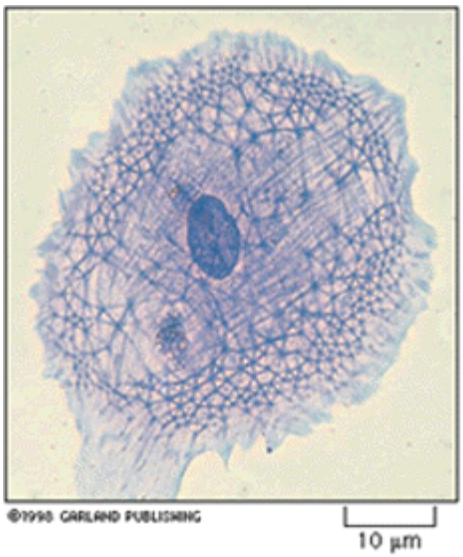
Muscle and Bone



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

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

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

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

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

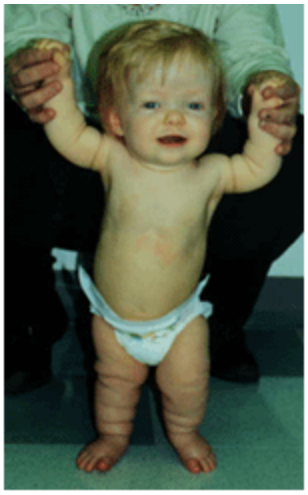
Achondroplasia

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

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

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

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



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

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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=20452381&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=100800] catalog of human genes and disorders

Websites

Achondroplasia UK [www.achondroplasia.co.uk/]support and patient information

Little People of America [www.lpaonline.org/index.html]support and information for families

GeneReviews [www.genetests.org/profiles/achondroplasia] a medical genetics resource

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

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

The literature

- Research articles online full text
- Books online books section
- OMIM catalog of human genes and disorders

Websites

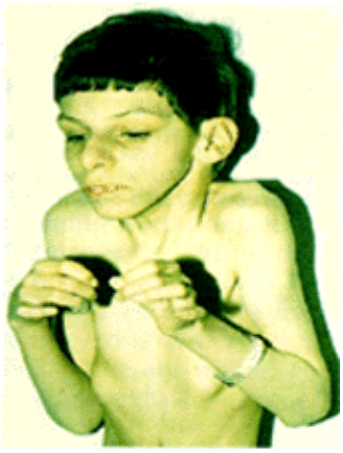
- Charcot-Marie-Tooth Association [www.charcot-marie-tooth.org/] patient support, education and research
- Charcot-Marie-Tooth International [www.cmtint.org/] run by and for people who have CMT disease
- GeneClinics [www.geneclinics.org/profiles/cmt/] a medical genetics resource

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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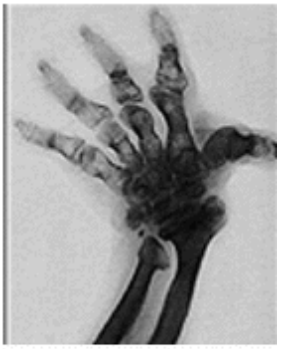
Diastrophic dysplasia

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

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

The literature

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=222600] catalog of human genes and disorders

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

Research articles online full text

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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

Ellis-van Creveld syndrome

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

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

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

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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=7657073&org=1] related sequences in different organisms

The literature

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=225500] catalog of human genes and disorders

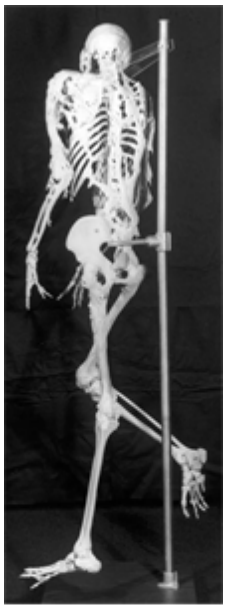
Fibrodysplasia ossificans progressiva

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

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

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

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



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

Courtesty of Muller Museum, College of Physicians of Philadelphia.

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=19528650&org=1] related sequences in different organisms

The literature

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=135100] catalog of human genes and disorders

Websites

International Fibrodysplasia Ossificans Progressiva Association [http://www.ifopa.org/] further information and patient support

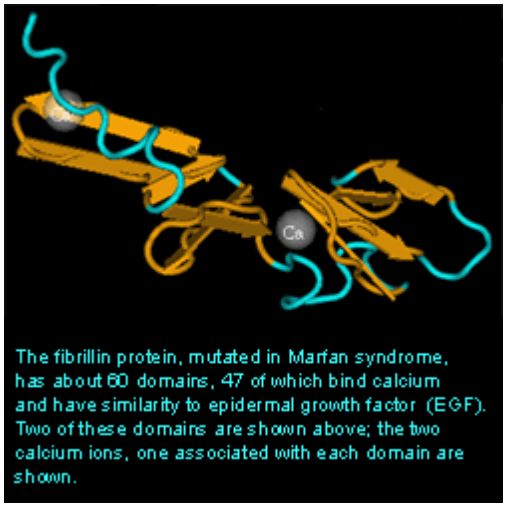
Marfan syndrome

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

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

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

To see the interactive version of this figure requires Cn3D [www.ncbi.nlm.nih.gov/Structure/CN3D/cn3d.shtml], a three-dimensional structure viewer.



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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557591&org=1] related sequences in different organisms

The literature

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=154700] catalog of human genes and disorders

Websites

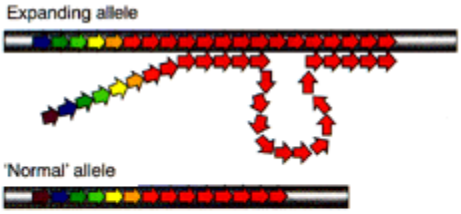
National Marfan Foundation [www.marfan.org/] nonprofit organization

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

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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