What are the neurofibromatoses?

The neurofibromatoses are genetic disorders of the nervous system that primarily affect the development and growth of neural (nerve) cell tissues. These disorders cause tumors to grow on nerves and produce other abnormalities such as skin changes and bone deformities. The neurofibromatoses occur in both sexes and in all races and ethnic groups. Scientists have classified the disorders as neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). Other or variant types of the neurofibromatoses may exist, but are not yet identified.

What is NF1?

NF1 is the more common type of the neurofibromatoses, occurring in about 1 in 4,000 individuals in the United States. Although many affected persons inherit the disorder, between 30 and 50 percent of new cases arise spontaneously through mutation (change) in an individual's genes. Once this change has taken place, the mutant gene can be passed on to succeeding generations.

Previously, NF1 was known as peripheral neurofibromatosis (or von Recklinghausen's neurofibromatosis) because some of the symptoms—skin spots and tumors—seemed to be limited to the outer nerves, or peripheral nervous system, of the affected person. This name is no longer technically accurate because central nervous system tumors are now known to occur in NF1.

What are the signs and symptoms of NF1?

In diagnosing NF1, a physician looks for two or more of the following:

- five or more light brown skin spots (café-au-lait macules) measuring more than 5 millimeters in diameter in patients under the age of puberty or more than 15 millimeters across in adults and children over the age of puberty;
- two or more neurofibromas (tumors that grow on a nerve or nerve tissue, under the skin) or one plexiform neurofibroma (involving many nerves);

- freckling in the arm pit or groin areas;
- benign growths on the iris of the eye (known as Lisch nodules or iris hamartomas);
- a tumor on the optic nerve (optic glioma);
- severe scoliosis (curvature of the spine);
- enlargement or deformation of certain bones other than the spine; and
- a parent, sibling, or child with NF1.

When do symptoms appear?

Symptoms, particularly those on the skin, are often evident at birth or during infancy, and almost always by the time a child is about 10 years old. Neurofibromas become evident at around 10 to 15 years of age. In most cases, symptoms are mild and patients live normal and productive lives. In some cases, however, NF1 can be severely debilitating.

Symptoms and severity of the disorder may vary among members of affected families.

How is NF1 treated?

Treatments are presently aimed at controlling symptoms. Surgery can help some bone malformations. For scoliosis, bone surgery may be combined with back braces. Surgery can also remove painful or disfiguring tumors; however, there is a chance that the tumors may grow back and in greater numbers. In the rare instances when tumors become malignant (3 to 5 percent of all cases), treatment may include surgery, radiation, or chemotherapy.

What is NF2?

This less common of the neurofibromatoses affects about 1 in 40,000 persons. NF2 is characterized by bilateral (occurring on both sides of the body) tumors on the eighth cranial nerve. It was formerly called bilateral acoustic neurofibromatosis or central neurofibromatosis because the tumors, which cause progressive hearing loss, were thought to grow primarily on the auditory nerve, a branch of the eighth cranial nerve responsible for hearing.

Scientists now know that the tumors typically occur on the vestibular nerve, another branch of the eighth cranial nerve near the auditory nerve. The tumors, called vestibular schwannomas for their location and for the type of cells in them, cause pressure damage to neighboring nerves. In some cases, the damage to nearby vital structures, such as other cranial nerves and the brainstem, can be life-threatening.

What are the signs and symptoms of NF2?

To determine if an individual has NF2, a physician looks for the following:

1. bilateral eighth nerve tumors,
2. a parent, sibling, or child with NF2 and a unilateral eighth nerve tumor, or
3. a parent, sibling, or child with NF2 and any two of the following:

- glioma,
- meningioma,
- neurofibroma,
- schwannoma, or
- cataract at an early age.

When do symptoms appear?

Affected individuals may notice hearing loss as early as the teen years. In addition to changes in hearing that may occur in one or both ears, other early symptoms may include tinnitus (ringing noise in the ear) and poor balance. Headache, facial pain, or facial numbness, caused by pressure from the tumors, may also occur.

How is NF2 treated?

Treatments for NF2 are aimed at controlling the symptoms. Improved diagnostic technologies, such as MRI (magnetic resonance imaging), can reveal tumors as small as a few millimeters in diameter, thus allowing early treatment. Surgery to remove tumors completely is one option, but may result in

hearing loss. Other options include partial removal of tumors, radiation, and, if the tumors are not progressing rapidly, the conservative approach of watchful waiting.

Are there prenatal tests for the neurofibromatoses?

Genetic testing is available for families with documented cases of NF1 and NF2. Genetic analysis can be used to confirm clinical diagnosis if the disease is a result of familial inheritance. New (spontaneous) mutations cannot be confirmed genetically. Prenatal diagnosis of familial NF1 or NF2 is also possible utilizing amniocentesis or chorionic villus sampling procedures. Genetic counselors can provide information about these procedures and offer guidance in coping with the neurofibromatoses.

What do scientists know about the neurofibromatoses?

Formerly the neurofibromatoses were grouped as one disorder with at least two variations. Scientists now know that NF1 and NF2 are two distinct entities because the genes believed to be responsible for them are located on different chromosomes. The NF1 gene is on chromosome 17, while the gene for NF2 is on chromosome 22.

Humans have 23 pairs of chromosomes, receiving one set of 23 chromosomes from each parent. Chromosomes carry genes that determine an individual's characteristics, such as sex, stature, hair and eye color, and distinctive family traits. Genes produce proteins that control an individual's development and health. If an inherited gene is defective, or a gene becomes defective spontaneously before birth, a genetic disorder may result. The neurofibromatoses are inherited as dominant disorders, which means that if either parent has the defective gene, each child born to that parent has a 50 percent chance of inheriting the defective gene.

What research is being done on the neurofibromatoses?

The National Institute of Neurological Disorders and Stroke (NINDS), a unit of the Federal Government's National Institutes of Health (NIH), has primary responsibility for conducting and supporting research on neurological disorders. The Institute sponsors basic studies aimed at understanding normal and abnormal development of the brain and nervous system, and clinical studies to improve diagnosis and treatment of neurological disorders. In conjunction with the NIH's National Cancer Institute, the NINDS encourages research specifically targeted on the neurofibromatoses.

Several years ago, research teams supported by the NINDS located the exact position of the NF1 gene on chromosome 17. The NF1 gene has been cloned and its structure analyzed. The product of the NF1 gene is a large and complex protein called neurofibromin. One portion of this protein is similar to a family of proteins called GAP (guanosine triphosphatase-activating protein). Scientists have demonstrated that GAP proteins play a significant role in tumor suppression in certain cancers. The proteins act as switches that regulate the complex chemical interactions and sequences of cell growth. The similarity of the NF1 protein to GAP proteins suggests that the NF1 protein may have a similar switching role in the development of neurofibromas. Scientists theorize that defects in the gene may lessen or inhibit the normal output of its protein and allow the irregular cell growth that may lead to tumor development.

In addition to the work on NF1, intensive efforts have led to the identification of the NF2 gene on chromosome 22. As in NF1, the NF2 gene product is a tumor suppressor protein (termed merlin or schwannomin). Basic studies in molecular genetics may lead one day to nonsurgical or pharmacologic treatments aimed at retarding or suppressing tumors associated with the neurofibromatoses.

The NINDS also encourages research aimed at developing improved methods of diagnosing the neurofibromatoses and at identifying factors that contribute to the wide variations of symptoms and severity of the disorders. Early diagnosis of the neurofibromatoses is essential so that affected individuals can obtain treatment, counseling, and referral to specialized facilities.

The Interinstitute Medical Genetics Research Program at the NIH Clinical Center conducts NF2 family history research, including a study involving individuals and families with NF2. With information from this study, investigators have confirmed the location of the NF2 gene on chromosome 22. Also, using specimens from some of the families, scientists have isolated and sequenced the NF2 gene, and have described two different patterns of clinical features in NF2 patients. Investigators are continuing to study these patterns to see if they correspond to specific types of gene mutations.

How can I help research?

The NINDS contributes to the support of two national human specimen banks, one at the Veterans Administration Medical Center in Los Angeles and the other at McLean Hospital near Boston. These banks supply investigators around the world with tissue from patients with neurological and other disorders. Both banks need tissue from individuals with NF1 or NF2 to enable scientists to study these disorders more intensely. Prospective donors may write to:

Dr. Wallace W. Tourtellotte, Director
Human Neurospecimen Bank
VAMC West Los Angeles
11301 Wilshire Boulevard
Los Angeles, California 90073
(310) 824-4307 (call collect)

Dr. Edward D. Bird, Director
Brain Tissue Bank, Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178
(617) 855-2400 (call collect 24 hours a day)
(800) BRAIN BANK (272-4622)

Where can I get more information?

You can obtain further information on the neurofibromatoses, including information about treatment centers and genetic counseling, from the following voluntary health organizations:

National Neurofibromatosis Fdn.
95 Pine Street, 16th Floor
New York, NY 10005
212-344-NNFF
800-323-7938

Neurofibromatosis, Inc.
8855 Annapolis Road
Suite 110
Lanham, Maryland 20706-2924
(410) 577-8984
(410) 461-5213 (TDD)
(800) 942-6825

For more information on research in the neurofibromatoses, you may wish to contact:

NIH Neurological Institute
Office of Scientific and Health Reports
P.O. Box 5801
Bethesda, Maryland 20824
(301) 496-5751
(800) 352-9424

National Cancer Institute
Information Office
Building 31, Room 10A24
9000 Rockville Pike
Bethesda, Maryland 20892
(301) 496-5583

Interinstitute Medical Genetics Program
National Institutes of Health Clinical Center
Building 10, Room 9C436
9000 Rockville Pike
Bethesda, Maryland 20892
(301) 496-1380