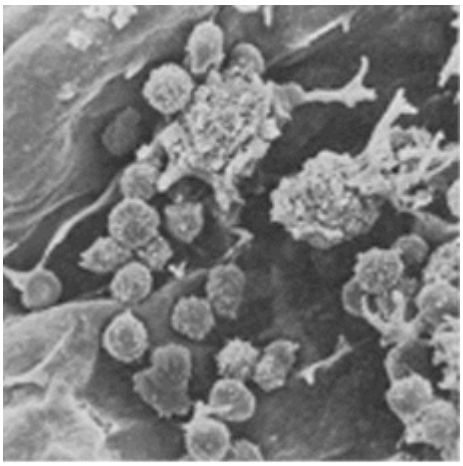
Diseases of the Immune System



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

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

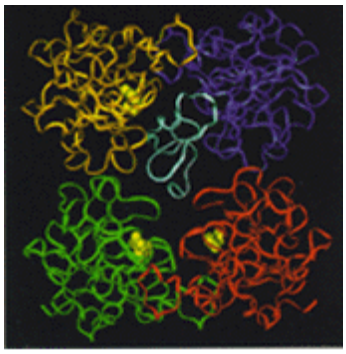
Most other immune disorders result from either an excessive immune response or an 'autoimmune attack'. Asthma, familial Mediterranean fever and Crohn's disease (inflammatory bowel disease) all result from an over-reaction of the immune system, while autoimmune polyglandular syndrome and some facets of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

Asthma

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4501969&org=1] related sequences in different organisms

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600807] catalog of human genes and disorders

Websites

Global initiative for asthma [www.ginasthma.com:80/] a project conducted in collaboration with the National Heart, Blood and Lung Institute, NIH, and the World Health Organization

National Heart, Blood and Lung Institute [www.nhlbi.nih.gov/health/public/lung/index.htm#asthma] information on asthma

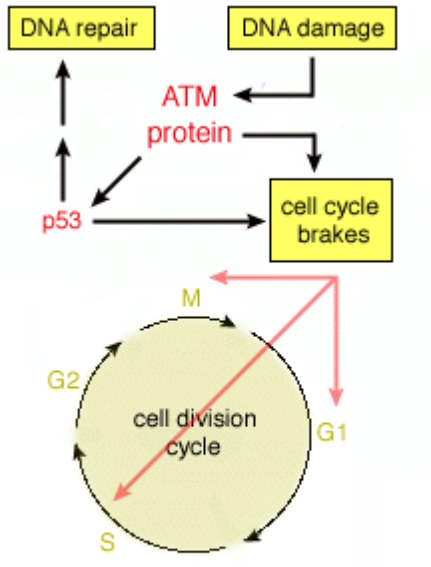
MEDLINE*plus* [www.nlm.nih.gov/medlineplus/asthma.html] links on asthma compiled by the National Library of Medicine

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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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

Autoimmune polyglandular syndrome

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

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

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

Important Links

Gene sequence

Genome view see gene locations

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

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

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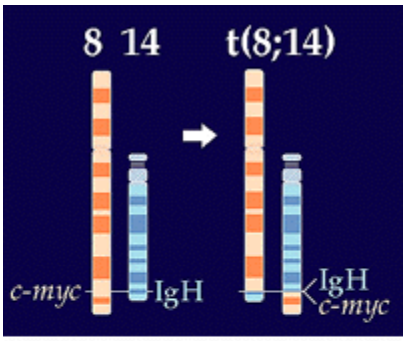
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=240300] catalog of human genes and disorders

Websites

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

Burkitt lymphoma



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

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

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

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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=12962935&org=1] related sequences in different organisms

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

American Cancer Society [www.cancer.org/] research and patient support

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

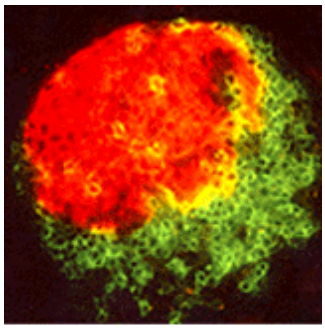
Diabetes, type 1

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

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

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

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



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

Important Links

Gene sequence

- Genome view see gene locations
- LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=diabetes&ORG=Hs&V=0] collection of gene-related information
- BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503951&org=1] related sequences in different organisms

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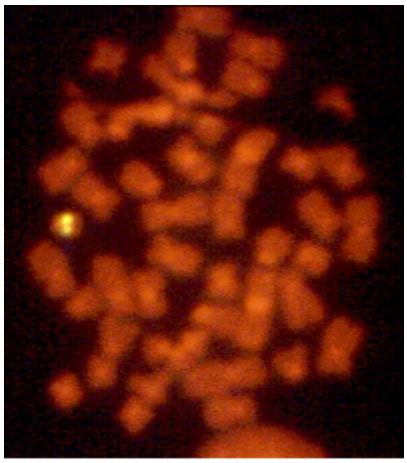
- Patient information on diabetes [www.niddk.nih.gov/health/diabetes/diabetes.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH
- Juvenile Diabetes Foundation [www.jdfcure.com] 'creating a world without diabetes'
- American Diabetes Association [www.diabetes.org/default.htm] research and information

DiGeorge syndrome

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=13027630&org=1] related sequences in different organisms

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Information and support [www.kumc.edu/gec/support/digeorge.html] for DiGeorge syndrome

GeneClinics [www.geneclinics.org/profiles/22q11deletion/] a medical genetics resource

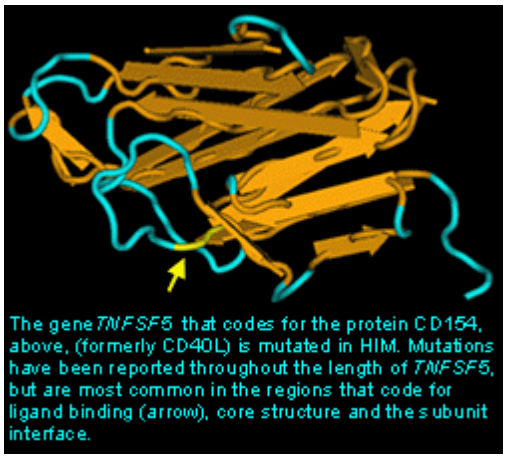
Immunodeficiency with hyper-IgM

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

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

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

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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557433&org=1] related sequences in different organisms

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Websites

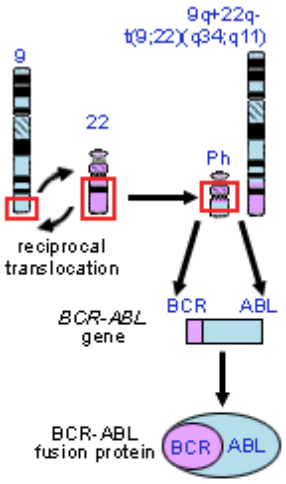
Primary immune deficiency [156.40.88.3/publications/pubs/primaryimmunobooklet.htm] National Institute of Allergy and Infectious Diseases, NIH

Leukemia, chronic myeloid

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=11038639&org=1] related sequences in different organisms

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

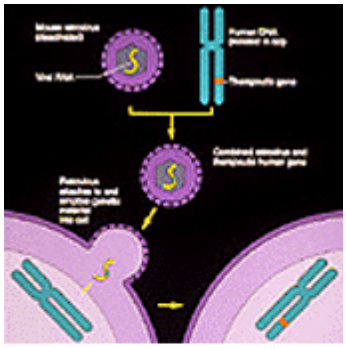
Severe combined immunodeficiency

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

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

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

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



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

Important Links

Gene sequence

Genome view see gene locations

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

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557681&org=1] related sequences in different organisms

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OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=202500] catalog of human genes and disorders

Websites

SCID Factsheet [www.niaid.nih.gov/factsheets/pid.htm] from the National Institute of Allergy and Infectious Diseases, National Institutes of Health