institute, NIH.]

"Glaucoma" is a term used for a group of diseases that can lead to damage to the eye's optic nerve and result in blindness. The most common form of the disease is open-angle glaucoma, which affects about 3 million Americans, half of whom don't know they have it. Glaucoma has no symptoms at first but over the years can steal its victims' sight, with side vision being affected first.

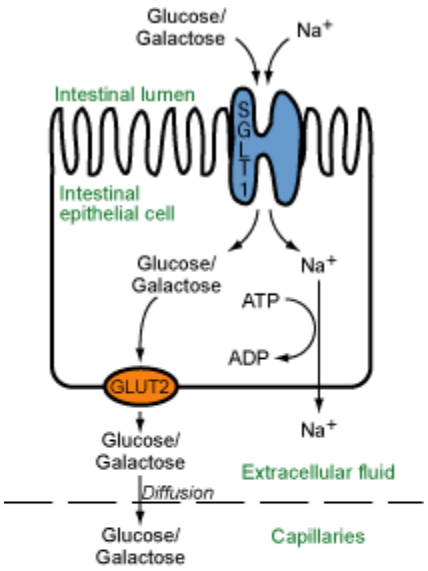
It is estimated that nearly 100,000 individuals in the US suffer from glaucoma due to a mutation in the GLC1A gene, found on chromosome 1. There has been some speculation as to the role of the gene product in the eye. As it is found in the structures of the eye involved in pressure regulation, it may cause increased pressure in the eye by obstructing the aqueous outflow.

With early treatment, serious loss of vision and blindness can be prevented. The cloning of the GLC1A gene is the first step toward an understanding of the pathology of glaucoma at the molecular level and may help in the development of tests for the early detection of the disease, as well as providing a basis for research into effective therapies.

Related diseases

See other Diseases of the Eye

Glucose galactose malabsorption



Co-transport of sodium and glucose or galactose by SGLT1. For every two sodium ions SGLT1 moves inside the cell down the sodium concentration gradient, one glucose or galactose molecule moves with it. The glucose/galactose is then transported into the extracellular fluid by GLUT2, and diffuses into the capillaries. Sodium is actively transported out of the cell into the intercellular space so as to maintain the intracellular sodium concentration gradient.

Glucose Galactose Malabsorption (GGM) is a rare metabolic disorder caused by a defect in glucose and galactose transport across the intestinal lining. GGM is characterized by severe diarrhea and dehydration as early as the first day of life and can result in rapid death if lactose (milk sugar), sucrose (table sugar), glucose, and galactose are not removed from the diet. Half of the 200 severe GGM cases found worldwide result from familial intermarriage. At least 10% of the general population has glucose intolerance, however, and it is possible that these people may have milder forms of the disease.

GGM is an autosomal recessive disorder in which affected individuals inherit two defective copies of the *SGLT1* gene, located on chromosome 22. Normally within the space enclosed by the small intestine (called the lumen), lactose is broken down into glucose and galactose by an enzyme called lactase, while sucrose is broken down into glucose and fructose by an enzyme called sucrase. The protein product of *SGLT1* then moves the glucose and the galactose from the lumen of the small intestine into intestinal cells. Usually the mutations carried by GGM individuals result in nonfunctional truncated SGLT1 proteins or in the improper placement of the proteins such that they can not transport glucose and galactose out of the intestinal lumen. The glucose and galactose, if left untransported, draw water out of the body into the intestinal lumen, resulting in diarrhea.

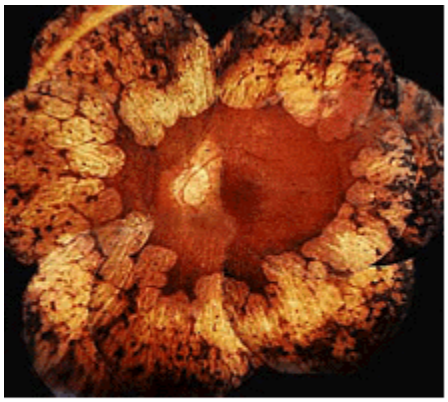
Although no cure exists for GGM, patients can control their symptoms (diarrhea) by removing lactose, sucrose, and glucose from their diets. Infants showing a prenatal diagnosis of GGM will thrive on a fructose-based replacement formula and will later continue their "normal" physical development on a fructose-based solid diet. Older children and adults with severe GGM can also manage their symptoms on a fructose-based diet and may show improved glucose tolerance and even clinical remission as they age.

Related diseases

See other Diseases of the Digestive System

See other Nutritional and Metabolic Diseases

Gyrate atrophy of the choroid and retina



The retina of a patient with gyrate atrophy of the choroidand retina of the eye caused by ornithine aminotransferase (OAT) deficiency. [Image credit: Muriel Kaiser-Kupfer, NEI, NIH, Bethesda, MD, USA and David Valle, Johns Hopkins University, Baltimore, MD, USA.]

People suffering from gyrate atrophy of the choroid (the thin coating of the eye) and retina face a progressive loss of vision, with total blindness usually occurring between the ages of 40 and 60. The disease is an inborn error of metabolism.

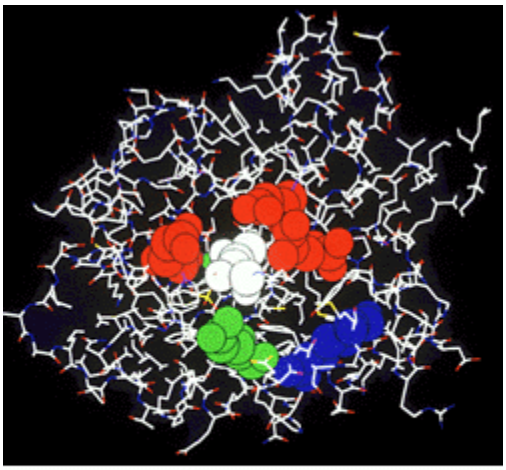
The gene whose mutation causes gyrate atrophy is found on chromosome 10, and encodes an enzyme called ornithine ketoacid aminotransferase (OAT). Different inherited mutations in OAT cause differences in the severity of symptoms of the disease. OAT converts the amino acid ornithine from the urea cycle ultimately into glutamate. In gyrate atrophy, where OAT function is affected, there is an increase in plasma levels of ornithine.

It is already known that reduction of the amino acid arginine in the diet has a salutary effect on most patients. Current lines of research into the disease include: (1) investigating how variant mutations of the alleles (versions of the gene inherited) interact in order to cause the differing symptoms of the disease and (2) work on mouse models of the disease is furthering our understanding, which is hoped will lead to a true cure.

Related diseases

See other Diseases of the Eye

Harvey Ras oncogene



The three-dimensional structure of Ras protein. Many of the mutations of Ras observed in human cancers have been pin-pointed and mapped onto this structure. [Image credit: Mark Boguski, NCBI, NIH, Bethesda, USA.]

Cancer occurs when the growth and differentiation of cells in a body tissue become uncontrolled and deranged. While no two cancers are genetically identical (even in the same tissue type), there are relatively few ways in which normal cell growth can go wrong. One of these is to make a gene that stimulates cell growth hyperactive; this altered gene is known as an 'oncogene'.

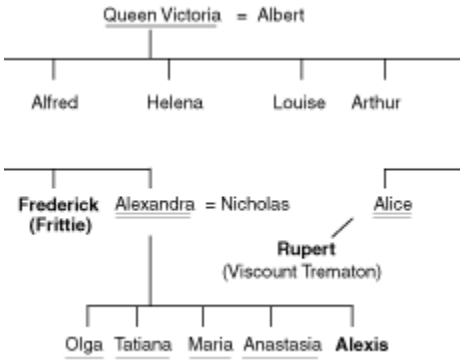
Ras is one such oncogene product that is found on chromosome 11. It is found in normal cells, where it helps to relay signals by acting as a switch. When receptors on the cell surface are stimulated (by a hormone, for example), Ras is switched on and transduces signals that tell the cell to grow. If the cell-surface receptor is not stimulated, Ras is not activated and so the pathway that results in cell growth is not initiated. In about 30% of human cancers, Ras is mutated so that it is permanently switched on, telling the cell to grow regardless of whether receptors on the cell surface are activated or not.

Usually, a single oncogene is not enough to turn a normal cell into a cancer cell, and many mutations in a number of different genes may be required to make a cell cancerous. To help unravel the intricate network of events that lead to cancer, mice are being used to model the human disease, which will further our understanding and help to identify possible targets for new drugs and therapies.

Related diseases

See other Cancers

Hemophilia A

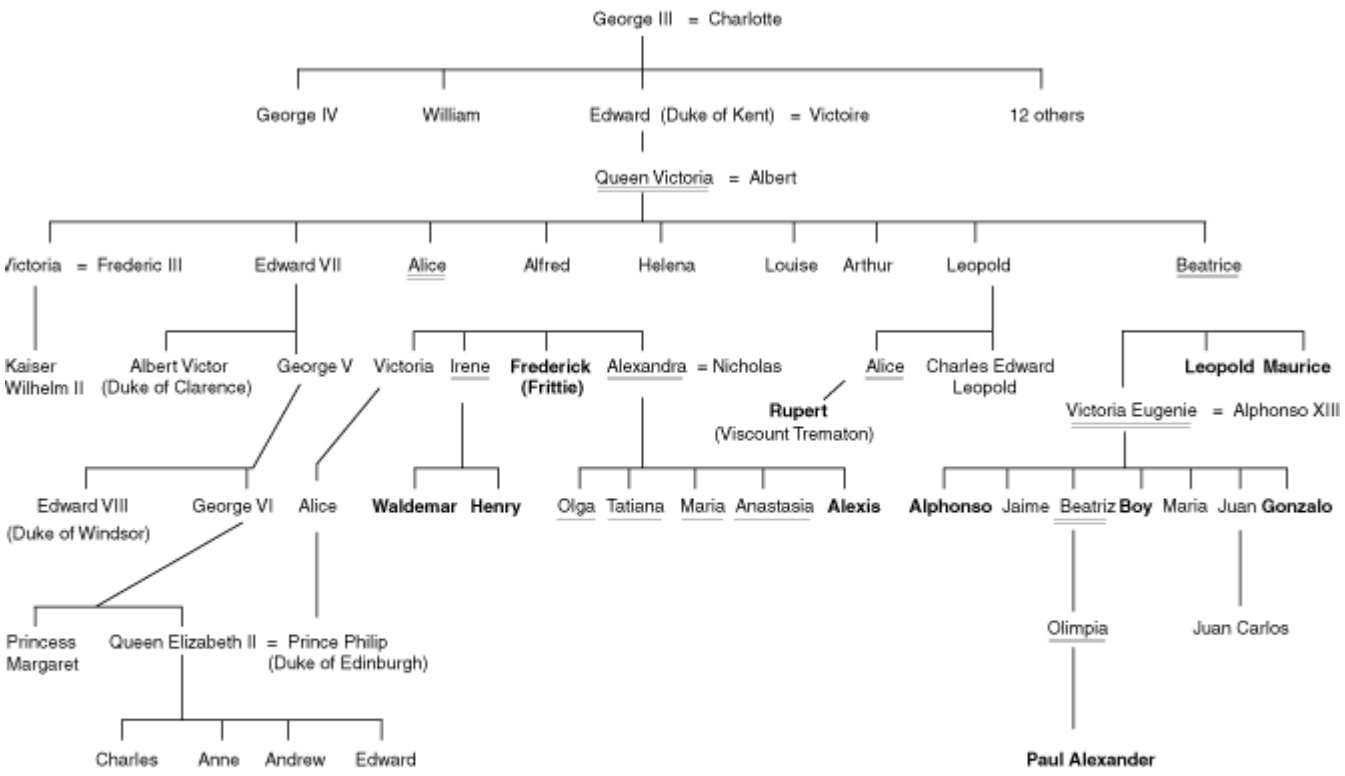


Click here to view the full chart

Hemophilia A is a hereditary blood disorder, primarily affecting males, characterized by a deficiency of the blood clotting protein known as Factor VIII that results in abnormal bleeding. Babylonian Jews first described hemophilia more than 1700 years ago; the disease first drew widespread public attention when Queen Victoria transmitted it to several European royal families. Mutation of the *HEMA* gene on the X chromosome causes Hemophilia A. Normally, females have two X chromosomes, whereas males have one X and one Y chromosome. Since males have only a single copy of any gene located on the X chromosome, they cannot offset damage to that gene with an additional copy as can females. Consequently, X-linked disorders such as Hemophilia A are far more common in males. The *HEMA* gene codes for Factor VIII, which is synthesized mainly in the liver, and is one of many factors involved in blood coagulation; its loss alone is enough to cause Hemophilia A even if all the other coagulation factors are still present.

Treatment of Hemophilia A has progressed rapidly since the middle of the last century when patients were infused with plasma or processed plasma products to replace Factor VIII. HIV contamination of human blood supplies and the consequent HIV infection of most hemophiliacs in the mid-1980s forced the development of alternate Factor VIII sources for replacement therapy, including monoclonal antibody purified Factor VIII and recombinant Factor VIII, both of which are used in replacement therapies today.

Development of a gene replacement therapy for Hemophilia A has reached the clinical trial stage, and results so far have been encouraging. Investigators are still evaluating the long-term safety of these therapies, and it is hoped that a genetic cure for hemophilia will be generally available in the future.



European royal family pedigree indicating instances of hemophilia. Bold denotes hemophiliac male. Double underline denotes hemophilia carrier female. Single underline denotes possible hemophilia carrier female. [Reproduced from Stevens, RF. (1999) *British Journal of Haematology* 105:25-32., with permission.]

Related diseases

See other Blood and Lymph Diseases

Hereditary hemochromatosis

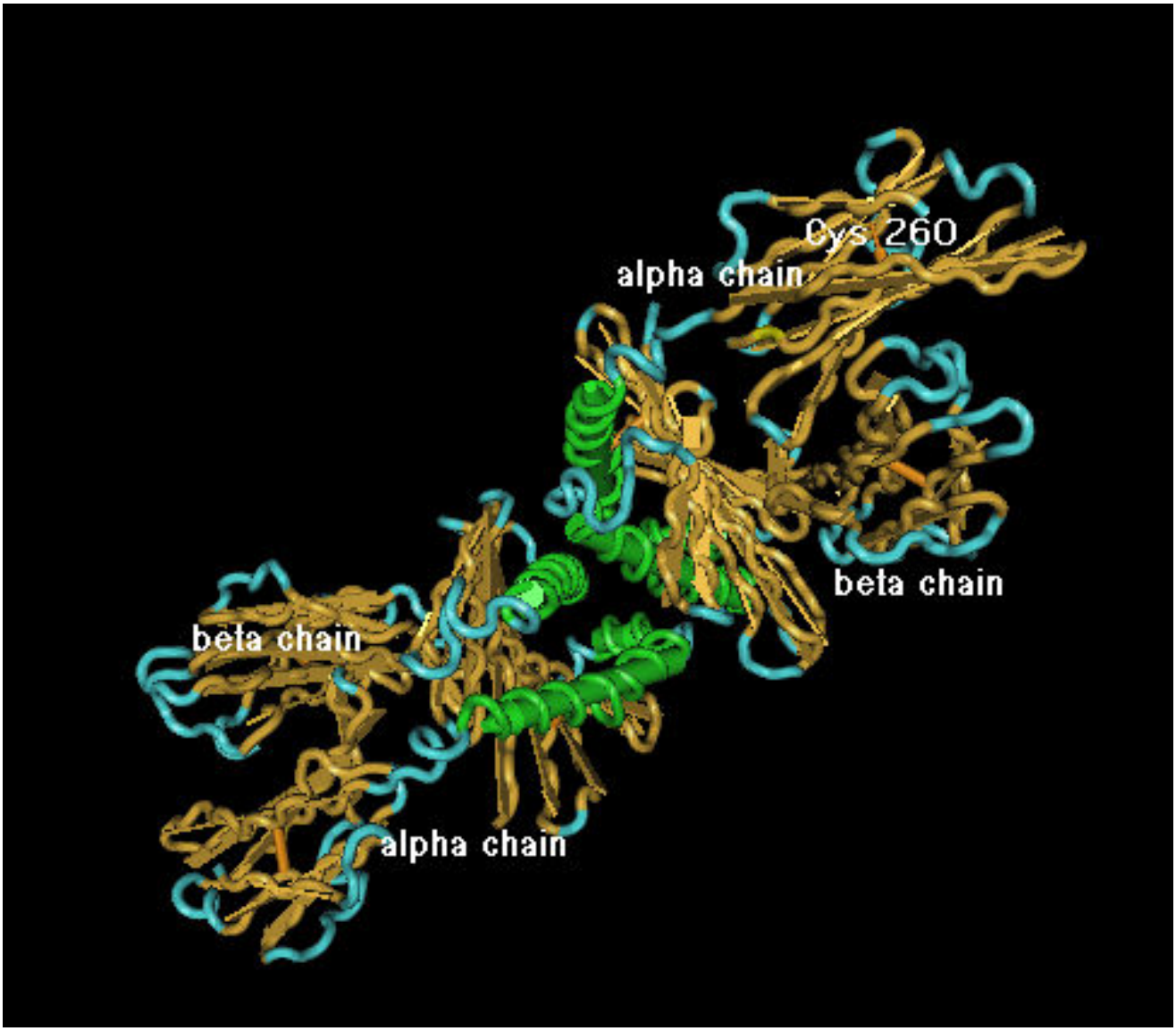
Hereditary hemochromatosis is an inherited disorder that increases the amount of iron that the body absorbs from the gut. Symptoms are caused by this excess iron being deposited in multiple organs of the body. Most commonly, excess iron in the liver causes cirrhosis, which may develop into liver cancer. Iron deposits in the pancreas can result in diabetes. Similarly, excess iron stores can cause cardiomyopathy, pigmentation of the skin, and arthritis.

Many mutations in the body's iron transport system can cause hemochromatosis; however, most cases are caused by mutations in the *HFE* gene. This is located on chromosome 6, and one mutation leads to the substitution of the 282nd amino acid. Cysteine becomes tyrosine, therefore the mutation is called C282Y. The switch of amino acids is thought to affect how the HFE protein interacts with the transferrin receptor (TFR1), which plays an important role in iron homeostasis. A less common mutation, H63D, has also been identified in the *HFE* gene.

Hemochromatosis is one of the most common autosomal recessive disorders among Caucasians in the United States; however, only a small proportion of these people suffer any symptoms. This may be attributable to both environmental (diet and blood loss) and genetic factors. Recent advances in the development of animal models that show the complications of hemochromatosis may soon provide useful tools in deciphering how other genes play a part in iron regulation.

Related diseases

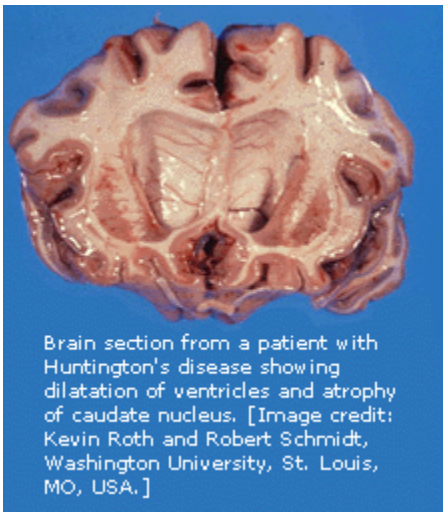
See other Nutritional and Metabolic Diseases



The HFE protein. The HFE protein is similar in structure to MHC class I, consisting of two pairs of alpha and beta chains. In the mature HFE protein, the mutation is called C260Y. This is because the body's processing of the protein removes 22 amino acids to produce the mature protein. The C260Y mutation occurs in the alpha 3 domain and disrupts the association between the chains. Mutant HFE is unable to bind to the iron-loaded transferrin receptor. Without this interaction, the receptor brings more iron into the cells.

To see the interactive version of this figure requires Cn3D, a three-dimensional structure viewer.

Huntington disease



Brain section from a patient with Huntington's disease showing dilatation of ventricles and atrophy of caudate nucleus. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Huntington disease (HD) is an inherited, degenerative neurological disease that leads to dementia. About 30,000 Americans have HD and about 150,000 more are at risk of inheriting the disease from a parent.

The HD gene, whose mutation results in Huntington disease, was mapped to chromosome 4 in 1983 and cloned in 1993. The mutation is a characteristic expansion of a nucleotide triplet repeat in the DNA that codes for the protein huntingtin. As the number of repeated triplets - CAG (cytosine, adenine, guanine) - increases, the age of onset in the patient decreases. Furthermore, because the unstable trinucleotide repeat can lengthen when passed from parent to child, the age of onset can decrease from one generation to the next. Since people who have those repeats always suffer from Huntington disease, it suggests that the mutation causes a gain-of-function, in which the mRNA or protein takes on a new property or is expressed inappropriately.

With the discovery of the HD gene, a new predictive test was developed that allows those at risk to find out whether or not they will develop the disease. Animal models have also been developed, and we know that mice have a gene that is similar to the human HD gene. Research on understanding the mechanism that causes the triplet repeat to increase is ongoing, since its discovery could be critical to the development of an effective treatment for this and other similar diseases.

Related diseases

See other Diseases of the Nervous System

Immunodeficiency with hyper-IgM

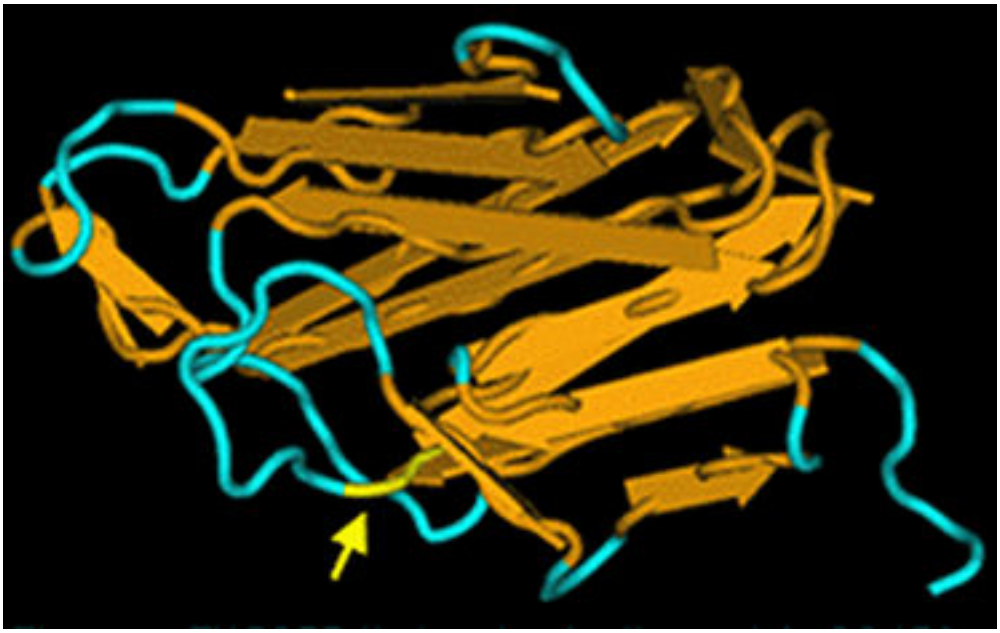
Immunodeficiency with hyper-IgM (HIM) is a rare primary immunodeficiency characterized by the production of normal to increased amounts of IgM antibody of questionable quality and an inability to produce sufficient quantities of IgG and IgA. Individuals with HIM are susceptible to recurrent bacterial infections and are at an increased risk of autoimmune disorders and cancer at an early age.

In a normal immune response to a new antigen, B cells first produce IgM antibody. Later, the B cells switch to produce IgG, IgA and IgE, antibodies that protect tissues and mucosal surfaces more effectively. In the most common form of HIM there is a defect in the gene *TNFSF5*, found on chromosome X at q26. This gene normally produces a CD40 antigen ligand (CD154), a protein on T cells which binds to the CD40 receptor on B and other immune cells. Without CD154, B cells are unable to receive signals from T cells, and thus fail to switch antibody production to IgA and IgG. The absence of CD 40 signals between other immune cells makes individuals with HIM susceptible to infections by opportunistic organisms such as Pneumocystis and Cryptosporidium species.

Treatment of HIM mainly consists of regular IV replacement of the missing IgG antibodies and prompt treatment of infections. Long lasting immunity, however, cannot be maintained without a bone marrow transplant, which is done when a suitable donor is available.

Related diseases

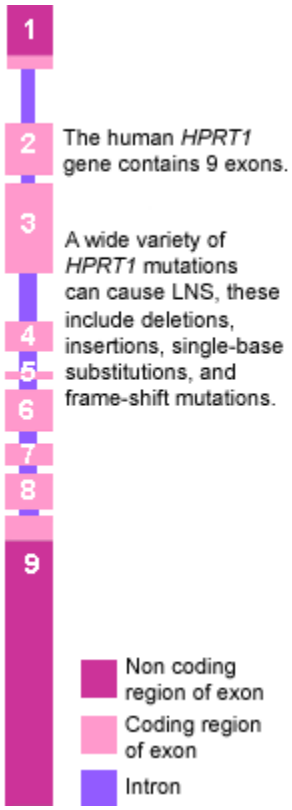
See other Diseases of the Immune System



CD40 antigen ligand (CD154). The gene *TNFSF5* that codes for the protein CD154 above, (formerly CD40L) is mutated in HIM. Mutations have been reported throughout the length of TNFSF5, but are most common in the regions that code for ligand binding (arrow), core structure and the subunit interface.

To see the interactive version of this figure requires Cn3D, a three-dimensional structure viewer.

Lesch-Nyhan syndrome



Lesch-Nyhan syndrome (LNS) is a rare inherited disease that disrupts the metabolism of the raw material of genes.

These raw materials are called purines, and they are an essential part of DNA and RNA. The body can either make purines (de novo synthesis) or recycle them (the resalvage pathway). Many enzymes are involved in these pathways. When one of these enzymes is missing, a wide range of problems can occur.

In LNS, there is a mutation in the *HPRT1* gene located on the X chromosome. The product of the normal gene is the enzyme hypoxanthine-guanine phosphoribosyltransferase, which speeds up the recycling of purines from broken down DNA and RNA. Many different types of mutations affect this gene, and the result is a very low level of the enzyme.

The mutation is inherited in an X-linked fashion. Females who inherit one copy of the mutation are not affected because they have two copies of the X chromosome (XX). Males are severely affected because they only have one X chromosome (XY), and therefore their only copy of the *HPRT1* gene is mutated.

Mutations of the *HPRT1* gene cause three main problems. First is the accumulation of uric acid that normally would have been recycled into purines. Excess uric acid forms painful deposits in the skin (gout) and in the kidney and bladder (urate stones). The second problem is self-mutilation. Affected individuals have to be restrained from biting their fingers and tongues. Finally, there is mental retardation and severe muscle weakness.

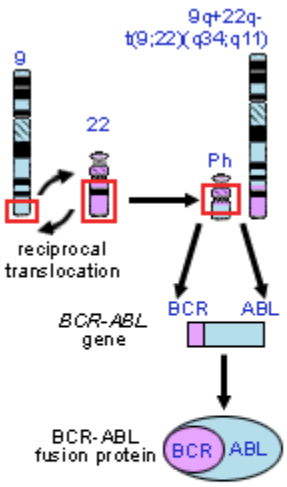
In the year 2000 it was shown that the genetic deficiency in LNS could be corrected *in vitro*. A virus was used to insert a normal copy of the *HPRT1* gene into deficient human cells. Such techniques used in gene therapy may one day provide a cure for this disease. For now, medications are used to decrease the levels of uric acid.

Related diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Leukemia, chronic myeloid



Leukemic white blood cells in CML contain a Philadelphia (Ph) chromosome, the result of a translocation between the long arms of chromosomes 9 and 22. The resulting fusion gene (*BCR-ABL*) produces an altered protein believed to play a key role in the development of CML.

Chronic myeloid leukemia (CML) is a cancer of blood cells, characterized by replacement of the bone marrow with malignant, leukemic cells. Many of these leukemic cells can be found circulating in the blood and can cause enlargement of the spleen, liver, and other organs.

CML is usually diagnosed by finding a specific chromosomal abnormality called the Philadelphia (Ph) chromosome (see figure), named after the city where it was first recorded. The Ph chromosome is the result of a translocation—or exchange of genetic material—between the long arms of chromosomes 9 and 22 . This exchange brings together two genes: the *BCR* (breakpoint cluster region) gene on chromosome 22 and the proto-oncogene *ABL* (Ableson leukemia virus) on chromosome 9. The resulting hybrid gene *BCR-ABL* codes for a fusion protein with tyrosine kinase activity, which activates signal transduction pathways, leading to uncontrolled cell growth.

A mouse model has been created that develops a CML-like disease when given bone marrow cells infected with a virus containing the *BCR-ABL* gene. In other animal models, the fusion proteins have been shown to transform normal blood precursor cells to malignant cells. To research the human disease, antisense oligomers (short DNA segments) that block *BCR-ABL* were developed that specifically suppressed the formation of leukemic cells while not affecting the normal bone marrow cell development. These and other experimental techniques may lead to future treatments for CML.

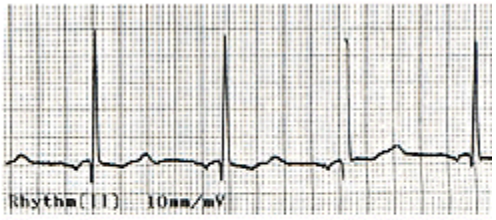
Related diseases

See other Blood and Lymph Diseases

See other Cancers

See other Diseases of the Immune System

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.

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.

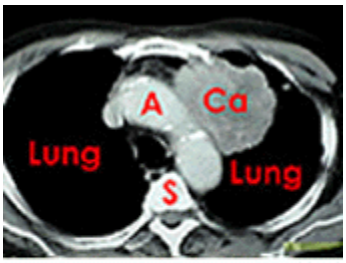
LQTS is usually inherited as an autosomal dominant trait. In the case of LQT1, which has been mapped to chromosome 11, mutations lead to serious structural defects in the person's cardiac potassium channels that do not allow proper transmission of the electrical impulses throughout the heart. There also 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.

Related diseases

See other Diseases of the Heart and Blood Vessels

Lung carcinoma, small cell



CT scan showing lung cancer. [Image credit: Pat Connelly, Miami Valley Hospital, Dayton, OH, USA.]

In the US, lung cancer is the most common cause of cancer deaths among both men and women. In fact, North Americans have the highest rates of lung cancer in the world. In 1997, some 178,100 new cases were diagnosed, and roughly 160,400 deaths occurred from the disease. Sadly, the 5-year survival rate for persons with lung cancer is only 14%. Since the 1940s, the increase in lung cancer mortality by gender has followed historic patterns of smoking, with a 20-year time lag. About 90% of male lung cancer deaths and 80% of female lung cancer deaths are attributable to cigarette smoking. Although smoking is by far the major risk factor for lung cancer, certain industrial substances, such as asbestos, and environmental factors can contribute.

Small cell lung carcinoma is distinctive from other kinds of lung cancer (metastases are already present at the time of discovery) and accounts for approximately 110,000 cancer diagnoses annually. A deletion of part of chromosome 3 was first observed in 1982 in small cell lung carcinoma cell lines.

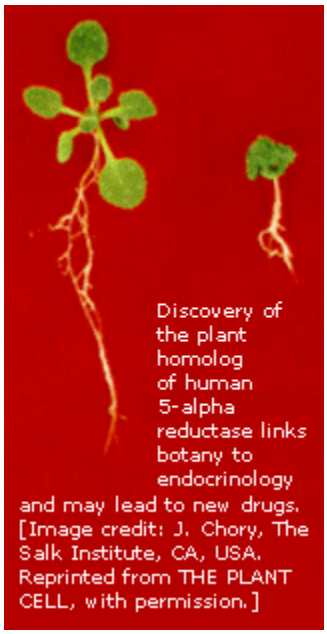
As with other cancers, mutations in a variety of molecules (oncogenes and tumor-suppressor genes) that control cell growth and division are observed, and no one mutation is likely to result in cancerous growth. Basic research into the function of these molecules—how and when they play their role—should help the fight against lung, and other, cancers and give clues to find appropriate therapies.

Related diseases

See other Cancers

See other Respiratory Diseases

Male pattern baldness



Discovery of the plant homolog of human 5-alpha reductase links botany to endocrinology and may lead to new drugs. [Image credit: J. Chory, The Salk Institute, CA, USA. Reprinted from THE PLANT CELL, with permission.]

5-alpha reductase is an enzyme that was first discovered in the male prostate. Here it catalyzes the conversion of testosterone to dihydrotestosterone, which in turn binds to the androgen receptor and initiates development of the external genitalia and prostate. The gene for 5-alpha reductase has been mapped to chromosome 5.

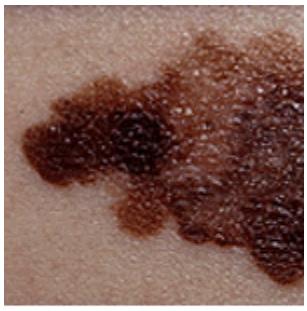
More recently, 5-alpha reductase was found in human scalp and elsewhere in the skin, where it carries out the same reaction as in the prostate. It is thought that disturbances in 5-alpha reductase activity in skin cells might contribute to male pattern baldness, acne, or hirsutism. The discovery of a plant homolog of human 5-alpha reductase may lead to new drugs, and the race is now on to find inhibitors of 5-alpha reductase.

Related diseases

See other Male-Specific Diseases

See other Skin and Connective Tissue Diseases

Malignant melanoma



Malignant melanoma is associated with mutation of a tumor suppressor gene involved in cell cycle control. [Image credit: National Cancer Institute, NIH, Bethesda, MD, USA .]

In 1997, it was expected that about 40,300 Americans would be diagnosed with malignant melanoma, the most aggressive kind of skin cancer. Melanomas are more common in people with lightly pigmented skin, and people who have had melanoma once have a high risk of developing new melanomas.

In some cases, the risk of developing melanoma runs in families, where a mutation in the *CDKN2* gene on chromosome 9 can underlie susceptibility to melanoma. *CDKN2* codes for a protein called p16 that is an important regulator of the cell division cycle; it stops the cell from synthesizing DNA before it divides. If p16 is not working properly, the skin cell does not have this brake on the cell division cycle and so can go on to proliferate unchecked. At some point this proliferation can be seen as a sudden change in skin growth or the appearance of a mole.

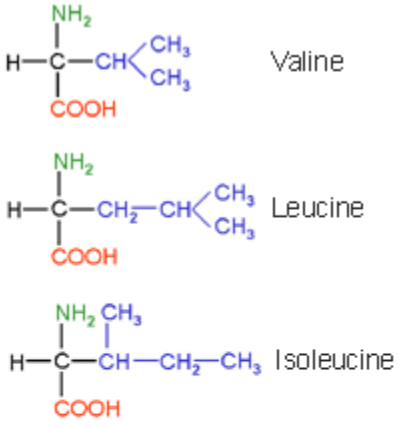
The most powerful weapons against melanoma are therefore 1) prevention, by using protective clothing and sun screen and 2) early detection, by recognizing changes in skin growths or the appearance of new growths. Insight may also be drawn for other cancer types by studying the molecular biology of p16, since the malfunction of other components of the p16 pathway have also been implicated in other cancers.

Related diseases

See other Cancers

See other Skin and Connective Tissue Diseases

Maple syrup urine disease



Amino acids contain an alpha carbon (**C**), an amino group (**NH2**), a carboxyl group (**COOH**), and a unique side group (**R**).

All branched-chain amino acids have side groups that contain a branched carbon chain.

Maple Syrup Urine Disease (MSUD) is an inherited disorder so named because one of its first signs is urine that has an odor reminiscent of maple syrup. The underlying defect disrupts the metabolism of certain amino acids. These are amino acids that have a branched side chain. Because they cannot be fully broken down, they accumulate in the urine, along with their metabolites (alpha-ketoacids) to give the distinctive smell. Left untreated, there is progressive neurodegeneration leading to death within the first months of life.

Three amino acids have branched side chains: valine, leucine, and isoleucine. They are an essential element in the diet and are broken down by the body to yield energy. One step in this breakdown involves the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, which consists of three catalytic components and two regulatory enzymes. In total, six gene loci encode for the BCKDH, and mutations in different loci are responsible for the genetic variety seen in MSUD.

The Mennonite community of Lancaster County, Pennsylvania is particularly afflicted by MSUD, with over 1 of 176 individuals affected. This is due to a high carrier rate of a mutation in the E1alpha-subunit of the BCKDH complex. By contrast, the disease is rare in the general population.

Currently treatment consists of restricting the dietary intake of branched-chain amino acids to the absolute minimum that is needed for growth. However, studies have already shown that it is possible to transfer subunits of the BCKDH enzyme into cells using a retrovirus. Similar advances in gene therapy may provide a future cure.

Related diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Marfan syndrome

Marfan syndrome is a connective tissue disorder, so affects many structures, including the skeleton, lungs, eyes, heart and blood vessels. The disease is characterized by unusually long limbs, and is believed to have affected Abraham Lincoln.

Marfan syndrome is an autosomal dominant disorder that has been linked to the *FBN1* gene on chromosome 15. *FBN1* encodes a protein called fibrillin, which is essential for the formation of elastic fibres found in connective tissue. Without the structural support provided by fibrillin, many tissues are weakened, which can have severe consequences, for example, ruptures in the walls of major arteries.

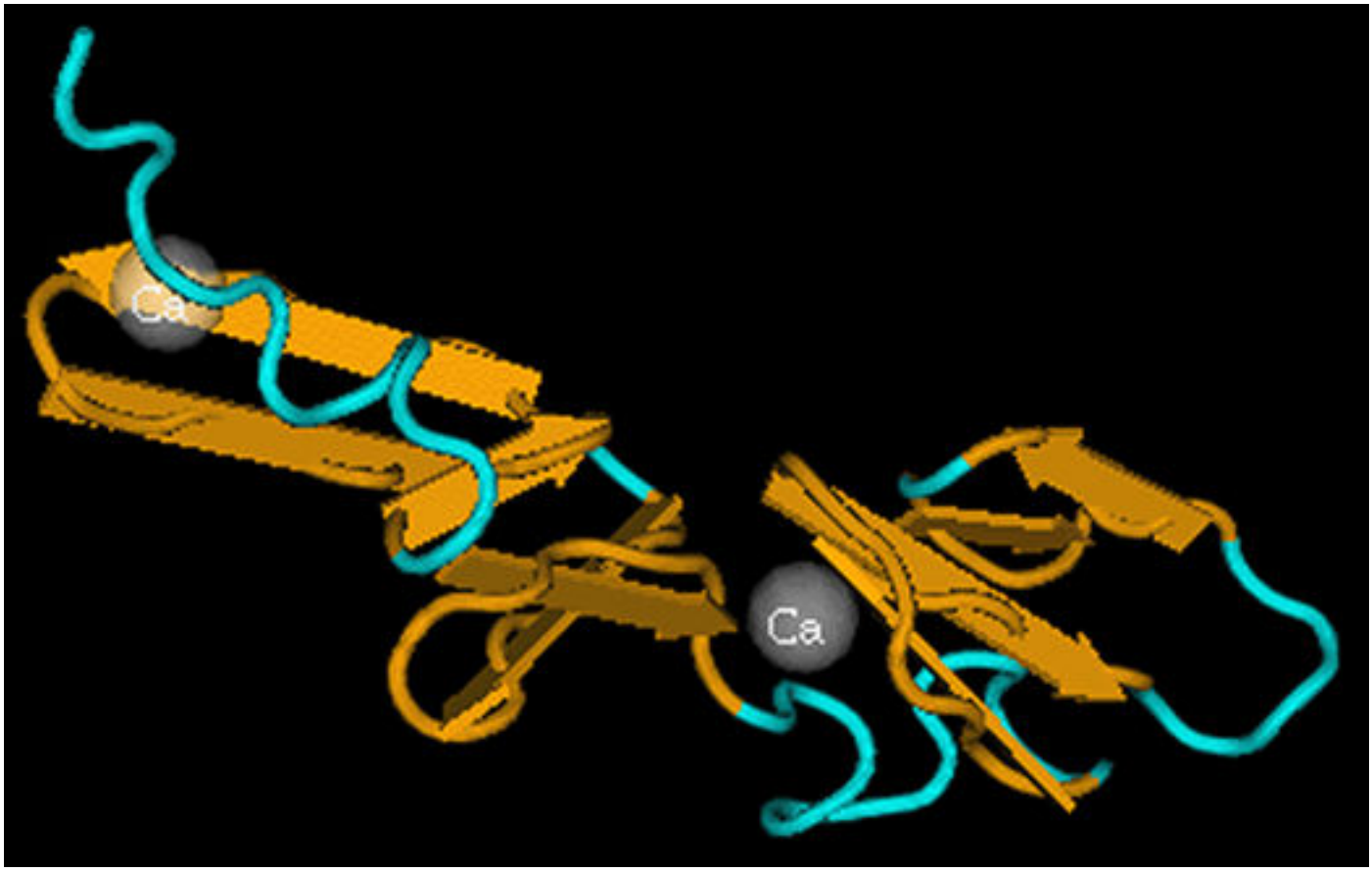
Beta blockers have been used to control some of the cardiovascular symptoms of Marfan syndrome; however, they are not effective against the skeletal and ocular problems, which can also be serious. A related disease has been found in mice, and it is hoped that the study of mouse fibrillin synthesis and secretion, and connective tissue formation, will further our understanding Marfan syndrome in humans.

Related diseases

See other Muscle and Bone Diseases

See other Neonatal Diseases

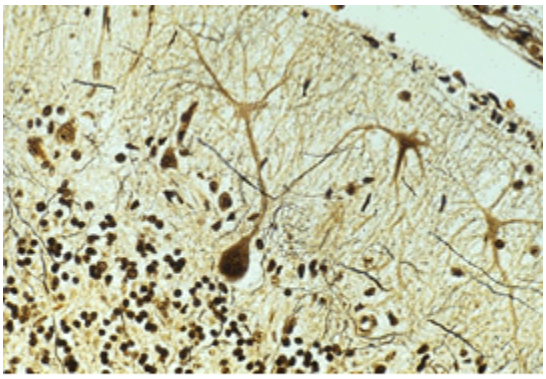
See other Skin and Connective Tissue Diseases



The fibrillin protein. The fibrillin protein, mutated in Marfan syndrome, has about 60 domains, 47 of which bind calcium and have similarity to epidermal growth factor (EGF). In this figure, two of these domains are shown with one calcium ion associated with each domain.

To see the interactive version of this figure requires Cn3D, a three-dimensional structure viewer.

Menkes syndrome



Abnormal Purkinje cell dendrites in the brain of a patient with Menkes disease. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Menkes syndrome is an inborn error of metabolism that markedly decreases the cells' ability to absorb copper. The disorder causes severe cerebral degeneration and arterial changes, resulting in death in infancy. The disease can often be diagnosed by looking at a victim's hair, which appears to be both whitish and kinked when viewed under a microscope.

Menkes' disease is transmitted as an X-linked recessive trait. Sufferers can not transport copper, which is needed by enzymes involved in making bone, nerve and other structures. A number of other diseases, including type IX Ehlers-Danlos syndrome, may be the result of allelic mutations (i.e. mutations in the same gene, but having slightly different symptoms) and it is hoped that research into these diseases may prove useful in fighting Menkes' disease.

If administered within the first few months of life, copper histidinate appears to be effective in increasing the life expectancy of some patients. However, this treatment only increases life expectancy from three to thirteen years of age, so can only be considered a palliative. A similar condition to Menkes' disease exists in mice; working with these model organisms will help give insight into human copper transport mechanisms, so helping to develop effective treatments for Menkes' sufferers.

Related diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

See other Skin and Connective Tissue Diseases

Multiple endocrine neoplasia

Multiple endocrine neoplasia (MEN) is a group of rare diseases caused by genetic defects that lead to hyperplasia (abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue) and hyperfunction (excessive functioning) of two or more components of the endocrine system.

Endocrine glands are different from other organs in the body because they release hormones into the bloodstream. Hormones are powerful chemicals that travel through the blood, controlling and instructing the functions of various organs. Normally, the hormones released by endocrine glands are carefully balanced to met the body's needs. When a person has MEN, specific endocrine glands, such as the parathyroid glands, the pancreas gland, and the pituitary gland, tend to become overactive. When these glands go into overdrive, the result can be: excessive calcium in the bloodstream (resulting in kidney stones or kidney damage); fatigue; weakness; muscle or bone pain; constipation; indigestion; and thinning of bones.

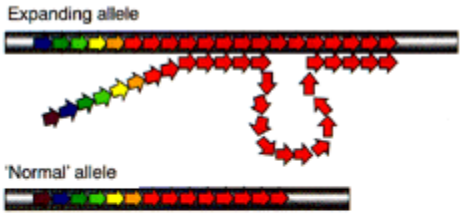
The MEN1 gene, which has been known for several years to be found on chromosome 11, was more finely mapped in 1997.

Related diseases

See other Cancers

See other Glands and Hormones Diseases

Myotonic dystrophy



Diseases such as myotonic dystrophy (DM) result from the effects of an expansion of a repeat sequence (red arrows) of DNA. In the case of DM, it is not yet clear whether the expansion effects just the myotonic dystrophy protein kinase gene, or multiple genes. [Reproduced from Richards, R.I. and Sutherland, G.R. (1997) Trends Biochem. Sci. 22, 432-43, with permission.]

Myotonic dystrophy is an inherited disorder in which the muscles contract but have decreasing power to relax. With this condition, the muscles also become weak and waste away. Myotonic dystrophy can cause mental deficiency, hair loss and cataracts. Onset of this rare disorder commonly occurs during young adulthood. However, it can occur at any age and is extremely variable in degree of severity.

The myotonic dystrophy gene, found on chromosome 19, codes for a protein kinase that is found in skeletal muscle, where it likely plays a regulatory role.

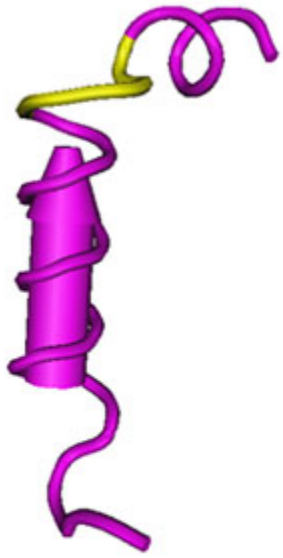
An unusual feature of this illness is that its symptoms usually become more severe with each successive generation. This is because mistakes in the faithful copying of the gene from one generation to the next result in the amplification of a genomic 'AGC/CTG triplet repeat', similar to that found in Huntington disease. Unaffected individuals have between 5 and 27 copies of AGC/CTG, myotonic dystrophy patients who are minimally affected have at least 50 repeats, while more severely affected patients have an expansion of up to several kilobase pairs.

Related diseases

See other Muscle and Bone Diseases

See other Diseases of the Nervous System

Narcolepsy



The human hypocretin-2 protein is 28 amino acids long. It contains two alpha-helix domains (shown in purple) that are connected by a flexible loop (shown in yellow).

Narcolepsy is a sleep disorder. Affected individuals are extremely drowsy during the daytime and may fall into a deep sleep at any time. After a short nap, the patient may feel refreshed, but it is only a short period of time before drowsiness returns.

The second major symptom of narcolepsy is called cataplexy. Cataplexy refers to a sudden weakness of the muscles that leads to collapse. This is often triggered by an emotional response such as laughter, surprise, or anger.

The normal stages of sleep include a phase of rapid eye movement (REM). It is during the REM phase of sleep when we dream and during this time that our muscles become completely relaxed. The problem in narcolepsy is that REM can occur while awake, resulting in half-sleep dreams and temporary paralysis.

The genetics of narcolepsy is complex, but it is thought that a newly discovered group of proteins may be involved. These proteins are called hypocretins (also known as orexins), and they signal messages in the brain. When hypocretins are given to rats, they induce wakefulness. Dogs that have a mutation in the hypocretin receptor Hcrt2 have narcolepsy. Mice that have a mutation in the hypocretin gene also have narcolepsy. A mutation in the hypocretin gene is extremely rare in human narcolepsy. However, affected individuals do have very low levels of hypocretins, suggesting the loss of the brain cells that secrete hypocretin.

Although there are rare families where narcolepsy is passed on through several generations, most cases of narcolepsy occur at random rather than being inherited. The likelihood of developing narcolepsy is influenced by proteins known as histocompatibility leukocyte antigens (HLA). HLA refers to a group of proteins (antigens) that influence the level to which white blood cells (leukocytes) accept transplanted tissue (histocompatibility). It is now known that hypocretin deficiency in humans is closely associated with the HLA protein DQB1*0602. It has been suggested that the cause of human narcolepsy is the body's immune cells attacking and damaging the neurons that secrete hypocretin.

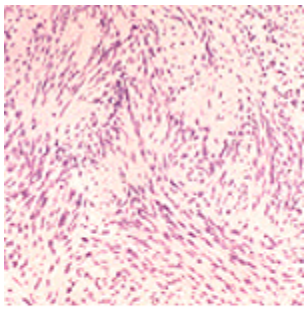
The daytime sleepiness of narcolepsy is treated with stimulants similar to amphetamine, and cataplexy is treated with antidepressants. More effective treatments are being investigated and may include replacing the missing hypocretins with drugs that stimulate the hypocretin receptors.

As our understanding grows about the mechanisms that underlie sleeping, wakefulness, and narcolepsy, we will progress toward finding a cure for this disease.

Related diseases

See other Diseases of the Nervous System

Neurofibromatosis



Microscopic section of a schwannoma, a tumor commonly found in patients with NF-2. [Image credit: K Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Neurofibromatosis, type 2, (NF-2) is a rare inherited disorder characterized by the development of benign tumors on both auditory nerves (acoustic neuromas). The disease is also characterized by the development of malignant central nervous system tumors as well.

The NF2 gene has been mapped to chromosome 22 and is thought to be a so-called 'tumor- suppressor gene'. Like other tumor suppressor genes (such as p53 and Rb), the normal function of NF2 is to act as a brake on cell growth and division, ensuring that cells do not divide uncontrollably, as they do in tumors. A mutation in NF2 impairs its function, and accounts for the clinical symptoms observed in neurofibromatosis sufferers. NF-2 is an autosomal dominant genetic trait, meaning it affects both genders equally and that each child of an affected parent has a 50% chance of inheriting the gene.

We are learning more about the function of the NF2 gene through studies of families with neurofibromatosis type 2 and through work in model organisms, particularly mice. The exact molecular function of NF2 in the cell is still unknown, although the protein is similar to the ERM family of cytoskeleton-membrane linker proteins. Further work on the binding partners of NF2 would help to identify potential specific targets for future drug therapies.

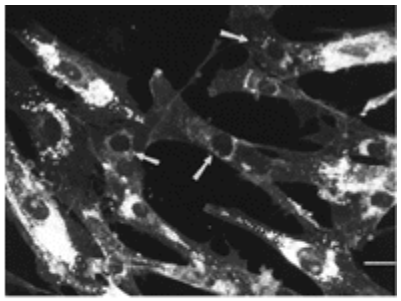
Related diseases

See other Cancers

See other Ear, Nose, and Throat Diseases

See other Diseases of the Nervous System

Niemann-Pick disease



Cells stained to show unesterified cholesterol in NP-C cells (white). The arrows show cell normalized by transfection with NPC1 DNA. [Reproduced with permission from Carstea et al. (1997) Science 277, 228-231.]

In 1914, German pediatrician Albert Niemann described a young child with brain and nervous system impairment. Later, in the 1920's, Luddwick Pick studied tissues after the death of such children and provided evidence of a new disorder, distinct from those storage disorders previously described.

Today, there are three separate diseases that carry the name Niemann-Pick: Type A is the acute infantile form, Type B is a less common, chronic, non-neurological form, while Type C is a biochemically and genetically distinct form of the disease. Recently, the major locus responsible for Niemann-Pick type C (NP-C) was cloned from chromosome 18, and found to be similar to proteins that play a role in cholesterol homeostasis.

Usually, cellular cholesterol is imported into lysosomes—'bags of enzymes' in the cell—for processing, after which it is released. Cells taken from NP-C patients have been shown to be defective in releasing cholesterol from lysosomes. This leads to an excessive build-up of cholesterol inside lysosomes, causing processing errors. NPC1 was found to have known sterol-sensing regions similar to those in other proteins, which suggests it plays a role in regulating cholesterol traffic.

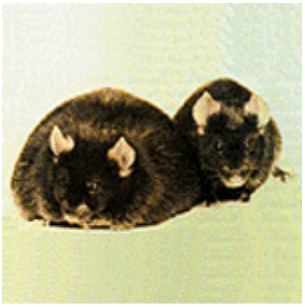
Related diseases

See other Blood and Lymph Diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Obesity



A mouse with the Obese (Ob) mutation and a normal mouse. [Image credit: Jeff Friedman, Rockfeller University, New York, NY, USA. Reprinted from Science, with permission.]

Obesity is an excess of body fat that frequently results in a significant impairment of health. Doctors generally agree that men with more than 25% body fat and women with more than 30% are obese. Obesity is a known risk factor for chronic diseases including heart disease, diabetes, high blood pressure, stroke and some forms of cancer. Evidence suggests that obesity has more than one cause: genetic, environmental, psychological and other factors may all play a part.

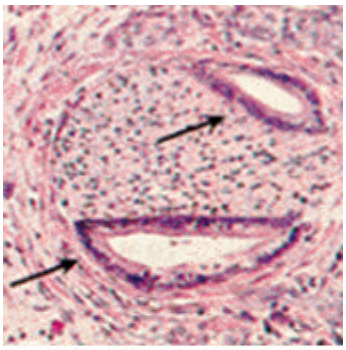
The hormone leptin, produced by adipocytes (fat cells), was discovered about three years ago in mice. Subsequently the human Ob gene was mapped to chromosome 7. Leptin is thought to act as a lipostat: as the amount of fat stored in adipocytes rises, leptin is released into the blood and signals to the brain that the body has enough to eat. However, most overweight people have high levels of leptin in their bloodstream, indicating that other molecules also effect feelings of satiety and contribute to the regulation of body weight.

The discovery of leptin has initiated a flurry of research into the molecular basis of weight control. A whole network of signals contributes to weight homeostasis, and other key players are being discovered on an ongoing basis. Mice have proved to be an extremely useful model for human obesity, and have helped to begin to unravel the components that contribute to maintaining body weight. Since the market for effective weight-reducing therapies is enormous, drug companies are working alongside basic scientists to find possible drug targets among the tangle of molecules that control body weight.

Related diseases

See other Nutritional and Metabolic Diseases

Pancreatic cancer



Loss of DPC4 (Smad4) gene causes pancreatic cancers to grow aggressively, as seen by tumor cells invading a nerve bundle. [Image credit: R.H. Hruban, Johns Hopkins University, Baltimore, MD, USA. Reprinted from SCIENCE, with permission.]

The pancreas is responsible for producing the hormone insulin, along with other substances. It also plays a key role in the digestion of protein. There were an estimated 27,000 new cases of pancreatic cancer in the US in 1997, with 28,100 deaths from the disease.

About 90% of human pancreatic carcinomas show a loss of part of chromosome 18. In 1996, a possible tumor suppressor gene, DPC4 (Smad4), was discovered from the section that is lost in pancreatic cancer, so may play a role in pancreatic cancer. There is a whole family of Smad proteins in vertebrates, all involved in signal transduction of transforming growth factor β (TGFβ) related pathways. Other tumor suppressor genes include p53 and Rb, which, if mutated or absent from the genome can contribute to cancerous growth in a variety of tissues.

DPC4 (Smad4) homologs exist in the worm (*Caenorhabditis elegans*), mouse and the fly (*Drosophila*). In *Drosophila*, when the gene is not present, there a number of developmental defects. Likewise, homozygous Smad4 mutant mouse embryos die before embryonic day 7.5, and have reduced size because of reduced cell proliferation. Research on these model organisms should help elucidate the role of Smad4 and related proteins in humans.

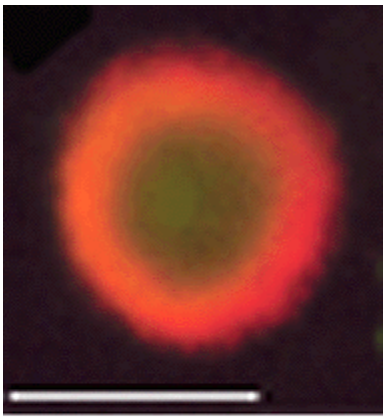
Related diseases

See other Cancers

See other Diseases of the Digestive System

See other Nutritional and Metabolic Diseases

Parkinson disease



An overlapping immunofluorescent stain showing alpha-synuclein localization in Lewy bodies of Parkinson's disease brain. The Lewy body is stained green (with antibody against ubiquitin), while alpha-synuclein is stained red. Where both ubiquitin and alpha-synuclein are found, the stain appears yellow/orange. With thanks to M. Polymeropoulos for supplying the picture.

Parkinson disease, first described by James Parkinson in 1817, is a growing national problem, with more than half a million Americans affected at any one time. Most people are over 50 years old when the disease appears, although it can occur in younger patients. It is a neurodegenerative disease that manifests as a tremor, muscular stiffness and difficulty with balance and walking. A classic pathological feature of the disease is the presence of an inclusion body, called the Lewy body, in many regions of the brain.

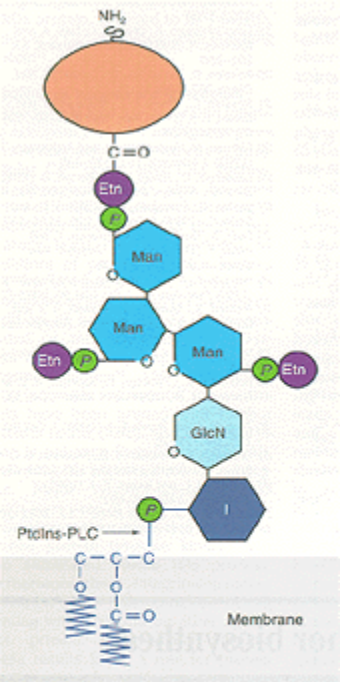
Until relatively recently, Parkinson disease was not though to be heritable, and research was primarily focused on environmental risk factors such as viral infection or neurotoxins. However, a positive family history was gradually perceived to be a risk factor, a view that was confirmed last year when a candidate gene for some cases of Parkinson disease was mapped to chromosome 4. Mutations in this gene have now been linked to several Parkinson disease families. The product of this gene, a protein called alpha-synuclein, is a familiar culprit: a fragment of it is a known constituent of Alzheimer disease plaques.

Since alpha-synuclein fragments are implicated in both Parkinson and Alzheimer diseases, there may be shared pathogenic mechanisms between the two, therefore research into one disease may aid understanding of the other. Further avenues for research are also being suggested by cross-species comparisons assisted by database searching. Among others, rats, cows and zebra finches all possess alpha-synuclein; in the rat they play a role in the sense of smell, while in the zebra finch it is thought to be involved in the process of song learning. Further work to elucidate the function of alpha-synuclein in humans, and therefore clues as to the pathology of Parkinson disease, should be assisted by studying these other species.

Related diseases

See other Diseases of the Nervous System

Paroxysmal nocturnal hemoglobinuria



A glycosylphosphatidylinositol (GPI) anchor - people with paroxysmal nocturnal hemoglobinuria (PNH) have a mutation in the first enzyme in the GPI anchor synthesis pathway. [Reproduced with permission from Takeda, J. and Kinoshita, T. (1995) Trends Biochem. Sci. 20, 367-371.]

The distinct and rather peculiar characteristics of paroxysmal nocturnal hemoglobinuria (PNH) have puzzled hematologists for more than a century. PNH is characterized by a decreased number of red blood cells (anemia), and the presence of blood in the urine (hemoglobinuria) and plasma (hemoglobinemia), which is evident after sleeping. PNH is associated with a high risk of major thrombotic events, most commonly thrombosis of large intra-abdominal veins. Most patients who die of their disease die of thrombosis.

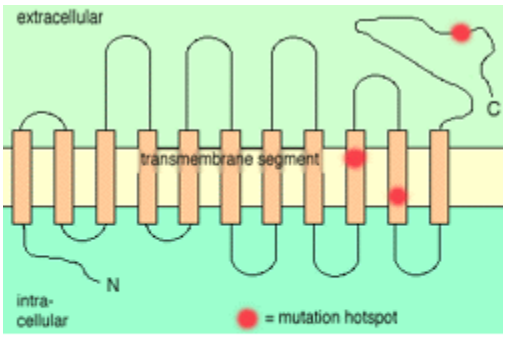
PNH blood cells are deficient in an enzyme known as PIG-A, which is required for the biosynthesis of cellular anchors. Proteins that are partly on the outside of cells are often attached to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor, and PIG-A is required for the synthesis of a key anchor component. If PIG-A is defective, surface proteins that protect the cell from destructive components in the blood (complement) are not anchored and therefore absent, so the blood cells are broken down.

The PIG-A gene is found on the X chromosome. Although not an inherited disease, PNH is a genetic disorder, known as an acquired genetic disorder. The affected blood cell clone passes the altered PIG-A to all its descendants—red cells, leukocytes (including lymphocytes), and platelets. The proportion of abnormal red blood cells in the blood determines the severity of the disease.

Related diseases

See other Blood and Lymph Diseases

Pendred syndrome



Model of the human pendrin protein, based on the predicted amino acid sequence. The approximate positions of mutations in some pendred syndrome patients are shown in red.

Pendred syndrome is an inherited disorder that accounts for as much as 10% of hereditary deafness. Patients usually also suffer from thyroid goiter. The recent discovery of the gene for Pendred syndrome illuminates a disorder that has confounded scientists for more than a century.

In December of 1997, scientists at NIH's National Human Genome Research Institute used the physical map of human chromosome 7 to help identify an altered gene, *PDS*, thought to cause pendred syndrome. The normal gene makes a protein, called pendrin, that is found at significant levels only in the thyroid and is closely related to a number of sulfate transporters. When the gene for this protein is mutated, the person carrying it will exhibit the symptoms of Pendred syndrome.

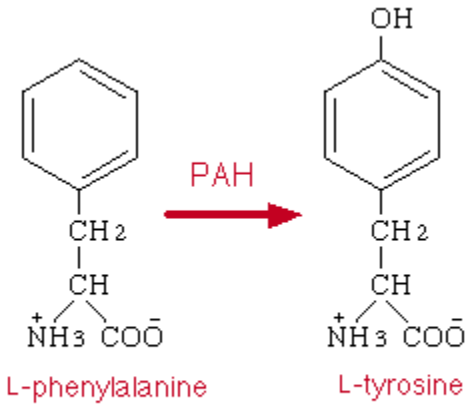
Because goiter is not always found in Pendred syndrome patients, it is possible that a defective pendrin gene will turn out to be responsible for some cases of deafness that had not previously been attributed to this disorder. The discovery of pendrin should also stimulate new angles of research into thyroid physiology and the role of altered sulfur transport in human disease.

Related diseases

See other Ear, Nose, and Throat Diseases

See other Glands and Hormones Diseases

Phenylketonuria



The enzyme phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine.

Phenylketonuria (PKU) is an inherited error of metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase. Loss of this enzyme results in mental retardation, organ damage, unusual posture and can, in cases of maternal PKU, severely compromise pregnancy.

Classical PKU is an autosomal recessive disorder, caused by mutations in both alleles of the gene for phenylalanine hydroxylase (PAH), found on chromosome 12. In the body, phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine, another amino acid. Mutations in both copies of the gene for PAH means that the enzyme is inactive or is less efficient, and the concentration of phenylalanine in the body can build up to toxic levels. In some cases, mutations in PAH will result in a phenotypically mild form of PKU called hyperphenylalanemia. Both diseases are the result of a variety of mutations in the PAH locus; in those cases where a patient is heterozygous for two mutations of PAH (ie each copy of the gene has a different mutation), the milder mutation will predominate.

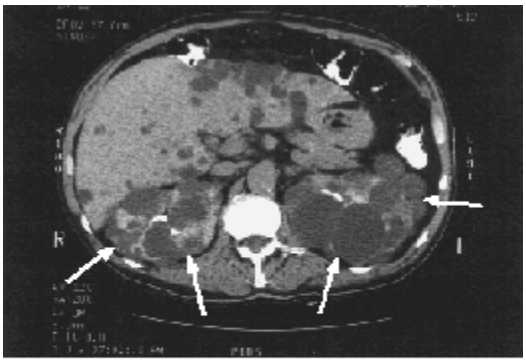
A form of PKU has been discovered in mice, and these model organisms are helping us to better understand the disease, and find treatments against it. With careful dietary supervision, children born with PKU can lead normal lives, and mothers who have the disease can produce healthy children.

Related diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Polycystic kidney disease



Contrast-enhanced abdominal computed tomography showing kidneys (arrows) containing numerous cystic masses. [Reproduced with permission from Fred, H.L. and Siddique, I. (1995) New Eng. J. Med. 333, 31.]

Adult polycystic kidney disease (APKD) is characterized by large cysts in one or both kidneys and a gradual loss of normal kidney tissue which can lead to chronic renal failure. The role of the kidneys in the body is to filter the blood, excreting the end-products of metabolism in the form of urine and regulating the concentrations of hydrogen, sodium, potassium, phosphate and other ions in the extracellular fluid.

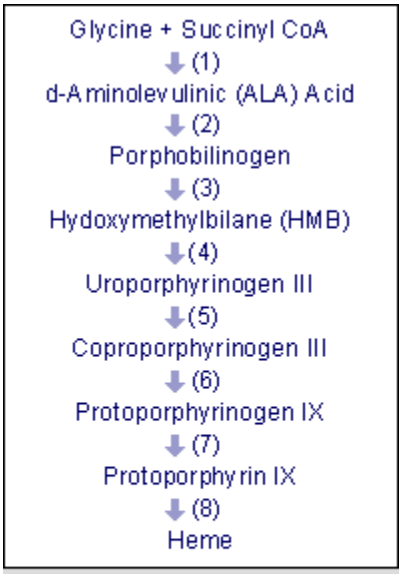
In 1994 the European Polycystic Kidney Disease Consortium isolated a gene from chromosome 16 that was disrupted in a family with APCD. The protein encoded by the PKD1 gene is an integral membrane protein involved in cell-cell interactions and cell-matrix interactions. The role of PKD1 in the normal cell may be linked to microtubule-mediated functions, such as the placement of Na(+), K(+)-ATPase ion pumps in the membrane. Programmed cell death, or apoptosis, may also be invoked in APKD. Further clarification of the pathogenesis of the disease await further research.

The so-called 'cpk mouse' is a well known model for the human disease. Studying the molecular basis of the disease in the mouse is expected to provide a better understanding of the human disease, and is hoped to lead to more effective therapies.

Related diseases

See other Cancers

Porphyria



Click here for further information.

Porphyria is a diverse group of diseases in which production of heme is disrupted. Porphyria is derived from the Greek word "porphyra", which means purple. When heme production is faulty, porphyrins are overproduced and lend a reddish-purple color to urine.

Heme is composed of porphyrin, a large circular molecule made from four rings linked together with an iron atom at its center. Heme is the oxygen-binding part of hemoglobin, giving red blood cells their color. It is also a component of several vital enzymes in the liver including the group known as cytochrome P450. This enzyme family is important in converting potentially harmful substances such as drugs to inactive products destined for excretion.

Heme synthesis takes place in several steps, each of which requires a specific enzyme of which there are 8 in total. The genes that encode these enzymes are located on different chromosomes, and mutations of these genes can be inherited in either an autosomal dominant or autosomal recessive fashion, depending on the gene concerned. Affected individuals are unable to complete heme synthesis, and intermediate products, porphyrin or its precursors, accumulate.

Environmental triggers are important in many attacks of porphyria. Example triggers include certain medications, fasting, or hormonal changes. Genetic carriers who avoid a triggering exposure may never experience symptoms.

The cutaneous porphyrias cause sun sensitivity, with blistering typically on the face, back of the hands, and other sun-exposed areas. The most common of these is porphyria cutanea tarda (PCT). Triggering factors are alcohol use, estrogen, iron, and liver disease, particularly hepatitis C.

The acute porphyrias typically cause abdominal pain and nausea. Some patients have personality changes and seizures at the outset. With time the illness can involve weakness in many different muscles.

The cutaneous and acute forms are treated differently. Cure of these genetic diseases awaits the results of ongoing research on the safest and most effective means of gene transfer or correction.

Step in Pathway	Enzyme	Disease caused by enzyme deficiency
1	ALA synthase	
2	ALA dehydratase	ALAD porphyria
3	HMB synthase	Acute intermittant porphyria
4	Uroporphyrinogen synthase (UROS)	Congenital erythropoietic porphyria
5	Uroporphyrinogen decarboxylase (UROD)	Porphyria cutanea tarda
6	Coproporphyrinogen oxidase	Hereditary copropophyria
7	Protoporphyrinogen oxidase	Variegate pophyria
8	Ferrochelatase	Erythropoietic protoporphyria

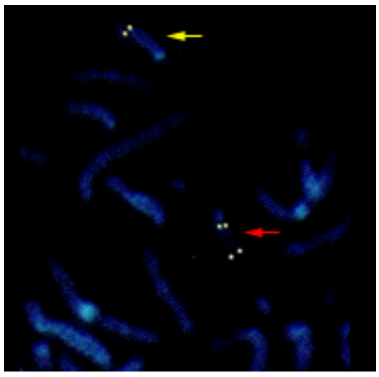
Related diseases

See other Blood and Lymph Diseases

See other Nutritional and Metabolic Diseases

See other Skin and Connective Tissue Diseases

Prader-Willi syndrome



In the Prader-Willi syndrome (PWS) cell above, the maternally derived chromosome 15 (red arrow) shows two signals: one from a control area (which is also seen in the paternally derived chromosome [yellow arrow]) and another, which is from the PWS region. This signal is missing from the paternal chromosome because the region is deleted in this PWS patient. [Reproduced with permission from Martin et al. (1998) Am J Psychiatry Sep;155(9):1265-73.]

Prader-Willi syndrome (PWS) is an uncommon genetic disorder characterized by mental retardation, decreased muscle tone, short stature, emotional lability and an insatiable appetite which can lead to life-threatening obesity. The syndrome was first described in 1956 by Drs. Prader, Labhart, and Willi.

PWS is caused by the absence of segment 11-13 on the long arm of the paternally derived chromosome 15. In 70-80% of PWS cases, the region is missing due to a deletion. Certain genes in this region are normally suppressed on the maternal chromosome, so, for normal development to occur, they must be expressed on the paternal chromosome. When these paternally derived genes are absent or disrupted, the PWS phenotype results. When this same segment is missing from the maternally derived chromosome 15, a completely different disease, Angelman syndrome, arises. This pattern of inheritance — when expression of a gene depends on whether it is inherited from the mother or the father — is called genomic imprinting. The mechanism of imprinting is uncertain, but, it may involve DNA methylation.

Genes found in the PWS chromosomal region code for the small ribonucleoprotein N (SNRPN). SNRPN is involved in mRNA processing, an intermediate step between DNA transcripton and protein formation. A mouse model of PWS has been developed with a large deletion which includes the SNRPN region and the PWS 'imprinting centre' (IC) and shows a phenotype similar to infants with PWS. These and other molecular biology techniques may lead to a better understanding of PWS and the mechanisms of genomic imprinting.

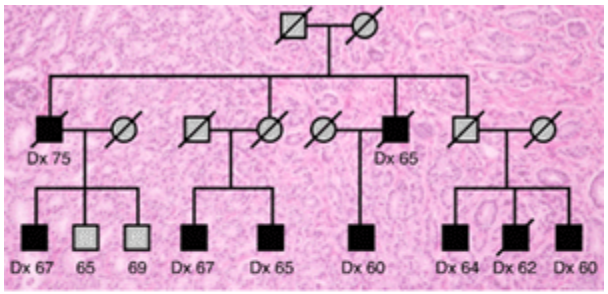
Related diseases

See other Neonatal Diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Prostate cancer



Hereditary prostate cancer (HPC) accounts for about 10% of all prostate cancer, and HPC1 is estimated to account for approximately 34% of these hereditary cases.

Background: histological section of a pateint with HPC. Foreground: pedigree of a typical family demonstrating multiple affected individuals (sold boxes) whose disease links to the HPC1 region on chromosome 1.
[With thanks to Jeffrey Trent and colleagues, NIHGR, NIH for supplying the image.]

The second leading cause of cancer death in American men, prostate cancer will be diagnosed in an estimated 184,500 American men in 1998 and will claim the lives of an estimated 39,200. Prostate cancer mortality rates are more than two times higher for African-American men than white men. The incidence of prostate cancer increases with age; more than 75% of all prostate cancers are diagnosed in men over age 65.

Despite the high prevalence of prostate cancer, little is known about the genetic predisposition of some men to the disease. Numerous studies point to a family history being a major risk factor, which may be responsible for an estimated 5-10% of all prostate cancers.

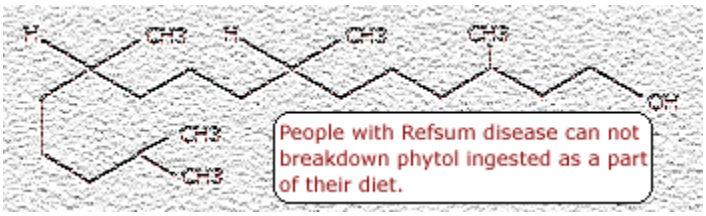
One of the most promising recent breakthroughs may be the discovery of a susceptibility locus for prostate cancer on chromosome 1, called HPC1, which may account for about 1 in 500 cases of prostate cancer. The next step will be to clone the gene. Once researchers have the sequence, they will be able to search the databases to compare the HPC1 sequence to previously characterized proteins from both humans and other animals. This should provide clues as to the function of HPC1 in the cell, and suggest potential starting points to find drug targets.

Related diseases

See other Cancers

See other Male-Specific Diseases

Refsum disease



Refsum disease is a rare disorder of lipid metabolism that is inherited as a recessive trait. Symptoms may include a degenerative nerve disease (peripheral neuropathy), failure of muscle coordination (ataxia), retinitis pigmentosa (a progressive vision disorder), and bone and skin changes. Refsum disease is characterized by an accumulation of phytanic acid in the plasma and tissues. is a derivative of phytol, a component of chlorophyll.

In 1997 the gene for Refsum disease was identified and mapped to chromosome 10. The protein product of the gene, PAHX, is an enzyme that is required for the metabolism of phytanic acid. Refsum disease patients have impaired PAHX - phytanic acid hydrolase. It is thought that Refsum disease is a peroxisomal disorder, since human PAHX contains PTS2 localization sequences, which target it to the peroxisome.

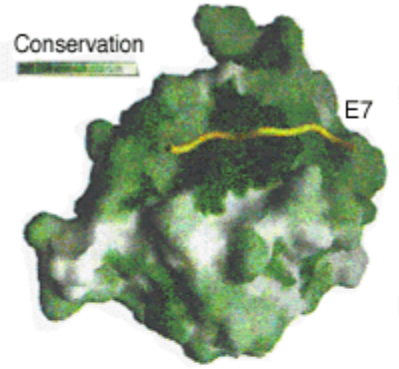
Our bodies can not synthesize phytanic acid: we have to obtain all of it from our food. Therefore, prolonged treatment with a diet deficient in phytanic acid can be beneficial.

Related diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Retinoblastoma



A complex of retinoblastoma protein (RB) with E7 - a viral oncoprotein that frequently binds to RB and blocks its function in cervical cancer. The degree of green color shows the conservation of amino acids in RB and related proteins. [Reproduced from Lee, J-O., Russo, A.A. and Pavletich, N.P. (1998) Nature 391, 859-865, with permission.]

Retinoblastoma occurs in early childhood and affects about 1 child in 20,000. The tumor develops from the immature retina - the part of the eye responsible for detecting light and color. There are both hereditary and non-hereditary forms of retinoblastoma. IN the hereditary form, multiple tumors are found in both eyes, while in the non-hereditary form only one eye is effected and by only one tumor.

In the hereditary form, a gene called Rb is lost from chromosome 13. Since the absence of Rb seemed to be linked to retinoblastoma, it has been suggested that the role of Rb in normal cells is to suppress tumor formation. Rb is found in all cells of the body, where under normal conditions it acts as a brake on the cell division cycle by preventing certain regulatory proteins from triggering DNA replication. If Rb is missing, a cell can replicate itself over and over in an uncontrolled manner, resulting in tumor formation.

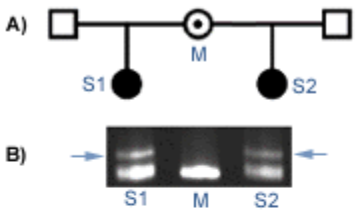
Untreated, retinoblastoma is almost uniformly fatal, but with early diagnosis and modern methods of treatment the survival rate is over 90%. Since the Rb gene is found in all cell types, studying the molecular mechanism of tumor suppression by Rb will give insight into the progression of many types of cancer, not just retinoblastoma.

Related diseases

See other Cancers

See other Diseases of the Eye

Rett syndrome



A) Pedigree of half-sisters (S1 and S2) with Rett syndrome and their carrier mother (M). **B)** Conformation-sensitive gel electrophoresis (CSGE) showing the same extra band (arrows) in the DNA of both half-sisters, not present in their mother (M). It is likely that the mother, who is normal, transmitted the disease to her daughters through a germline mutation present in her ovum, but not in the other cells of her body. [Adapted from Amir, R.E. et al. (1999) *Nature Genetics* 23, 185 –188., with permission.]

Rett syndrome (RTT) is a progressive neurodevelopmental disorder almost exclusively affecting females. With an incidence of about 1 in 10,000 births, it is a common cause of profound mental impairment in girls. Typically, babies with RTT develop normally until the age of 6 to 18 months, when their developmental milestones regress. They lose purposeful use of their hands and are seriously disabled for life, with reduced muscle tone and seizures. A temporary "autistic-like" phase often occurs at the onset of the disorder, and older children are known for their social engagement through intense eye gaze.

RTT is caused by mutations in the gene MeCP2, found on the X chromosome. MeCP2 is called a "transcriptional repressor" because it codes for a protein that controls the expression of other genes. Depending on what part of the gene contains the mutation, partial loss of this protein changes the environment experienced by developmentally important proteins which, in turn, leads to the RTT phenotype.

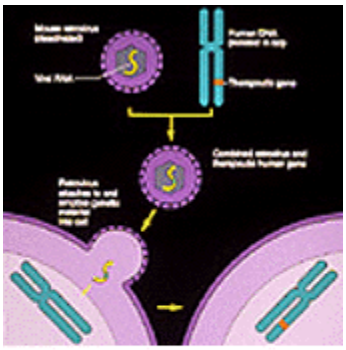
MeCP2 mutations seem to be more common in the X chromosome from sperm cells, which may explain why RTT is rare in boys, who do not inherit an X chromosome from their father. Girls, however, inherit one copy of the X chromosome from each parent. Girls with RTT have one functional copy of MeCP2 to counteract the mutated MeCP2 copy. But, in a normal process called X inactivation, one X chromosome is randomly inactivated in every cell. This results in the normal copy of MeCP2 being inactivated in some cells but not in others. X-inactivation coupled with the specific MeCP2 mutation type causes the range of symptoms seen in RTT. By studying the relationships between the MeCP2 proteins and the proteins affected by it, investigators hope to develop treatments for Rett syndrome.

Related diseases

See other Female-Specific Diseases

See other Diseases of the Nervous System

Severe combined immunodeficiency



Gene therapy has been attempted to treat severe combined immunodeficiency caused by a missing enzyme, adenosine deaminase. [Image credit: National Cancer Institute.]

Severe combined immunodeficiency (SCID) represents a group of rare, sometimes fatal, congenital disorders characterized by little or no immune response. The defining feature of SCID, commonly known as "bubble boy" disease, is a defect in the specialized white blood cells (B- and T-lymphocytes) that defend us from infection by viruses, bacteria and fungi. Without a functional immune system, SCID patients are susceptible to recurrent infections such as pneumonia, meningitis and chicken pox, and can die before the first year of life. Though invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients.

All forms of SCID are inherited, with as many as half of SCID cases linked to the X chromosome, passed on by the mother. X-linked SCID results from a mutation in the interleukin 2 receptor gamma (IL2RG) gene which produces the common gamma chain subunit, a component of several IL receptors. IL2RG activates an important signalling molecule, JAK3. A mutation in JAK3, located on chromosome 19, can also result in SCID. Defective IL receptors and IL receptor pathways prevent the proper development of T-lymphocytes that play a key role in identifying invading agents as well as activating and regulating other cells of the immune system.

In another form of SCID, there is a lack of the enzyme adenosine deaminase (ADA), coded for by a gene on chromosome 20. This means that the substrates for this enzyme accumulate in cells. Immature lymphoid cells of the immune system are particularly sensitive to the toxic effects of these unused substrates, so fail to reach maturity. As a result, the immune system of the afflicted individual is severely compromised or completely lacking.

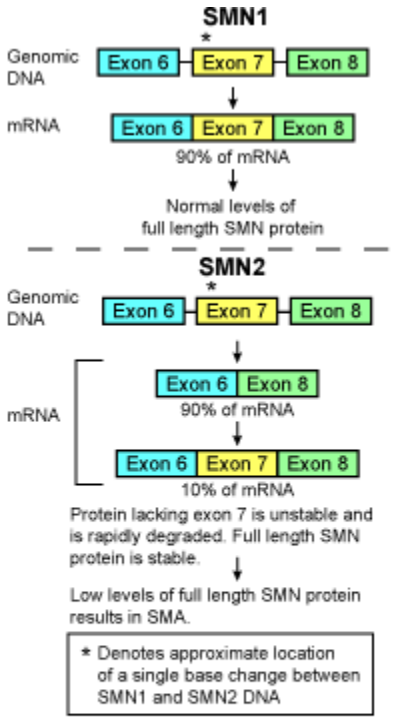
Some of the most promising developments in the search for new therapies for SCID center on 'SCID mice', which can be bred deficient in various genes including ADA, JAK3, and IL2RG. It is now possible to reconstitute the impaired mouse immune system by using human components, so these animals provide a very useful model for studying both normal and pathological immune systems in biomedical research.

Related diseases

See other Diseases of the Immune System

See other Neonatal Diseases

Spinal muscular atrophy



SMN1 DNA differs from SMN2 DNA by a single base. This single base change does not allow exon 7 to be consistently included in the mRNA product. The lack of an adequate amount of full-length SMN1 protein results in SMA. Adapted from Monani, UR, *et al*. (2000) *Human Molecular Genetics* 9(16): 2451-7, with permission.

Death of spinal motor neurons and subsequent muscle paralysis characterize Spinal Muscular Atrophy (SMA), a hereditary neuromuscular disorder that is the most common genetic cause of childhood fatality. The age of onset and severity of SMA varies from an infantile onset form (type I) which causes early death from respiratory failure, to milder juvenile onset forms in which affected individuals show reduced life expectancy (type II), and are unable to walk (types II and III).

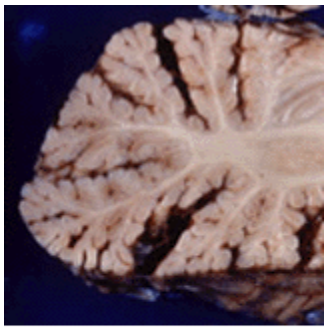
Expression of the disease requires mutation of both alleles of the survival motor neuron gene (SMN1) found on chromosome 5, making SMA an autosomal recessive disorder. Typically, the mutations are caused by a deletion within SMN1, or when the SMN1 gene is replaced by an almost identical gene called SMN2, also located on chromosome 5. Both SMN1 and SMN2 code for identical proteins, but the SMN1 gene produces the full-size protein, whereas the SMN2 gene produces truncated versions of the protein, and a small amount of the full-size protein. Deletions within both copies of the SMN1 gene results in type I SMA, whereas the milder forms of SMA usually occur when SMN1 is replaced by SMN2, increasing the number of copies of SMN2. The more SMN2 genes an affected individual has, the more full-length protein will be produced, and the milder the resultant form of the disease. The protein encoded by SMN1 and SMN2, which is known to play a crucial role in the production of mRNA, is expressed throughout the body, but is found in especially high levels within the spinal motor neurons.

The function of SMN1 is currently being investigated by studies in rats and transgenic mice. It is hoped that the characterization of this protein and its function will eventually lead to a therapy that may be used in conjunction with genetic testing already in place to help control the incidence and/or severity of SMA.

Related diseases

See other Diseases of the Nervous System

Spinocerebellar ataxia



Degeneration of the cerebellum leads to loss of muscle coordination in patients with spinocerebellar atrophy. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Persons with spinocerebellar ataxia experience a degeneration of the spinal cord and the cerebellum, the small fissured mass at the base of the brain, behind the brain stem. The cerebellum is concerned with coordination of movements, so the "wasting away" of this critical control center results in a loss of muscle coordination. Atrophy in the spine can bring spasticity.

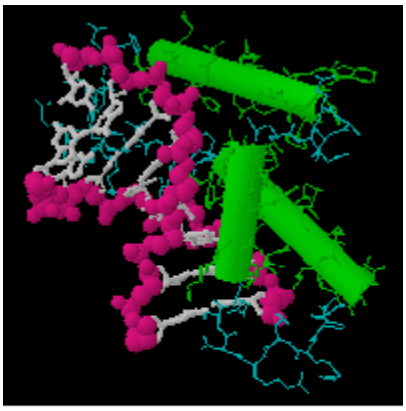
There are many types of spinocerebellar ataxia and about 30 different gene mutations have been found. One of the common genetic defects is a an expansion of a CAG triplet repeat. In this way, it is similar to fragile-X syndrome, Huntington disease and myotonic dystrophy, all of which exhibit a triplet repeat expansion of a gene. In the case of spinocerebellar ataxia I, the gene is SCA1, found on chromosome 6. The protein product of the gene - called ataxin-1 - varies in size, depending on the size of the CAG triplet repeat.

A homolog of human ataxin-1 has been found in mice, where it is found on chromosome 13 instead of chromosome 6. The two proteins are highly similar, except that in the mouse, the poly-glutamine tract (coded for by the CAG repeat) is missing, suggesting that it is not essential for normal function in mice.

Related diseases

See other Diseases of the Nervous System

SRY: Sex determination



SRY (green) binds to DNA (pink) and distorts its shape. In so doing, it regulates genes that control the development of the testes.

We have come a long way in our understanding of sexual dimorphism since 355 BC. In those days, Aristotle suggested that the difference between the two sexes was due to the heat of semen at the time of copulation: hot semen generated males, whereas cold semen made females. Thankfully, we now know a little more about the molecular events of sex determination.

Usually, a woman has two X chromosomes (XX) and a man one X and one Y (XY). However, both male and female characteristics can sometimes be found in one individual, and it is possible to have XY women and XX men. Analysis of such individuals has revealed some of the molecules involved in sex determination, including one called SRY, which is important for testis formation.

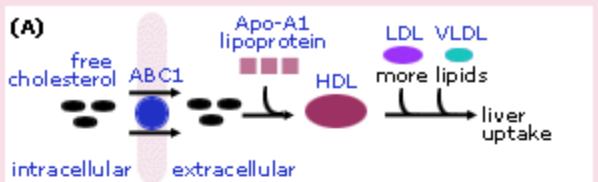
SRY (which stands for sex-determining region Y gene) is found on the Y chromosome. In the cell, it binds to other DNA and in doing so distorts it dramatically out of shape. This alters the properties of the DNA and likely alters the expression of a number of genes, leading to testis formation. Most XX men who lack a Y chromosome do still have a copy of the SRY region on one of their X chromosomes. This copy accounts for their maleness. However, because the remainder of the Y chromosome is missing they frequently do not develop secondary sexual characteristics in the usual way.

Since human SRY is similar to SRY of mice, a model of SRY function has been developed in mice. This has been particularly important in discovering the interactions of SRY with other genes in male sex determination.

Related diseases

See other Male-Specific Diseases

Tangier disease



(A) In normal cells ABC1 helps cholesterol exit the cell where it combines with lipid poor Apo-A1 lipoprotein to form high density lipoprotein (HDL). HDL picks up more lipids from low density (LD) and very low density (VLDL) lipoproteins and transfers the cholesterol to the liver, where it is processed.

(B) In Tangier disease, mutations in ABC1 cause cholesterol to accumulate within the cell.

[Adapted from Young and Fielding (1999) Nat Genet. Aug;22(4):316-8, with permission]

Tangier disease (TD) is a genetic disorder of cholesterol transport named for the secluded island of Tangier, located off the coast of Virginia. TD was first identified in a five-year-old inhabitant of the island who had characteristic orange tonsils, very low levels of high density lipoprotein (HDL) or 'good cholesterol', and an enlarged liver and spleen.

TD is caused by mutations in the *ABC1* (ATP-binding cassette) gene on chromosome 9q31. *ABC1* codes for a protein that helps rid cells of excess cholesterol. This cholesterol is then picked up by HDL particles in the blood and carried to the liver, which processes the cholesterol to be reused in cells throughout the body. Individuals with TD are unable to eliminate cholesterol from cells, leading to its buildup in the tonsils and other organs.

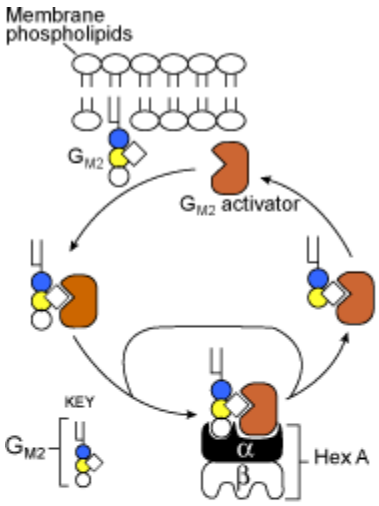
The discovery of this important cholesterol transport gene may lead to a better understanding of the inverse relationship between HDL levels and coronary artery disease, an important killer in the US. New drugs that regulate HDL levels may be developed and such drugs would not only help individuals with TD, but also people with more common disorders such as familial HDL deficiency. This is a good illustration of how research into rare diseases can sometimes help more common disorders.

Related diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Tay-Sachs disease



Model for G_{M2} ganglioside metabolism. Under normal conditions, β-hexosaminidase works in the lysosome of nerve cells to breakdown unwanted ganglioside G_{M2}, a component of the nerve cell membrane. This requires three components: an α-subunit, a β-subunit and an activator subunit. In Tay Sachs disease, the alpha subunit of hexosaminidase malfunctions, leading to a toxic build-up of the G_{M2} ganglioside in the lysosyme. [Adapted from: Chavany, C. and Jendoubi, M. (1998) *Mol. Med. Today*, 4: 158-165, with permission.]

Tay-Sachs disease, a heritable metabolic disorder commonly associated with Ashkenazi Jews, has also been found in the French Canadians of Southeastern Quebec, the Cajuns of Southwest Louisiana, and other populations throughout the world. The severity of expression and the age at onset of Tay-Sachs varies from infantile and juvenile forms that exhibit paralysis, dementia, blindness and early death to a chronic adult form that exhibits neuron dysfunction and psychosis.

Tay-Sachs is an autosomal recessive disease caused by mutations in both alleles of a gene (*HEXA*) on chromosome 15. *HEXA* codes for the alpha subunit of the enzyme β-hexosaminidase A. This enzyme is found in lysosomes, organelles that break down large molecules for recycling by the cell. Normally, β-hexosaminidase A helps to degrade a lipid called GM2 ganglioside, but in Tay-Sachs individuals, the enzyme is absent or present only in very reduced amounts, allowing excessive accumulation of the GM2 ganglioside in neurons. The progressive neurodegeneration seen in the varied forms of Tay-Sachs depends upon the speed and degree of GM2 ganglioside accumulation, which in turn is dependent upon the level of functional β-hexosaminidase A present in the body.

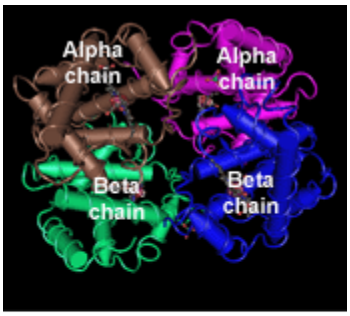
A mouse model has been developed for Tay-Sachs, although its usefulness is limited since Tay-Sachs mice possess a minor alternative pathway for breaking down GM2 ganglioside. Treatment of the late onset form of Tay-Sachs with a ganglioside synthesis inhibitor shows promise. The effectiveness this and other treatments on individuals with the infantile (the most common) form of the disease is extremely limited since the extent of neurological damage prior to birth is unknown. The difficulty in reversing such damage will make it hard to develop an effective treatment for the infantile form of the disease. It is hoped, however, that the latter onset forms of Tay-Sachs may prove responsive to treatment, and such treatment combined with the DNA and enzymatic screening programs currently in use will lead to the eventual control of this disease.

Related diseases

See other Diseases of the Nervous System

See other Nutritional and Metabolic Diseases

Thalassemia



Adult hemoglobin (HbA) contains two alpha chains and two beta chains. In thalassemia, there is deficient synthesis of either the alpha chains or the beta chains. Symptoms are a result of not only low levels of HbA, but also the relatively high levels of the chain that is synthesized.

Thalassemia is an inherited disease of faulty synthesis of hemoglobin. The name is derived from the Greek word "thalassa" meaning "the sea" because the condition was first described in populations living near the Mediterranean Sea; however, the disease is also prevalent in Africa, the Middle East, and Asia.

Thalassemia consists of a group of disorders that may range from a barely detectable abnormality of blood, to severe or fatal anemia. Adult hemoglobin is composed of two alpha (α) and two beta (β) polypeptide chains. There are two copies of the hemoglobin alpha gene (*HBA1* and *HBA2*), which each encode an α-chain, and both genes are located on chromosome 16. The hemoglobin beta gene (*HBB*) encodes the β-chain and is located on chromosome 11.

In α-thalassemia, there is deficient synthesis of α-chains. The resulting excess of β-chains bind oxygen poorly, leading to a low concentration of oxygen in tissues (hypoxemia). Similarly, in β-thalassemia there is a lack of β-chains. However, the excess α-chains can form insoluble aggregates inside red blood cells. These aggregates cause the death of red blood cells and their precursors, causing a very severe anemia. The spleen becomes enlarged as it removes damaged red blood cells from the circulation.

Deletions of *HBA1* and/or *HBA2* tend to underlie most cases of α-thalassemia. The severity of symptoms depends on how many of these genes are lost. Loss of one or two genes is usually asymptomatic, whereas deletion of all four genes is fatal to the unborn child.

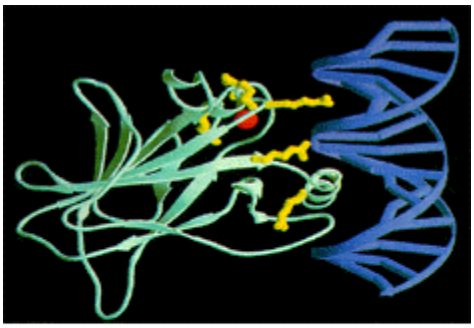
In contrast, over 100 types of mutations affect *HBB*, and deletion mutations are rare. Splice mutations and mutations that occur in the *HBB* gene promoter region tend to cause a reduction, rather than a complete absence, of β-globin chains and so result in milder disease. Nonsense mutations and frameshift mutations tend to not produce any β-globin chains leading to severe disease.

Currently, severe thalassemia is treated by blood transfusions, and a minority of patients are cured by bone marrow transplantation. Mouse models are proving to be useful in assessing the potential of gene therapy.

Related diseases

See other Blood and Lymph Diseases

The p53 tumor suppressor protein



The structure of the core domain of the p53 protein (light blue) bound to DNA (dark blue) The six most frequently mutated amino acids in human cancers are shown in yellow - all are residues important for p53 binding to DNA. Red ball: zinc atom. [Reproduced from Cho, Y., et al. (1994) Science, 265, 346-355, with kind permission.]

The p53 gene like the Rb gene, is a tumor suppressor gene, i.e., its activity stops the formation of tumors. If a person inherits only one functional copy of the p53 gene from their parents, they are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. This condition is rare, and is known as Li-Fraumeni syndrome. However, mutations in p53 are found in most tumor types, and so contribute to the complex network of molecular events leading to tumor formation.

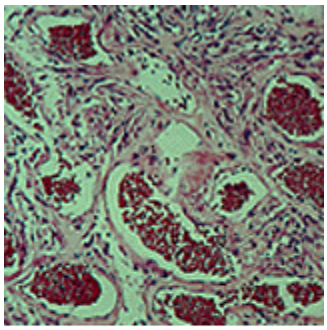
The p53 gene has been mapped to chromosome 17. In the cell, p53 protein binds DNA, which in turn stimulates another gene to produce a protein called p21 that interacts with a cell division-stimulating protein (cdk2). When p21 is complexed with cdk2 the cell cannot pass through to the next stage of cell division. Mutant p53 can no longer bind DNA in an effective way, and as a consequence the p21 protein is not made available to act as the 'stop signal' for cell division. Thus cells divide uncontrollably, and form tumors.

Help with unraveling the molecular mechanisms of cancerous growth has come from the use of mice as models for human cancer, in which powerful 'gene knockout' techniques can be used. The amount of information that exists on all aspects of p53 normal function and mutant expression in human cancers is now vast, reflecting its key role in the pathogenesis of human cancers. It is clear that p53 is just one component of a network of events that culminate in tumor formation.

Related diseases

See other Cancers

Tuberous sclerosis



Microscopic section of angiomyolipoma, a benign tumor of the kidney present in many patients with tuberous sclerosis. [Image credit: Moyra Smith, Johns Hopkins University, Baltimore, MD, USA.]

Tuberous sclerosis is an hereditary disorder characterized by benign, tumor-like nodules of the brain and/or retinas, skin lesions, seizures and/or mental retardation. Patients may experience a few or all of the symptoms with varying degrees of severity.

Two genes for tuberous sclerosis have been found: TSC1 on chromosome 9, and TSC2 on chromosome 16. It took four years to pin down a specific gene from the TSC1 region of chromosome 9: in 1997, a promising candidate was found. Called hamartin by the discoverers, it is similar to a yeast protein of unknown function, and appears to act as a tumor suppressor: without TSC1, growth of cells proceeds in an unregulated fashion, resulting in tumor formation. TSC2 codes for a protein called tuberin, which, through database searches, was found to have a region of homology to a protein found in pathways that regulate the cell (GAP3, a GTPase-activation protein).

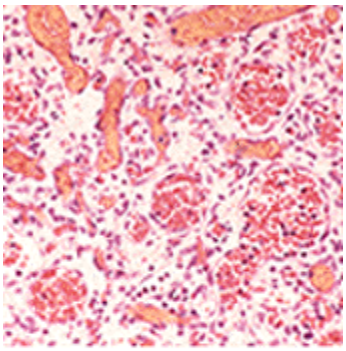
TSC1 has a homolog in yeast, which provides a system in which to model the human disease.

Related diseases

See other Cancers

See other Diseases of the Nervous System

Von Hippel-Lindau syndrome



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.]

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 affect 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.

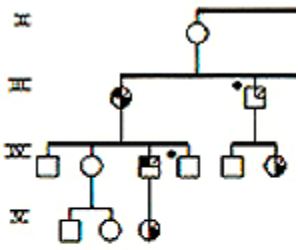
Related diseases

See other Cancers

See other Diseases of the Heart and Blood Vessels

See other Diseases of the Nervous System

Waardenburg syndrome



Part of a pedigree of Waardenburg syndrome, indicating the occurrence of deafness and changes in pigmentation, including a white forelock. [Image credit: Victor McKusick, Johns Hopkins University, Baltimore, MD, USA.]

The main characteristics of Waardenburg syndrome (WS) include: a wide bridge of the nose; pigmentary disturbances such as two different colored eyes, white forelock and eyelashes and premature graying of the hair; and some degree of cochlear deafness. The disease was named for Petrus Johannes Waardenburg, a Dutch ophthalmologist (1886-1979) who was the first to notice that people with two different colored eyes frequently had hearing problems.

The several types of WS are inherited in dominant fashion, so researchers typically see families with several generations who have inherited one or more of the features. Type I of the disorder is characterized by displacement of the fold of the eyelid, while Type II does not include this feature, but instead has a higher frequency of deafness.

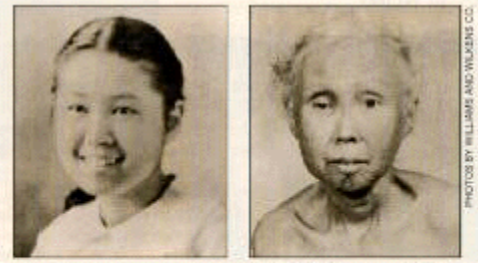
The discovery of the human gene that causes Type I WS came about after scientists speculated that the gene that causes 'splotch mice' (mice with a splotchy coat coloring) might be the same gene that causes WS in humans. They located the human gene to chromosome 2 and found it was the same as mouse Pax3. Pax3 is one of a family of eight mouse Pax genes that are involved in regulating embryonic development at the level of transcription.

With a mouse model to draw from, scientists are learning much about how Pax3 causes Waardenburg syndrome.

Related diseases

See other Neonatal Diseases

Werner syndrome



Taking its toll. As a teenager (left) this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent. [Image credit: William and Wilkens Publishing Inc.]

Werner syndrome is a premature aging disease that begins in adolescence or early adulthood and results in the appearance of old age by 30-40 years of age. Its physical characteristics may include short stature (common from childhood on) and other features usually developing during adulthood: wrinkled skin, baldness, cataracts, muscular atrophy and a tendency to diabetes mellitus, among others.

The disorder is inherited and transmitted as an autosomal recessive trait. Cells from WS patients have a shorter lifespan in culture than do normal cells. The gene for Werner disease (WRN) was mapped to chromosome 8 and cloned: by comparing its sequence to existing sequences in GenBank, it is a predicted helicase belonging to the RecQ family. However, it has yet to be shown to have real helicase activity (as a DNA unwinder important for DNA replication). The molecular role of WRN in Werner syndrome therefore remains to be proven, as does any role it might have in the aging process in general.

A yeast protein similar to the human WRN protein, called SGS1, has been found. Mutations in SGS1 cause yeast to have a shorter lifespan than yeast cells without the mutation, and shown other signs typical of aging in yeast, such as an enlarged and fragmented nucleolus. Using yeast as a model for human aging in general, may give insight into the mechanisms of Werner syndrome and related diseases.

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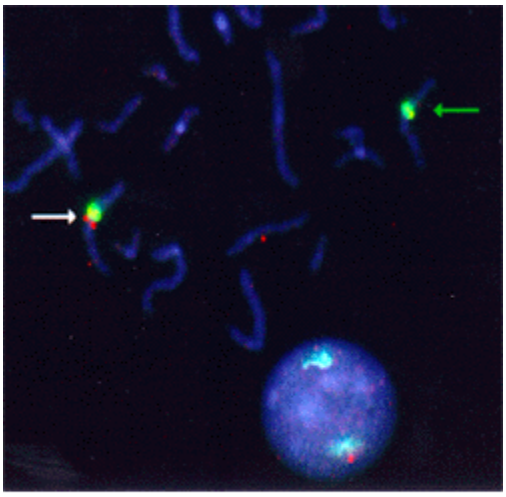
Williams syndrome



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.]

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.

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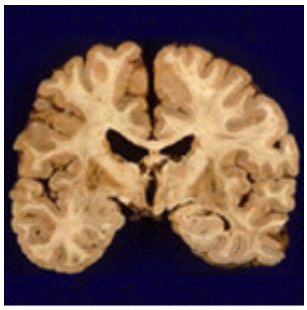
Wilson's disease



In Wilson's disease, toxic levels of copper accumulate and damage many tissues and organs, including the basal ganglia of the brain. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Wilson's Disease is a rare autosomal recessive disorder of copper transport, resulting in copper accumulation and toxicity to the liver and brain. Liver disease is the most common symptom in children; neurological disease is most common in young adults. The cornea of the eye can also be affected: the 'Kayser-Fleischer ring' is a deep copper-colored ring at the periphery of the cornea, and is thought to represent copper deposits.

The gene for Wilson's disease (ATP7B) was mapped to chromosome 13. The sequence of the gene was found to be similar to sections of the gene defective in Menkes disease, another disease caused by defects in copper transport. The similar sequences code for copper-binding regions, which are part of a transmembrane pump called a P-type ATPase that is very similar to the Menkes disease protein.

A homolog to the human ATP7B gene has been mapped to mouse chromosome 8, and an authentic model of the human disease in rat is also available (called the Long-Evans Cinnamon [LEC][rat). These systems will be useful for studying copper transport and liver pathophysiology, and should help in the development of a therapy for Wilson disease.

Related diseases

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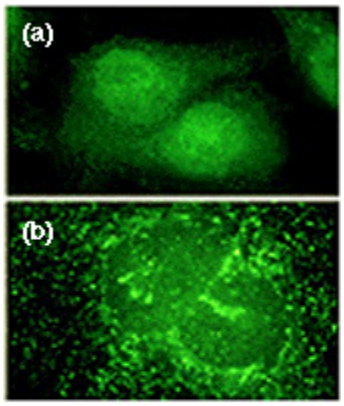
Zellweger syndrome



Peroxisomes are not detected in Zellweger syndrome fibroblasts (a), but can be reconstituted by transfection with PXR1 gene (b). [Image credit: Nancy Braverman, Gabrielle Dodt, Hugo Moser, Stephen Gould and David Valle, Johns Hopkins UNiversity, Baltimore, MD, USA.

Zellweger syndrome is a rare hereditary disorder affecting infants, and usually results in death. Unusual problems in prenatal development, an enlarged liver, high levels of iron and copper in the blood, and vision disturbances are among the major manifestations of Zellweger syndrome.

The PXR1 gene has been mapped to chromosome 12; mutations in this gene cause Zellweger syndrome. The PXR1 gene product is a receptor found on the surface of peroxisomes - microbodies found in animal cells, especially liver, kidney and brain cells. The function of peroxisomes is not fully understood, although the enzymes they contain carry out a number of metabolically important reactions. The PXR1 receptor is vital for the import of these enzymes into the peroxisomes: without it functioning properly, the peroxisomes can not use the enzymes to carry out their important functions, such as cellular lipid metabolism and metabolic oxidations.

There is a yeast homolog to human PXR1, which should allow powerful molecular genetic techniques to be used in the investigation of the normal role of peroxisomes in cells, as well as the molecular events that occur in disease states.

Related diseases

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