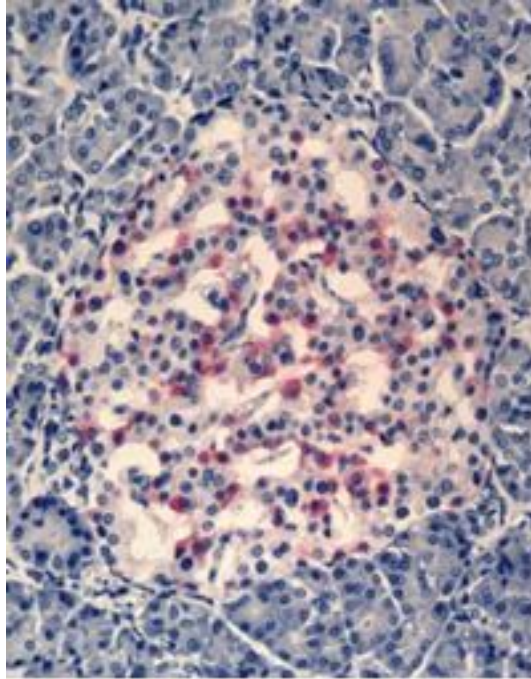


Glands and Hormones



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 controlling sugar metabolism; delta cells produce somatostatin, which inhibits growth hormone, insulin, glucagon and other physiologically important compounds. (Reproduced from Brown Medical School Slide Collection, with permission.)

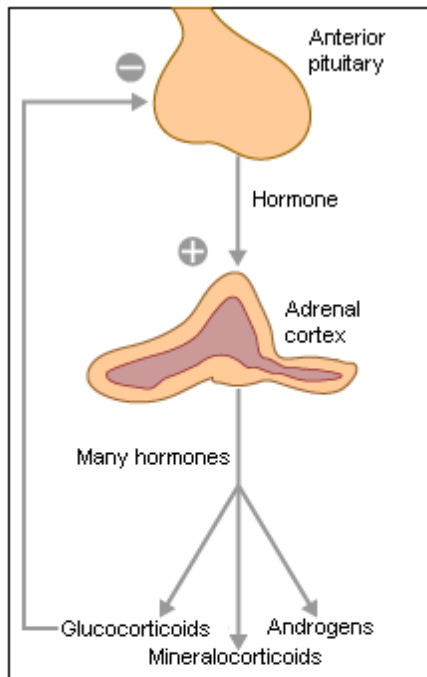
The endocrine system is a complex collection of hormone-producing glands that control basic body functions such as metabolism, growth and sexual development. The endocrine glands consist of: pineal; pituitary; thyroid and parathyroids; thymus; adrenals; pancreas; ovaries (female); and testes (male).

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.

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.

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503195&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

Websites

MEDLINEplus [<http://www.nlm.nih.gov/medlineplus/ency/article/000411.htm>] Medical encyclopedia from the National Library of Medicine, NIH

GeneReviews [www.geneclinics.org/profiles/cah] a medical genetics resource

Adrenoleukodystrophy

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=7262393&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

Websites

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

GeneClinics [www.geneclinics.org/profiles/x-ald/] a medical genetics resource

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.

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557291&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

Websites

American Autoimmune Related Diseases Association [www.aarda.org/] research and patient support

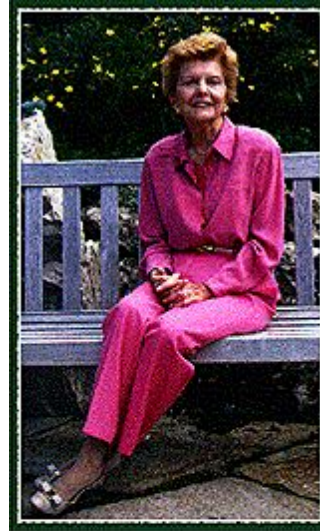
Breast and ovarian cancer

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 US in 1997. While ovarian cancer accounts for fewer deaths than breast cancer, it 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 an individual carries 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.

So 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, 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.



"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.

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=6552299&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

GeneReviews [www.geneclinics.org/profiles/brca1/index.html] a medical genetics resource

Cockayne syndrome

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 interact 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.



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.]

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557467&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

Diabetes, type 1

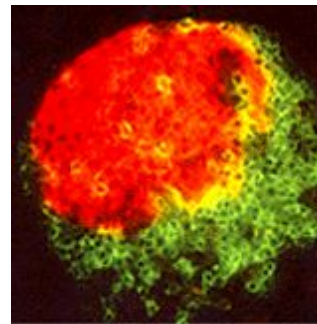
Diabetes is a chronic metabolic disorder that adversely affects the body's ability to manufacture and use insulin, a hormone necessary for the conversion of food into energy. The disease greatly increases the risk of blindness, heart disease, kidney failure, neurological disease, and other conditions 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.



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

Important Links

Gene sequence

Genome view see gene locations

LocusLink collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503951&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

Websites

Patient information on diabetes [www.niddk.nih.gov/health/diabetes/diabetes.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Juvenile Diabetes Research Foundation International [<http://www.jdf.org/>] 'dedicated to finding a cure'

American Diabetes Association [www.diabetes.org/default.htm] research and information

Diastrophic dysplasia

Diastrophic dysplasia (DTD) is a rare growth disorder in which patients are usually short, have club feet, and have malformed hands and 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.



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

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557539&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

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 meet 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.

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557745&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM catalog of human genes and disorders

Websites

Fact sheet [www.niddk.nih.gov/health/endo/pubs/fmen1/fmen1.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

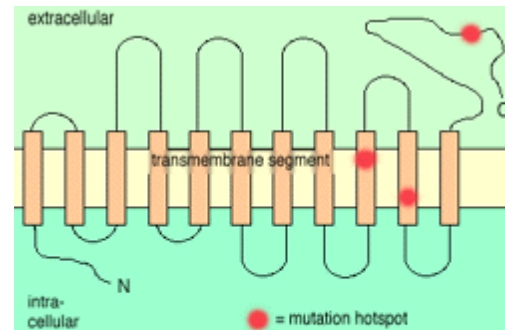
Pendred syndrome

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.



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.

Important Links

Gene sequence

Genome view see gene locations

Entrez Gene collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4505697&org=1] related sequences in different organisms

The literature

Research articles online full text

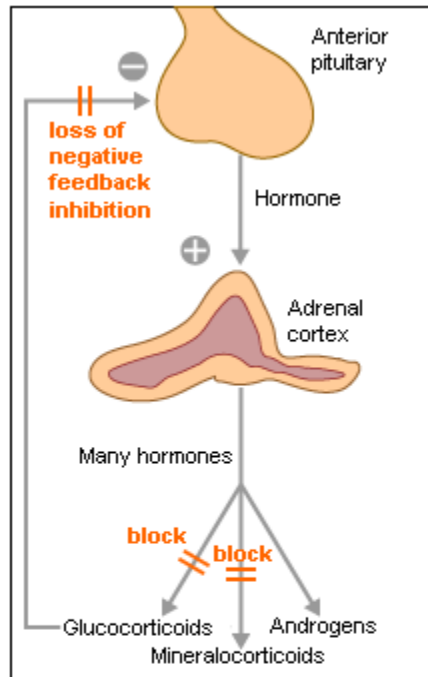
Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=274600] catalog of human genes and disorders

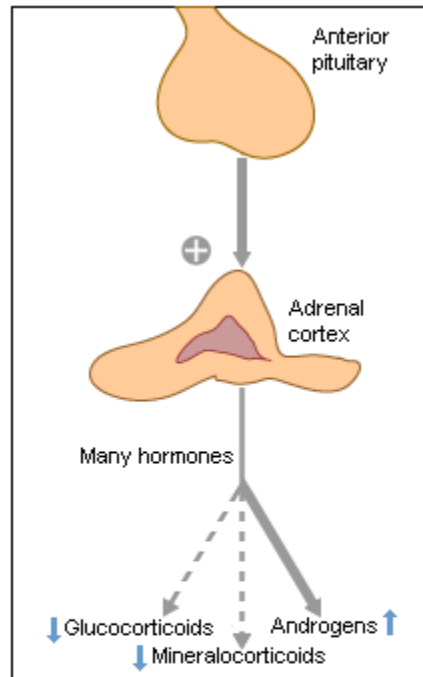
Websites

Research News [www.nhgri.nih.gov/NEWS/Pendred/] from the National Human Genome Research Institute, NIH

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



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.