



Cancer Predisposition Clinic

Hereditary Neuroblastoma

Also called: ALK-related neuroblastic tumor susceptibility, PHOX2B-related neuroblastic tumor susceptibility

What is hereditary neuroblastoma?

Neuroblastoma is a cancer of the nerve cells. It mainly affects children before the age of 5 years and rarely occurs in adults. A neuroblastoma develops when young nerve cells called neuroblasts grow uncontrollably to form a tumor. Most of the time, neuroblastomas begin in the nerve tissue of the adrenal glands. These glands are small, hormone-producing organs that are located on top of each kidney. Hormones are chemicals that are important for sending messages in the body. Sometimes neuroblastomas begin in the nerve cells of the abdomen, chest, neck or pelvis.

Neuroblastoma most often occurs in children who have no family history of the disease. This is called sporadic neuroblastoma. However, in 1–2% of cases, an increased chance of developing neuroblastoma can be inherited from a parent. This is called hereditary neuroblastoma. Children with hereditary neuroblastoma are more likely to have a higher number of tumors and to be diagnosed at a younger age than people with sporadic neuroblastoma.

Hereditary neuroblastoma often varies in how severe it is, even among people in the same family. Some people may have many tumors, while others do not even develop one tumor. Even within the same person with the condition, some tumors might shrink and go away on their own, while other tumors are more aggressive and continue to grow.

What causes hereditary neuroblastoma?

Hereditary neuroblastoma is caused by changes in one of two genes: *ALK* or *PHOX2B*. Genes carry information telling cells within the body how to function. The *ALK* and *PHOX2B* genes control how and when nerve cells grow, divide and die. Researchers believe that *ALK* and certain *PHOX2B* mutations can lead to neuroblastoma by influencing the growth and development of nerve cells, which makes them more likely to become cancerous.

Most people without hereditary neuroblastoma carry two working copies of the *ALK* and *PHOX2B* genes in their cells. One copy is inherited from the mother and one from the father. Cells from people with hereditary neuroblastoma carry one working copy of the *ALK* or *PHOX2B* gene and one copy that is changed. This change causes the gene to not work properly. It is called a mutation. Among people with hereditary neuroblastoma, mutations in the *ALK* gene are more common than those in the *PHOX2B* gene.

Most children with hereditary neuroblastoma caused by a mutation in the *ALK* gene have inherited the mutation from a parent. However, some children with *ALK* gene mutations are the first people in their families to carry the mutation.

Most children with hereditary neuroblastoma caused by a certain type of mutation in the *PHOX2B* gene did not inherit the mutation from a parent. These children have no history of the condition in their families. In these cases, the change either happened in an egg or sperm cell when the child was formed or in one of the child's cells during pregnancy. These children are the first in their families to have hereditary neuroblastoma related to *PHOX2B*.

No matter how they acquired the mutation, people with hereditary neuroblastoma have a 50% (1 in 2) chance of passing it on to their children.

What is the cancer risk for people with hereditary neuroblastoma?

People with an altered *ALK* or a certain type of altered *PHOX2B* gene are at increased risk to develop tumors including neuroblastoma, ganglioneuroblastoma and ganglioneuroma. The risk is highest in infancy and decreases by late childhood. It is currently believed that people with an *ALK* mutation have a 50–60% chance of developing a tumor.

Doctors do not know precisely what the risk is for people with a *PHOX2B* mutation because it is rarer. The risk for neuroblastoma depends on the type of mutation in the *PHOX2B* gene. The *PHOX2B* gene makes a protein that is made up of different sections, including two sections in which there are several copies of an amino acid (a protein building block) known as “alanine”. These sections are called “polyalanine repeat sequences” or PAR. Most people have 20 alanine repeats in the 2nd polyaniline repeat section of both of their *PHOX2B* genes (20/20). People with 29 to 33 PARs in one copy of their *PHOX2B* gene (20/29–20/33) have an increased risk of developing neuroblastic tumors such as neuroblastomas, ganglioneuroblastomas and ganglioneuromas. Mutations located outside the PARs are called “non-polyalanine repeat mutations” (or NPARM) and also increase the risk for neuroblastic tumors. The risk for neuroblastic tumors is higher in patients with a NPARM than a PARM.

What are other symptoms or physical findings seen in people with hereditary neuroblastoma?

People with hereditary neuroblastoma may have other medical issues besides the increased risk of tumors. Some of these issues are caused by the growing tumors. Not all people with hereditary neuroblastoma will have all the symptoms listed below:

- Flu-like symptoms (fever, feeling tired/fatigue, pain, loss of appetite, weight loss or diarrhea)
- Swelling in abdomen (belly), if a tumor is present
- Trouble breathing, if a tumor is in the chest
- Horner syndrome, if a tumor is in the neck—this condition causes nerve damage in the neck and results in drooping eyelids, small pupils, decreased sweating and red skin.
- Some tumors can release hormones that may cause high blood pressure, rapid heartbeat, flushing of the skin and sweating.
- Opsoclonus myoclonus syndrome—a very rare condition that causes rapid eye movements and jerky muscle motions.

Patients with *PHOX2B* mutations often have other conditions affecting the nervous system, including the following:

- Hirschsprung disease—a condition affecting the large intestine (colon) in which some nerves are missing. This results in bowel blockage or trouble going passing bowel movements.
- Decreased esophageal motility—a condition affecting the esophagus, the tube that connects the mouth and the stomach. In this condition, the transfer of food from the mouth to the stomach does not work as well as it should.
- Congenital central hypoventilation syndrome—a condition of the central nervous system in which breathing control is absent or not working properly.

These neurological conditions are not seen in people with *ALK* mutations.

How are people with hereditary neuroblastoma screened for tumors?

Currently, neuroblastoma screening is only recommended for individuals with *PHOX2B* NPARM, *PHOX2B* longer PARMs (20/28-20/33), or *ALK* gene mutations.

People with hereditary neuroblastoma should be managed by a healthcare provider who knows this condition well and who specializes in treating neuroblastomas. Children with hereditary neuroblastoma should have regular screenings to detect tumors as early as possible. The goal of screening is finding and treating tumors early to allow the best outcome for patients.

Screening for neuroblastoma and other related tumors includes the following:

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- **Yearly physical exams** by a doctor who knows hereditary neuroblastoma well.
- **Urine testing** for the levels of certain kinds of hormones called catecholamines (these are also called HVA and VMA). The level of catecholamines in the urine is often higher in people with neuroblastoma tumors than in those without. This testing should be started at diagnosis for patients with an *ALK* mutation or a *PHOX2B* NPARM and should be repeated every 3 months from birth to age 6 years, and then every 6 months starting at age 6 years and discontinued at age 10 years.
- **Ultrasound** of the abdomen and **chest X-ray**. These should be started at diagnosis and repeated every 3 months from birth to age 6 years, and then every 6 months starting at age 6 years and discontinued at age 10 years for patients with an *ALK* mutation or a *PHOX2B* NPARM. Patients with a *PHOX2B* PARM between 20/28 and 20/33 should have annual abdominal ultrasounds and chest x-rays. If a tumor is suspected, more detailed images should be taken using CT or MRI scans and the child should be seen by a pediatric cancer specialist (pediatric oncologist).
- **Yearly checkups** with a pediatrician.

It is possible that recommendations may change over time as we learn more about hereditary neuroblastoma. Parents should discuss all screening options for their child with a healthcare provider who knows hereditary neuroblastoma well. Because it is a complex condition, it is very important that parents seek out an experienced doctor for their child.

How is genetic testing for hereditary neuroblastoma done?

The doctor may suspect hereditary neuroblastoma after looking at a person's medical or family history. In most cases, a doctor or genetic counselor will ask questions about a person's health and the health of other family members.

The genetic counselor or doctor will record which family members have developed tumors, what types of tumors, and at what ages the tumors occurred. From this information they will create a family tree.

Doctors and genetic counselors will look at the family tree to find out:

- If there are more cancers than normal,
- If cancers occurred at younger-than-expected ages, and
- If the types of tumors match up with what might be seen in those with hereditary neuroblastoma.

If hereditary neuroblastoma is suspected in a child or other family members, the doctor or genetic counselor will likely recommend genetic testing of the *ALK* gene, the *PHOX2B* gene or both.

Diagnostic genetic testing

If the doctor or genetic counselor suspects that a person has hereditary neuroblastoma, diagnostic testing may take place as follows:

- A blood sample is collected.
- DNA is isolated from the cells in the sample. A person's genes are made of DNA.
- Both copies of the person's *ALK* gene, *PHOX2B* gene or both are checked for possible changes. A genetic specialist compares the two copies of the person's *ALK* gene or *PHOX2B* gene to normal copies of those genes. If there are differences, the specialist decides if they might cause a certain condition such as hereditary neuroblastoma.
- If a mutation is found in the *ALK* gene or *PHOX2B* gene, the genetic counselor will work with the family in the following ways:
 - To help the family understand the cancer risks of hereditary neuroblastoma
 - To find out if other family members should consider testing for the mutation
 - To help with decisions about prenatal genetic testing.

It is important to remember that genetic testing does not always find mutations in the *ALK* or *PHOX2B* genes for all people with hereditary neuroblastoma. A person can still have hereditary neuroblastoma even if no mutations are found in these genes. There may be other genes that are related to the condition that doctors do not yet know about.

Prenatal genetic testing

Parents may undergo prenatal testing to find out if the pregnancy is affected with a known *ALK* or *PHOX2B* mutation in the family. Testing may take place either before pregnancy occurs or during pregnancy.

People considering prenatal testing should work with a genetic counselor to review the pros and cons of the testing. The genetic counselor can also help parents consider how they wish to handle the results of the testing.

Testing that occurs before pregnancy—Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This special type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for a known *ALK* or *PHOX2B* mutation before placing them into the uterus.

Testing that occurs during pregnancy—Testing can be used to see if a pregnancy is affected with a known *ALK* or *PHOX2B* mutation. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)**—during the first trimester (first three months)
- **Amniocentesis**—during the second trimester or later (last six months)

Collected tissue can be checked for the presence of the *ALK* or *PHOX2B* mutation identified in the family. Both of these tests carry minor risks and should be discussed with an experienced doctor or genetic counselor.

Special concerns

Genetic testing for hereditary neuroblastoma is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic counselor before testing is done. If they choose testing, they should review the test results with a genetics healthcare provider to be sure they understand the meaning of the results.

Sometimes children or adults with hereditary neuroblastoma can feel sad, anxious or angry. Parents who pass on an *ALK* or *PHOX2B* mutation to one or more of their children can feel guilty. Some people with an *ALK* or *PHOX2B* mutation could have trouble getting disability coverage, life insurance or long-term care insurance in some states. More information about genetic discrimination can be found at www.ginahelp.org.

Are there other special health care needs for children with hereditary neuroblastoma?

People of any age with hereditary neuroblastoma have a higher risk of cancer. They should monitor their health and adopt healthful habits throughout life. It is important to continue to have regular physical checkups and screenings. That way, any cancer can be found early at the most treatable stage.

Other ideas to reduce the risk of cancer:

- Eat a healthful diet with lots of fruits and vegetables
- Get regular exercise
- Avoid smoking or using tobacco products
- Avoid secondhand smoke
- Avoid excess sun exposure and always wear sunscreen and hat when out in the sun

People with hereditary neuroblastoma should watch closely for general signs or symptoms that could signal cancer:

- Unexplained weight loss

- Loss of appetite
- Pain in abdomen
- Blood in the stool or changes in bowel habits
- Aches, pains, lumps or swelling that cannot be explained
- Headaches or changes in vision or nerve function that do not go away

It is important to seek medical help if anything unusual appears.

What other information and resources are there for children with hereditary neuroblastoma and their families?

Resources about hereditary neuroblastoma:

- The Neuroblastoma Children’s Cancer Society
(www.neuroblastomacancer.org)
- Children’s Neuroblastoma Cancer Foundation
(www.cncfhope.org)
- American Cancer Society – Neuroblastoma
(www.cancer.org/cancer/neuroblastoma/)

More resources about genetic testing and hereditary cancer:

- Making Sense of Your Genes: A Guide to Genetic Counseling
(www.ncbi.nlm.nih.gov/books/NBK115508/)
- Young People with Cancer: A Parent’s Guide
(www.cancer.gov/publications/patient-education/young-people)

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