Medical Texts

Tay Sachs
Healthy babies develop vision, movement, hearing, and other vital functions in part because enzymes clear out fatty protein and other unwanted material that can interfere with growth.
But a baby with Tay-Sachs disease is born without one of those important enzymes, Hexosaminidase A (Hex A). So, as those fatty proteins build up in the brain, they hurt the baby's sight, hearing, movement, and mental development. Children with the disease usually die before the age of five.

A child can only get Tay-Sachs by inheriting it. The genetic trait is relatively common among certain ethnic groups, such as Ashkenazi Jews. Tay-Sachs can be detected before birth, so couples in at-risk ethnic groups who are thinking of having children may want to get a blood test to find out whether their child would be likely to have it.

Who Is at Risk for Tay-Sachs?
Each year, about 16 cases of Tay-Sachs are diagnosed in the United States. Although Ashkenazi Jews (Jews of central and eastern European descent) are at the highest risk, it is now also prevalent in non-Jewish populations, including people of French-Canadian/Cajun heritage.
Some people carry the genetic mutation that causes Tay-Sachs, but do not develop the full-blown disease. Among Ashkenazi Jews, 1 in 27 people are carriers; in the general population, 1 in 250 people are.
A child can only have Tay-Sachs disease if both parents are carriers of the gene.
Tay-Sachs is a recessive trait.

Achondroplasia dwarfism occurs as a sporadic mutation in approximately 85% of cases (associated with advanced paternal age) or may be inherited in an **autosomal dominant** genetic disorder that is a common cause of dwarfism. A person with achondroplasia is heterozygous and has only one mutated gene (the other is normal). If both parents of a child have achondroplasia, and both parents pass on the mutant gene, then it is very unlikely that the homozygous child will live past a few months of its life (often the child is stillborn). It is possible for two parents with achondroplasia to pass on normal genes and have children of average adult heights. The disorder itself is caused by a change in the DNA for fibroblast growth factor receptor 3 which causes an abnormality of cartilage formation. Achondroplastic dwarfs have short stature, with an average adult height of 131 cm (4 feet, 3½ inches) for males and 123 cm (4 feet, ½ inch) for females.
The prevalence is approximately 1 in 25,000.

Down Syndrome
Trisomy of the 21 chromosome.

Genetic Screening of Newborn Infants: What Should We Test And Why?

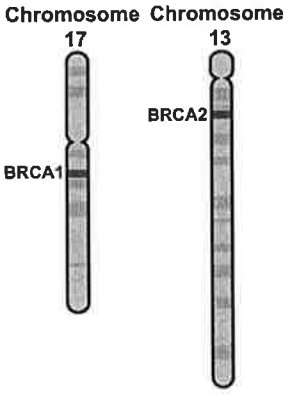
Breast Cancer Genes BRCA1 and BRCA2

Clinical description

Cancers cause cells in the body to change, to divide out of control (forming masses of tissue called tumors) and to spread to other parts of the body. They are named for the part of the body where they begin. Breast cancer, the second major cause of death by cancer in American women, is often detected when there are visible changes in the breast, such as a lump, thickening, swelling, skin irritation or nipple discharge. The risk of breast cancer increases with age.

Genetics

Only 5 - 10 percent of all breast cancer cases are believed to have a genetic link. Of these, an estimated two-thirds are caused by mutations in either BRCA1 or BRCA2, genes thought to play a role in fixing damaged DNA. About 50 - 60 percent of individuals with certain mutations in either of these two genes will develop breast cancer by age 70.



Inheritance

Autosomal dominant.

Incidence

The frequency of breast cancer in women is 1 in 8. Caucasian women have a higher risk of developing breast cancer than African-American, Asian or Hispanic women. The vast majority of affected women do not have a genetic predisposition to the disease. The prevalence of cancer-predisposing mutations in BRCA1 is 1 in 500 - 1000. The prevalence for BRCA2 mutations is unknown. A higher frequency of mutations in both genes is seen in the Ashkenazi Jewish population.

Diagnosis without genetic screening

Mutations in BRCA1 and BRCA2 are associated with early age of cancer onset, cancer in both breasts, and male breast cancer. Clinical breast exams and mammography can detect breast cancer at onset.

Clinical outcome without screening and treatment

Cancer can spread throughout the body if not treated and survival rate is reduced.

Clinical outcome with screening and treatment

There is no certain way to prevent breast cancer. However, some lifestyle risk factors have been identified including diet and alcohol use. It is important to identify breast cancer early to optimize treatment. If a genetic predisposition to breast cancer is known, there are drugs available which have been shown to reduce the likelihood of developing the disorder. Some high-risk women may consider a preventive mastectomy (removal of one or both breasts), although this does not guarantee that breast cancer will not develop. After such an operation, breast reconstruction may be possible and has become an important part of rehabilitation and therapy.

Testing

More than 235 mutations have been identified in BRCA1 and about 100 mutations have been identified in BRCA2. No currently available technique can detect all of the cancer-predisposing mutations in BRCA1 or BRCA2. Myriad Genetics has developed a test that analyzes about 16,500 base pairs for the two genes. The test costs $2,580 U.S. However, it is estimated that about 30 percent of BRCA mutations are not detected by currently available tests.

Genetic counseling

Genetic counseling for adults is offered before and after genetic testing. It is recommended that at-risk families consider a genetic testing strategy. Individuals with breast cancer in a family are strongly encouraged to be tested for mutations prior to unaffected family members. The test results from the affected family members will identify a particular type of mutation more likely to be associated with breast cancer. This information can then be used to test unaffected family members for the same mutation, thus making their results more meaningful.

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Sickle Cell Disease

Clinical description

Sickle cell disease describes a group of inherited disorders of red blood cells. Red blood cells are responsible for delivering oxygen to different parts of the body; normally they are round and contain a molecule called hemoglobin, which carries oxygen. If the gene encoding hemoglobin is mutated, it causes a change in the shape of the molecule. When the mutated hemoglobin delivers oxygen to the tissues, the red blood cell collapses, resulting in a long, flat sickle-shaped cell. These cells clog blood flow, resulting in a variety of symptoms including pain, increased infections, lung blockage, kidney damage, delayed growth and anemia (low blood cell count).

Genetics

The gene encoding the beta chain of the hemoglobin molecule, located on chromosome 11, can be mutated in a variety of ways that result in different types of sickle cell disease. Some mutations are more common than others. The three most common types of sickle cell disease in the United States are hemoglobin SS (Hb SS), hemoglobin SC (Hb SC), and hemoglobin sickle beta-thalassemia (HbS beta-thalassemia).

Inheritance

Autosomal recessive.

Incidence

Sickle cell disease affects more than 50,000 Americans. Although the disease occurs in high frequency in individuals of Mediterranean, Caribbean, Indian, Arab and Southeast Asian descent, the disease exhibits the highest frequency in people of African descent.

In African-Americans the incidence is 1 in 375 for HbSS, 1 in 835 for HbSC and 1 in 1,667 for HbS beta-thalassemia. In addition, 1 in 12 African-Americans are carriers for the disorder (have sickle cell trait). In United States populations, the prevalence of all types of sickle cell disease is equal to 1 in 58,000 Caucasians; 1 in 1,100 Hispanics (eastern states); 1 in 32,000 Hispanics (western states); 1 in 11,500 Asians; and 1 in 2,700 Native Americans.

Diagnosis without genetic screening

Clinical diagnosis is rarely made before 1 year of age, when symptoms lead to further investigation.

Clinical outcome without screening and treatment

Complications include increased infections, kidney damage, leg ulcers, bone damage and delayed growth. Ten percent mortality occurs in early infancy and childhood. Hospitalizations for sickle cell disease cost the U.S. government an estimated $475 million per year, at an average of $6,300 per hospitalization.

Clinical outcome with screening and treatment

With treatment, the incidence of early death is significantly reduced. When diagnosed, newborns are placed on penicillin until age six to prevent infections. Parents are educated in guidelines to follow with their child, including taking folic acid to make new red blood cells, drinking lots of water, avoiding extreme temperatures, and getting regular checkups with a physician.

Testing

Sickle cell diseases can be identified using isoelectric focusing of hemoglobin from filter paper blood spots.

Note: In the past, screening programs for sickle cell disease led to discrimination against individuals identified as being carriers for the disorder (having sickle cell trait). These individuals do not display the disorder but were treated as potentially ill, and often restricted from certain jobs and barred from joining the military. Problems that developed from the early sickle cell disease screening programs have resulted in regulations that govern current screening programs.

Genetic counseling

Genetic counseling is needed in order to provide rapid access to medical care for the affected individual. In addition, it is important to provide genetic counseling for carrier individuals in order to

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prevent any feelings of stigmatization or confusion about the meaning of their genetic status and so that they may make informed decisions about future offspring. Fears about confidentiality, discrimination in the work place, and insurability need to be addressed.

References

Ashley-Koch A., Yang Q., and Olney RS. Hemoglobin S allele and sickle cell disease. ***American Journal of Epidemiology.*** **2000;151:839-845.**

http://www.cdc.gov/genetics/hugenet/reviews/sickle.htm
This paper, available from the Center for Disease Control, provides some advanced information on the incidence of sickle cell disorder in certain populations. Last site update August 5, 1998. Accessed May 14, 2001.

Joint Center for Sickle Cell and Thalassemic Disorders
http://sickle.bwh.harvard.edu/menu_sickle.html
Contains comprehensive, detailed information about sickle cell disease. Covers hemoglobin, syndrome definitions and management considerations, including newborn screening programs. Also includes basic and clinical research. Last site update July 2, 1999. Accessed May 14, 2001.

Sickle Cell Information Center Home Page
http://www.emory.edu/PEDS/SICKLE/
An comprehensive site with information on sickle cell anemia, health care guidelines, teacher and student resources and interpreting newborn screening results. Also includes a useful Powerpoint presentation and sickle cell tutorial. Last site update April 2001. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

Cystic Fibrosis

Clinical description

Cystic fibrosis (CF) is caused by changes in a protein that controls the transfer of chloride and sodium ions (salts) across cell membranes. Disruption of salt transfer results in abnormal gland secretions and dehydration due to increased loss of salt and water during sweating. CF affects almost all of the glands in the body that secrete fluid, resulting in a variety of symptoms. Secretions may be thick and cause blockage in the pancreas, intestines and lungs. Mucus blockage also provides places for bacteria to multiply, increasing the probability of infection. CF children show poor digestion, dehydration, coughing and vomiting. As the disease progresses, teenagers show slowed growth, delayed puberty and reduced physical endurance. Adults show more serious complications such as collapsed lung, heart failure, infertility and frequent infections that eventually lead to death.

Genetics

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene on chromosome 7 which codes for the protein that controls ion transfer across cell membranes. Molecular analysis has identified approximately 100 mutations in the CFTR gene. Different mutations determine the severity of symptoms seen in CF patients.

Inheritance

Autosomal recessive.

Incidence

CF is the most common hereditary disease leading to death among Caucasian people in the United States. The incidence of the disorder is: 1 in 2,500 Caucasians; 1 in 14,000 blacks; 1 in 11,500 Hispanics; and 1 in 25,000 Asians

Diagnosis without genetic screening

Half of the patients with CF are undiagnosed during the first year of life and 25 percent remain undiagnosed by the end of the second year.

Clinical outcome without screening and treatment

If not diagnosed early, 13 percent of newborns and infants will die. Most untreated CF individuals will not live past their late 20's. In general, males live longer than females.

Clinical outcome with screening and treatment

If diagnosed and treated, newborn and infant mortality is reduced. Half of the people with CF live longer than 28 years due to availability of an increasingly wide range of treatments. These include physical therapy, enzyme replacements, supplemental salt, antibiotics to control infection, oxygen therapy, surgery and organ transplantation. Treatment for CF costs an average of $40,000 U.S. per year per patient in direct medical costs alone. Gene therapy is under investigation and evaluation.

Testing

Mutation in the CFTR gene results in an increase in an enzyme called trypsinogen. The initial newborn screen tests for this enzyme using a dried blood sample. However, this is not a conclusive test for CF. Measuring the salt levels in sweat can usually confirm the diagnosis.

Genetic counseling

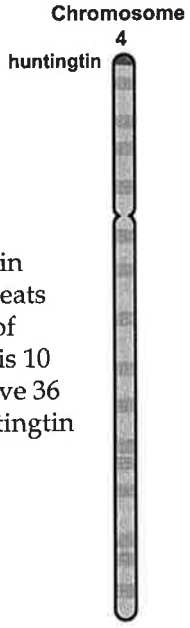
Prenatal diagnosis is possible for most families. Carrier screening of the general population is possible using DNA mutation analysis. CF carrier testing is not recommended at this time unless a family history of CF is present. It is difficult to detect all carriers. Only 80 - 90 percent of carriers will be identified with the available tests. Newborn screening is recommended to prevent malnutrition as well as improve lung condition. Embryo screening for CF is available for carrier parents prior to embryo implantation during an in-vitro fertilization procedure.

Genetic Screening of Newborn Infants: What Should We Test And Why?

Huntington's Disease

Clinical description

Huntington's disease is characterized by the progressive death of certain nerve cells in the brain. Symptoms generally appear between the ages of 35-40 years and include depression, mood swings, forgetfulness, involuntary twitching and lack of coordination. As the disease progresses, involuntary movements increase, memory declines, and walking, speaking and swallowing ability gradually diminish. Eventually affected persons are unable to care for themselves and death soon follows from choking, infections or heart failure. About 10 percent of patients have juvenile Huntington's disease, in which symptoms develop before age 20.



Genetics

Huntington's is caused by excessive repeating of the DNA bases CAG (trinucleotide repeats) in the huntingtin gene on chromosome 4. The more repeats an individual has, the earlier the age of onset. The normal number of repeats is 10 - 35. Huntington's disease patients have 36 - 121 repeats. The function of the huntingtin protein is not yet fully understood.

Inheritance

Autosomal dominant.

Incidence

1 in 20,000 Caucasians (except in Finland, where the incidence is much lower); 1 in 100,000 African Americans. 1 in 1,000,000 Africans; and 1 in 300,000 Asians.

Diagnosis without genetic screening

Symptoms are usually not observed before disease onset. Individuals with a family history of this disorder may show symptoms earlier.

Clinical outcome without screening and treatment

Involuntary movements and mental disturbances continue to increase.

Clinical outcome with screening and treatment

No cure is currently available for Huntington's disease. However, involuntary movements, rigidity and psychiatric symptoms can be suppressed or reduced with certain drugs. Neural and stem cell transplantation may be a potential option for treatment in the future.

Testing

The huntingtin gene is analyzed in a blood sample to determine the number of CAG repeats.

Genetic counseling

Genetic counseling is offered before and after testing to individuals who have a family history of Huntington's disease. Because this disorder shows dominant inheritance, a child with an affected parent has a 50 percent chance of inheriting the disorder. Some individuals may choose not to know their prognosis, rather than live with the knowledge that they have a disorder with no cure. Others would rather have a definitive diagnosis and choose to be tested. Personal life choices, such as decisions about childbearing, can be affected by test results. Genetic screening allows individuals to plan for their future and the future of their families. There are support groups for individuals who test positive for Huntington's and for their caregivers, which help to ease the distresses they must face.

References

Caring for People with Huntington's Disease
http://www.kumc.edu/hospital/huntingtons/
Maintained by the Department of Neurology at the Kansas University Medical Center. Information includes a description of Huntington's disease, specific care issues and a list of other Internet resources. An excellent feature of the site is a question and answer page for students writing school reports on the disorder. This page is constructed from questions students e-mailed to a doctor at the hospital. If the question isn't already addressed on the site students can e-mail questions about Huntington's Disease and receive answers within 1-2 days. Last site update February 23, 2001. Accessed May 14, 2001.