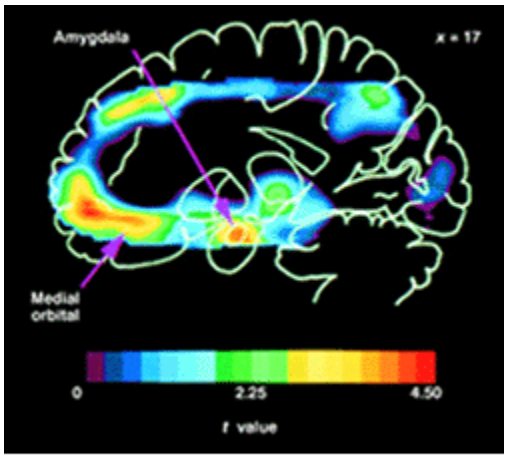
The Nervous System



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.

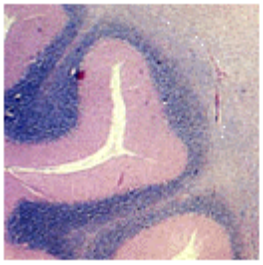
Several diseases that directly affect the nervous system have a genetic component: some are due to a mutation in a single gene, others are proving to have a more complex mode of inheritance. As our understanding of the pathogenesis of neurodegenerative disorders deepens, common themes begin to emerge: 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.

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
- LocusLink [www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=215] 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 [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300100] catalog of human genes and disorders

Websites

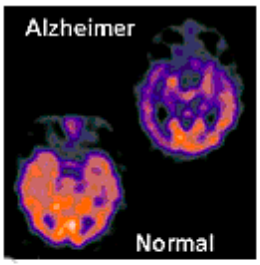
- Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/adrenolu_doc.htm] from The National Institute of Neurological Disorders and Stroke, NIH
- GeneClinics [www.geneclinics.org/profiles/x-ald/] a medical genetics resource

Alzheimer disease

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506163&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=104300] catalog of human genes and disorders

Websites

Alzheimer's Association [www.alz.org/] or call 1-800-272-3900

Alzheimer's Disease Education and Referral Center [www.alzheimers.org/] a service of the National Institute on Aging, National Institutes of Health

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

MEDLINE*plus* [www.nlm.nih.gov/medlineplus/alzheimersdisease.html] links on Alzheimer's disease compiled by the National Library of Medicine

Amyotrophic 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.

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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507149&org=1] related sequences in different organisms

The literature

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Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=105400] catalog of human genes and disorders

Websites

The ALS Association [www.alsa.org] from the National Institute of Neurological Disorders and Stroke

MEDLINE *plus* [www.nlm.nih.gov/medlineplus/amyotrophiclateralsclerosis.html] links compiled by the National Library of Medicine

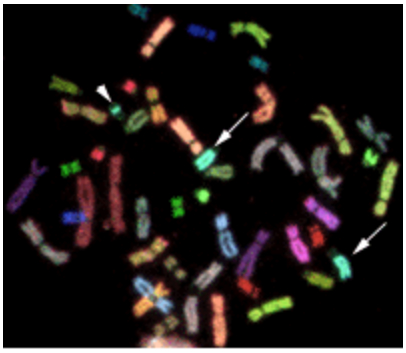
Angelman syndrome

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.



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 15, 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. [Reproduced with permission from Uhrig, S. et al. (1999) Multiplex-Fish for pre- and postnatal diagnostic applications. Am J Hum Genet. Aug; 65(2):448-62, published by the University of Chicago Press, copyright 1999 by the American Society for Human Genetics. All rights reserved.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507799&org=1] related sequences in different organisms

The literature

Research articles online full text

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=105830] catalog of human genes and disorders

Websites

Angelman Syndrome Foundation, USA [chem-faculty.ucsd.edu/harvey/asfsite/] provides information, education and support

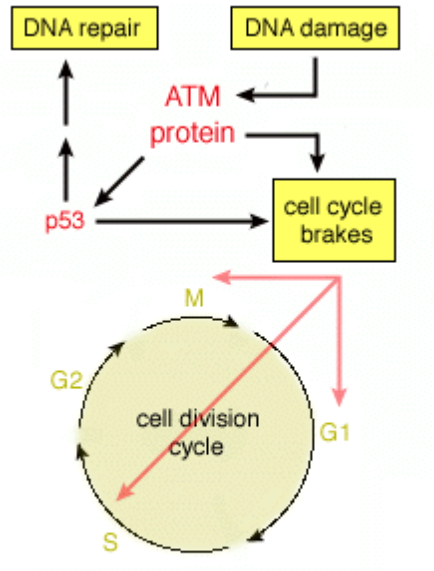
GeneClinics [www.geneclinics.org/profiles/angelman/] a medical genetics resource

Ataxia telangiectasia

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

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

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

Websites

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

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

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.

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4505907&org=1] related sequences in different organisms

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Websites

Charcot-Marie-Tooth Association [www.charcot-marie-tooth.org/] patient support, education and research

Charcot-Marie-Tooth International [www.cmtint.org/] run by and for people who have CMT disease

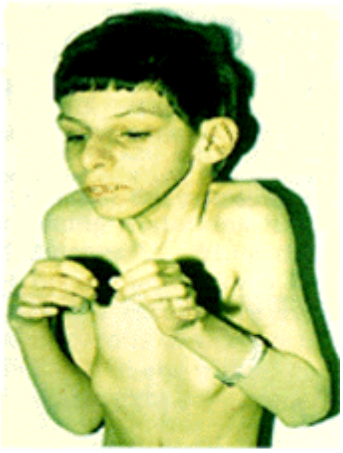
GeneClinics [www.geneclinics.org/profiles/cmt/] a medical genetics resource

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 chromosme 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.



Cockayne syndrome sufferers have multisystemic 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

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

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

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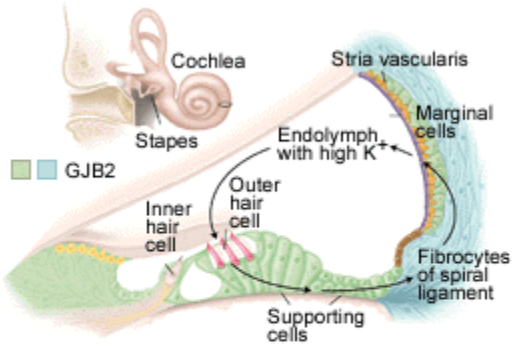
Deafness

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=2706] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=6980948&org=1] related sequences in different organisms

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Websites

NIDCD [www.nih.gov/nidcd/] National Institute on Deafness and Other Communication Disorders

Info to Go [clerccenter.gallaudet.edu/InfoToGo/index.html] from Gallaudet University

GeneClinics [www.geneclinics.org/profiles/dfnb1/] a medical genetics resource

MEDLINE*plus* [www.nlm.nih.gov/medlineplus/hearingdisordersdeafness.html] links compiled by the National Library of Medicine

Duchenne muscular dystrophy

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.

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.

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5032281&org=1] related sequences in different organisms

The literature

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Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=310200] catalog of human genes and disorders

Websites

Muscular Dystrophy Association [www.mdausa.org/] for Research and Care news

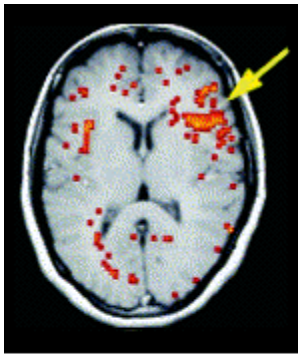
Parent Project [www.parentdmd.org/] Muscular Dystrophy Research for all

Epilepsy

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.

TThere 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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=11321613&org=1] related sequences in different organisms

The literature

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Websites

Epilepsy Foundation [www.efa.org/] national foundation for epilepsy information and service

Information Sheet [www.ninds.nih.gov/health_and_medical/disorders/epilepsy.htm] from the National Institute of Neurological Disorders and Stroke, NIH

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.

Important Links

Gene sequence

Genome view see gene locations

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

The literature

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Websites

News release [www.ninds.nih.gov/WHATSNEW/PRESSWHN/1997/tremor.htm] from the National Institute of Neurological Disorders and Stroke, NIH

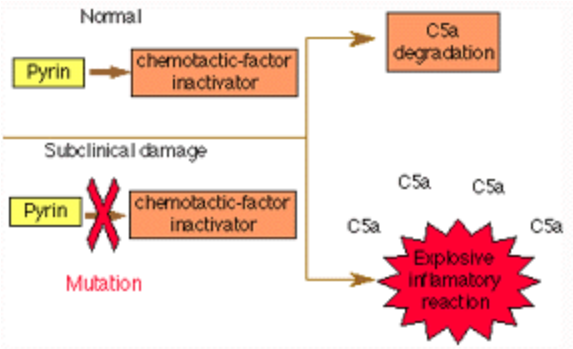
Information [www.essentialtremor.org/] from the Essential Tremor Foundation

Familial Mediterranean fever

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557743&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

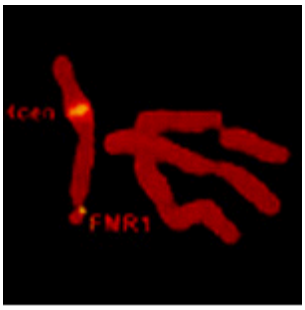
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=249100] catalog of human genes and disorders

Fragile X syndrome

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503765&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=309550] catalog of human genes and disorders

Websites

Fact sheet [www.nichd.nih.gov/publications/pubs/fragilextoc.htm] from the National Institute of Child Health and Human Development, NIH

National Fragile X Foundation [www.fragilex.org] US-based research, information and support

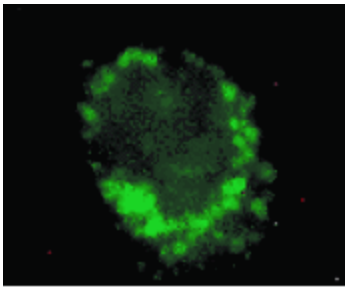
GeneClinics [www.geneclinics.org/profiles/fragilex/] a medical genetics resource

Friedreich's ataxia

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.



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

Important Links

Gene sequence

- Genome view see gene locations
- LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=FRDA&ORG=Hs&V=0] collection of gene-related information
- BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503785&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=229300] catalog of human genes and disorders

Websites

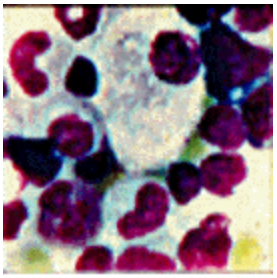
- National Ataxia Foundation [www.ataxia.org/] supporting research into Hereditary Ataxia
- GeneClinics [http://www.geneclinics.org/profiles/friedreich/] a medical genetics resource

Gaucher disease

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.



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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503935&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=230800] catalog of human genes and disorders

Websites

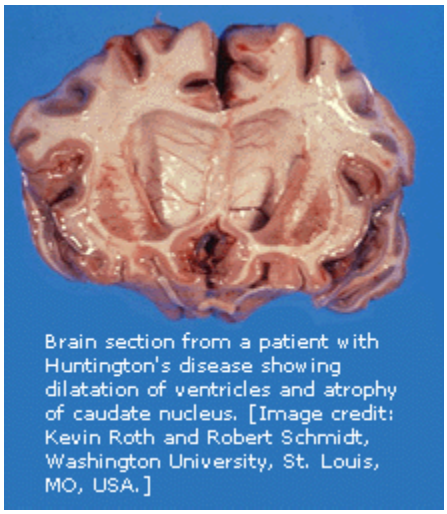
National Gaucher Foundation [neuro-www2.mgh.harvard.edu/gaucher/ngfusa.html] supporting research into the causes of Gaucher disease

Huntington disease

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4753163&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=143100] catalog of human genes and disorders

Websites

Huntington Disease Society of America [www.hdsa.org/] information for patients and the public

GeneClinics [http://www.geneclinics.org/profiles/huntington/] a medical genetics resource

Lesch-Nyhan syndrome

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

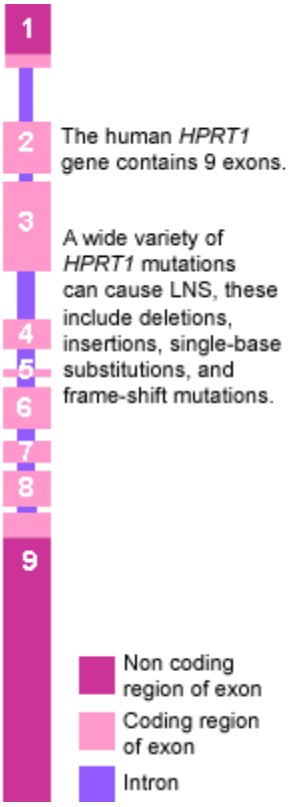
These raw materials are called purines, and they are an essential part of DNA and RNA. The body can either make purines (de novo synthesis) or recycle them (the resalvage pathway). Many enzymes are involved in these pathways. When one of these enzymes is missing, a wide range of problems can occur.

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.



Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4504483&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=308950] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/XXXXX.htm]from XXXXX, NIH

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

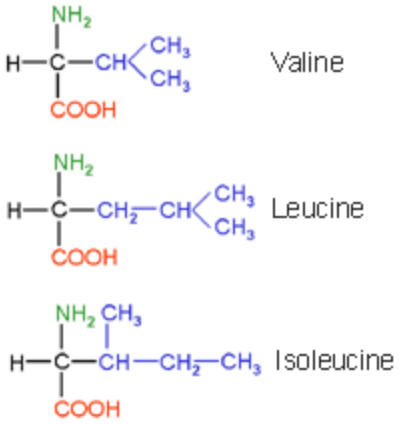
Maple syrup urine disease

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.



Amino acids contain an alpha carbon (C), an amino group (NH_2), a carboxyl group (COOH), and a unique side group (R).

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

Important Links

Gene sequence

- Genome view see gene locations
- LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=maple+syrup+urine+disease&ORG=Hs&V=0] collection of gene-related information
- BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=548403&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=248600] catalog of human genes and disorders

Websites

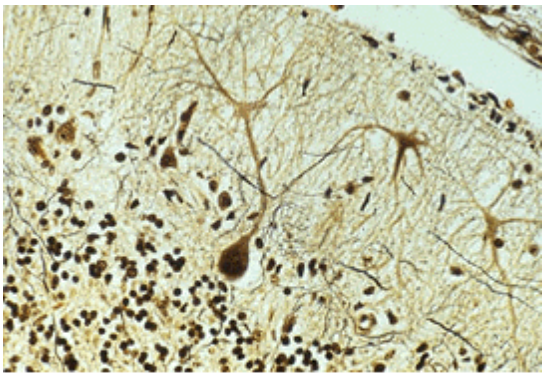
- MSUD Family Support Group [www.msud-support.org/] patient information and support

Menkes syndrome

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4502321&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

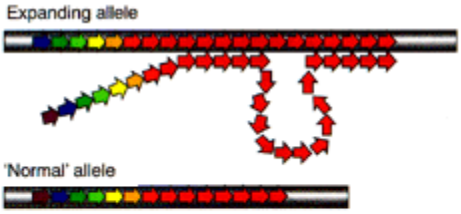
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=309400] catalog of human genes and disorders

Myotonic dystrophy

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 kilo-base pairs.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=10334852&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=160900] catalog of human genes and disorders

Websites

GeneClinics [www.geneclinics.org/profiles/myotonic-d/] a medical genetics resource

Narcolepsy

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.

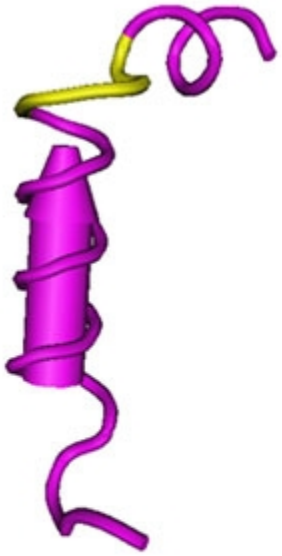
The normal stages of sleep include a phase of rapid eye movement (REM). It is during the REM phase of sleep when we dream and during this time that our muscles become completely relaxed. The problem in narcolepsy is that REM can occur while awake, resulting in half-sleep dreams and temporary paralysis.

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.



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).

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557635&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=161400] catalog of human genes and disorders

Websites

MEDLINEplus [http://www.nlm.nih.gov/medlineplus/ency/article/000802.htm]Medical encylopedia from the National Library of Medicine, NIH

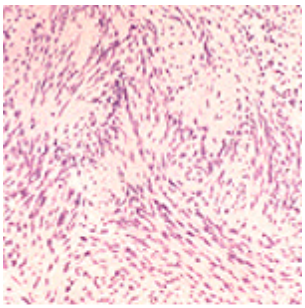
Factsheet [http://www.ninds.nih.gov/health_and_medical/disorders/narcolep_doc.htm]Patient information from National Institute of Neurological Disorders and Stroke, NIH

Neurofibromatosis

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557793&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

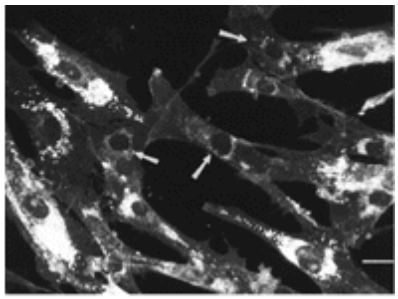
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=101000] catalog of human genes and disorders

Niemann–Pick disease

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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557803&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=257200] catalog of human genes and disorders

Websites

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

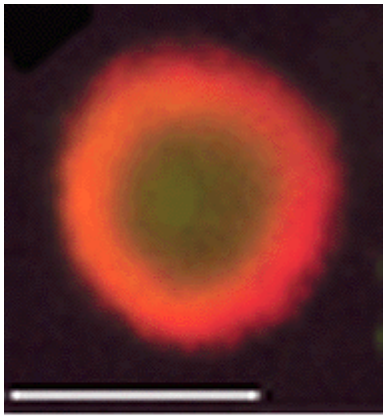
National Niemann-Pick Disease Foundation [www.nnpdf.org] an educational, support and fund-raising organization

Parkinson disease

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.



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.

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507109&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

Research News [www.nhgri.nih.gov/DIR/LGDR/PARK2/] on Parkinson disease from The National Human Genome Research Institute, NIH

The Parkinson Web [pdweb.mgh.harvard.edu/] general information, with links to other Parkinson Disease Web sites.

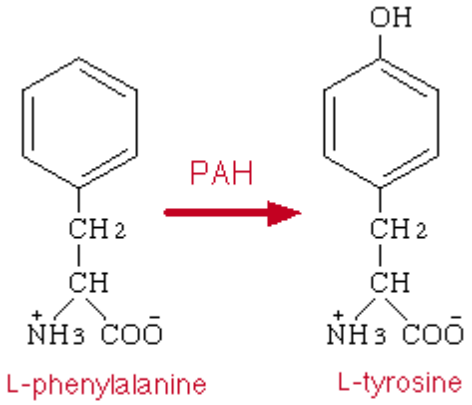
MEDLINE*plus* [www.nlm.nih.gov/medlineplus/parkinsonsdisease.html] links on Parkinson disease compiled by the National Library of Medicine

Phenylketonuria

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.



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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557819&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=261600] catalog of human genes and disorders

Websites

National PKU News [www.pkunews.org] news and information about PKU

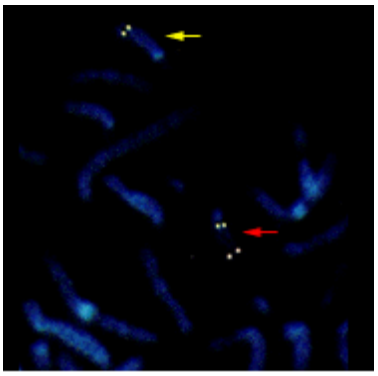
GeneClinics [www.geneclinics.org/profiles/pku/] a medical genetics resource

Prader-Willi syndrome

Prader-Willi syndrome (PWS) is an uncommon inherited 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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=14748674&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=176270] catalog of human genes and disorders

Websites

Prader-Willi Syndrome Association (USA) [www.pwsausa.org/] information, education, and support services

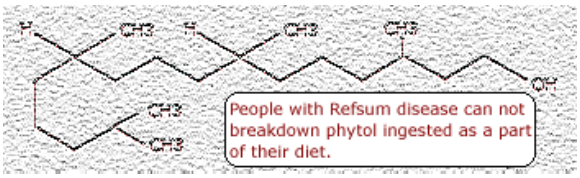
GeneClinics [www.geneclinics.org/profiles/pws/] a medical genetics resource

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.



Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5453884&org=1] related sequences in different organisms

The literature

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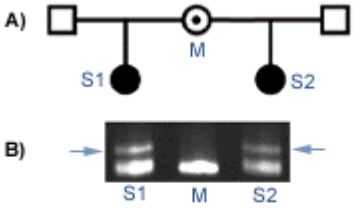
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=266500] catalog of human genes and disorders

Rett syndrome

Rett syndrome (RTT) is a progressive neurodevelopmental disorder that almost exclusively affects females. It has an incidence of about 1 in 10,000 births, making it one of the most common causes of profound mental retardation in girls. Individuals with RTT develop normally until the age of 6 to 18 months, when they begin to lose purposeful use of their hands and speech. Affected individuals also show reduced muscle tone, wringing hand movements, autistic-like behavior and seizures.

A gene which causes RTT, *MeCP2*, has been found on the long arm of chromosome X (Xq28). Normally, females have two X chromosomes and males have an X and a Y. Since males do not have an additional copy of X to offset a defect, most X-linked diseases affect males. Then, why are males not affected by RTT? One possible explanation is that the absence of a functional copy of *MeCP2* is lethal to the male fetus before birth. Researchers have shown this to be the case in a mouse model. Another question is why females are affected by RTT, even though one of their X chromosomes is normal. This is likely due to X inactivation, a normal process whereby one X chromosome is randomly inactivated in every cell. This partial deficiency - where the normal copy of *MeCP2* is active in some cells and inactive in others - allows girls with RTT to survive and develop normally during early infancy.

MeCP2 is believed to code for a protein which controls gene expression in the cell. Although it is not clear what the mechanism is, partial loss of this protein may lead to over expression of certain genes, leading to the RTT phenotype. With the discovery of *MeCP2*, investigators hope to develop a test for RTT which will allow for early diagnosis, prenatal detection and, ultimately, presymptomatic therapy.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4826830&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=312750] catalog of human genes and disorders

Websites

Information Sheet [www.ninds.nih.gov/health_and_medical/disorders/rett_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH

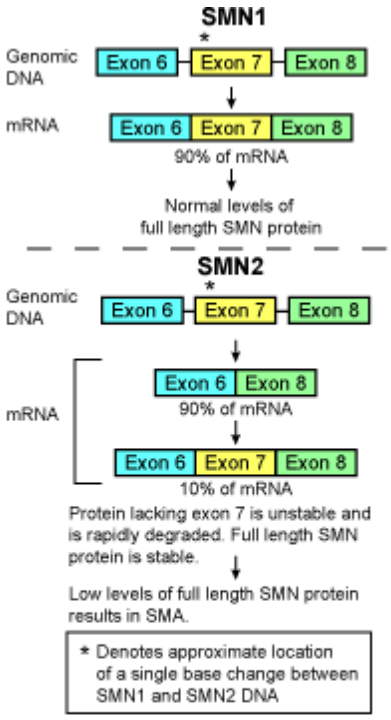
International Rett Syndrome Association [www.rettsyndrome.org/] support and information for families

Spinal muscular atrophy

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.



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.

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507091&org=1] related sequences in different organisms

The literature

Research articles online full text

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600354] catalog of human genes and disorders

Websites

Spinal Muscular Atrophy Foundation [www.smafoundation.org] raises funds for SMA research

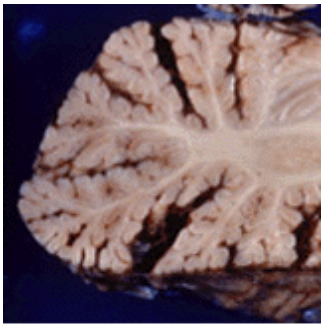
Families of Spinal Muscular Atrophy [www.fsma.org/] supports families affected by SMA

Spinocerebellar ataxia

Persons with spinocerebellar ataxia, of which there are several types, 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.

The basic defect in all types of spinocerebellar ataxia 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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506793&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=164400] catalog of human genes and disorders

Websites

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

The National Ataxia Foundation [www.ataxia.org/] supporting research into hereditary ataxia

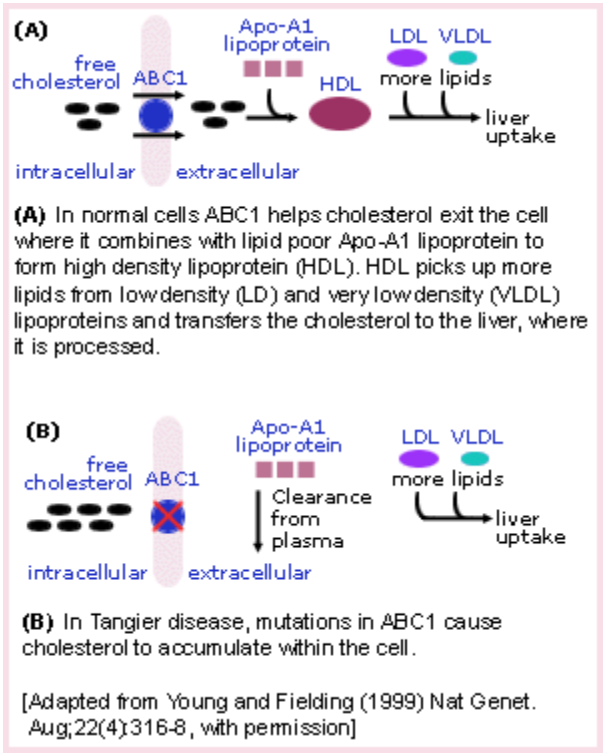
GeneClinics [http://www.geneclinics.org/profiles/sca1/index.html] a medical genetics resource

Tangier disease

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.



(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]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5915658&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=205400] catalog of human genes and disorders

Websites

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

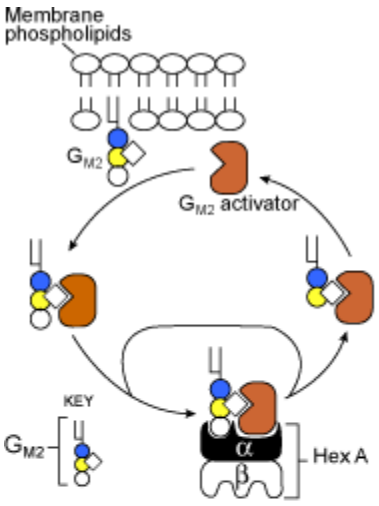
National Heart, Lung and Blood Institute, NIH [www.nhlbi.nih.gov/health/public/heart/] cardiovascular information

Tay-Sachs disease

Tay-Sachs disease, a heritable metabolic disorder commonly associated with Ashkenazi Jews, has also been found in the French Canadians of South-eastern 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.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4504371&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=272800] catalog of human genes and disorders

Websites

Fact Sheet [www.ninds.nih.gov/health_and_medical/disorders/taysachs_doc.htm] from National Institute of Neurological Disorders and Stroke

NTSAD [www.ntsad.org/] National Tay-Sachs and Allied Diseases Association

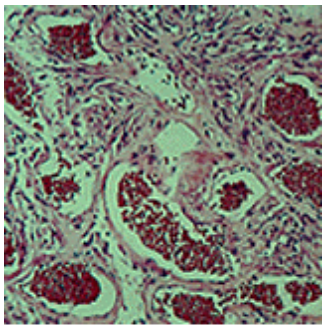
GeneClinics [www.geneclinics.org/profiles/tay-sachs/] a medical genetics resource

Tuberous sclerosis

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 loci 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).

SC1 has a homolog in yeast, which provides a system in which to model the human disease.



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.]

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507693&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=191100] 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

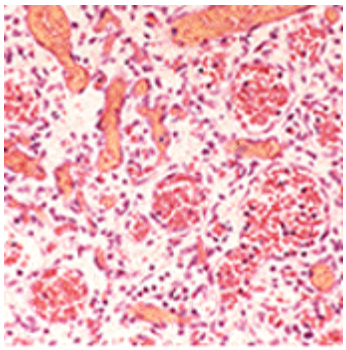
GeneClinics [www.geneclinics.org/profiles/brca1/index.html] a medical genetics resource

Von Hippel-Lindau syndrome

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

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

The literature

Research articles online full text

Books online books section

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

Websites

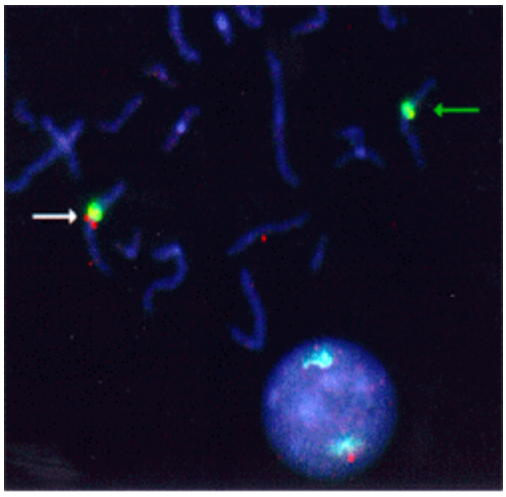
Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/vonhippe_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH

Williams syndrome

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

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

The literature

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=194050] catalog of human genes and disorders

Websites

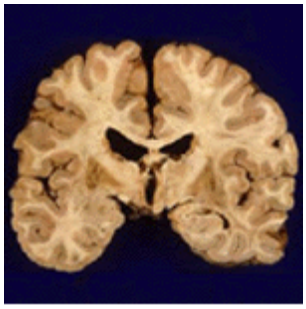
GeneClinics [www.geneclinics.org/profiles/williams/] a medical genetics resource

Wilson's disease

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.



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.]

Important Links

Gene sequence

- Genome view see gene locations
- LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=ATP7B&ORG=Hs&V=0] collection of gene-related information
- BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4502323&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=277900] catalog of human genes and disorders

Websites

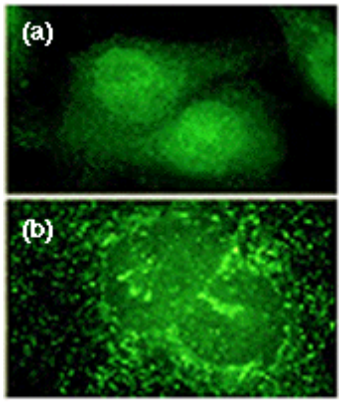
- Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/wilsons_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH
- GeneClinics [www.geneclinics.org/profiles/wilson/] a medical genetics resource

Zellweger syndrome

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.



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.

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506347&org=1] related sequences in different organisms

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Websites

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