# Noonan Syndrome

*Also called: Noonan-Ehmke syndrome, pseudo-Ullrich-Turner syndrome, Ullrich-Noonan syndrome*

## What is Noonan syndrome?

Noonan syndrome is a genetic condition that affects many areas of the body. People with Noonan syndrome often have some of the following features:

- Facial features (most obvious in babies and children and more subtle in adults):
  - A deep groove in the philtrum (the area between the nose and mouth)
  - Widely-spaced eyes that are vivid blue or blue-green in color. The eyes may have epicanthal folds (skin folds of the upper eyelid that partially cover the inner corners of the eyes) and thick or droopy eyelids
  - Low-set ears that are rotated backward or are unusually fleshy
- Broad neck or webbed neck
- Short stature (height for age less than the third percentile)
- Lymphedema (puffiness) in the hands and feet in newborns
- Feeding problems in newborns and infants
- Abnormal heart, present at birth (congenital heart defects), such as the following:
  - Pulmonary valve stenosis (heart valve disorder in which blood does not flow through the heart properly)
  - Hypertrophic cardiomyopathy (thickening of the heart muscle)
  - Atrial septal defect (abnormal hole between the two sides of the heart)
- Blood clotting (coagulation) defects
- Unusual shape of the chest, such as superior pectus carinatum (protruding chest) or inferior pectus excavatum (sunken chest)
- Low-set nipples
- Undescended testicles in males (cryptorchidism) and possible infertility
- Delayed puberty in males and females

Along with these features, about 25% of people with Noonan syndrome have special educational needs or intellectual disability.

Not all of these descriptions will apply to every person with Noonan syndrome.

## What is the cancer risk for people with Noonan syndrome?

People with Noonan syndrome are at a slightly increased risk of developing some types of cancers and blood disorders, including the following:

- Myeloproliferative disorder (abnormal production of cells in the bone marrow)
- Juvenile myelomonocytic leukemia (cancer of white blood cells in children)
- Neuroblastoma (cancer of the nerves)
- Embryonal rhabdomyosarcoma (cancer of the muscles)

In addition, people with Noonan syndrome are at a slightly increased risk of developing certain noncancerous tumors:

- Giant cell lesions (noncancerous tumor-like growths that most frequently occur in the jaws)
- Granular cell tumors (noncancerous tumors generally involving the skin or the mucus membranes)

Doctors do not know the exact risk of developing tumors or cancer for people with Noonan syndrome. The overall risk appears to be very low. At this time there are no standard cancer screening recommendations for people with Noonan syndrome.

## What are other conditions related to Noonan syndrome?

At least three conditions are closely related to Noonan syndrome that have some similar features.

One condition is known as Noonan syndrome with multiple lentigines (NSML), previously called LEOPARD syndrome (Lentigines, ECG abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth, Deafness). People with Noonan syndrome with multiple lentigines share many of the same features seen in people with Noonan syndrome, but typically have more skin findings. These include café au lait patches (coffee-colored, flat birthmarks) and lentigines (small colored spots on the skin with clearly-defined edges). Some patients with Noonan syndrome with multiple lentigines may also develop hearing loss.

A second condition related to Noonan syndrome is cardiofaciocutaneous (CFC) syndrome. People with cardiofaciocutaneous syndrome have facial, skeletal and cardiac features that are similar to those seen in people with Noonan syndrome. People with cardiofaciocutaneous syndrome, however, have more distinct facial features that are sometimes called “coarse.” These features may include sparse eyebrows and eyelashes, and follicular hyperkeratosis (white bumps on the skin). People with cardiofaciocutaneous syndrome may also have more severe feeding problems than people with Noonan syndrome do. These problems include gastroesophageal reflux (severe heartburn), aspiration (inhaling food particles), vomiting and oral aversion (unwillingness to put things into the mouth). Most people with cardiofaciocutaneous syndrome have intellectual disability.

A third condition related to Noonan syndrome is Costello syndrome. People with Costello syndrome can share features seen in Noonan syndrome and cardiofaciocutaneous syndrome. In addition, people with Costello syndrome can have more problems in the brain. The cancer risk is also higher in people with Costello syndrome, estimated to be 15% during a person’s lifetime.

## What causes Noonan syndrome?

Genes carry information telling cells within the body how to function. Noonan syndrome is caused by a change in any one of a group of genes that includes *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1,* and *LZTR1*. These genes are needed for growth and development.

Most people without Noonan syndrome carry two working copies of each these genes in their cells. One copy of each gene is inherited from the mother and one copy of each gene is inherited from the father. Cells from people with Noonan syndrome carry one working copy and one copy that is changed of *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1*, or two changed copies of *LZTR1*. These changes cause the gene to not work properly. It is called a mutation.

Mutations in *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1,* and *LZTR1* account for 75–80% of Noonan syndrome cases. Mutations in *PTPN11* are found in about 50% of cases, *SOS1* in 10–13% of cases, and *RAF1, RIT1,* and *KRAS* each in 5% of cases. Mutations in *BRAF* or *NRAS* are found in

only a small number of Noonan syndrome cases. For the remaining 20–25% of people with the condition who do not have mutations in any of these genes, doctors do not yet know what other genes are related to Noonan syndrome.

Some children with Noonan syndrome inherit a gene mutation in *PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, and *LZTR1* from a parent who also has the syndrome. Other people with Noonan syndrome have a new gene mutation that did not come from a parent. These children have no history of the syndrome 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 Noonan syndrome.

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

## How is genetic testing for Noonan syndrome done?

The health care provider may suspect Noonan syndrome after looking at a person's medical or family history. In most cases, a health care provider or genetic counselor will ask questions about a person's health and the health of other family members. If Noonan syndrome is suspected in a child or other family members, the health care provider or genetic counselor will likely recommend genetic testing of one or more of the genes that are associated with the syndrome (*PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, or *LZTR1*).

### Diagnostic genetic testing

If the health care provider or genetic counselor suspects that a person has Noonan syndrome, 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 genes are checked for possible changes. A genetic specialist compares the two copies of the patient's genes to normal copies of the genes. If there are differences, the specialist decides if they might cause a certain condition such as Noonan syndrome.
- If mutations in the tested gene or genes are found, the genetic counselor will work with the family in the following ways:
    - To help the family understand Noonan syndrome
    - To find out if other family members should consider testing
    - To help with decisions about prenatal genetic testing

It is important to remember that genetic testing does not always find a mutation in *PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, or *LZTR1* for all people with Noonan syndrome. A person can still have Noonan syndrome even if no mutations in these genes are found. There are likely to be more, undiscovered genes that play a role in the development of Noonan syndrome.

### Prenatal genetic testing

Parents may undergo prenatal testing to find out if the pregnancy is affected with a known family mutation in *PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, or *LZTR1*. 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 mutation in *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1,* or *LZTR1* 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 mutation in *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1,* or *LZTR1*. 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 a known mutation in *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1,* or *LZTR1* that has already been 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 Noonan syndrome 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 the health care provider or genetic counselor to be sure they understand the meaning of the results.

Sometimes children or adults with Noonan syndrome can feel sad, anxious or angry. Parents who pass on a mutation in *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1,* or *LZTR1* to one or more of their children can feel guilty. Some people with a mutation in one of these genes could have trouble getting disability coverage, life insurance or long-term care insurance. More information about genetic discrimination can be found at www.ginahelp.org.

## Are there other special health care needs for children with Noonan syndrome?

Parents should seek out a health care provider with experience managing patients with Noonan syndrome for their child. There are clinics throughout the country that specialize in taking care of people with Noonan syndrome. For more information, please see the “Resources” section below.

People with Noonan syndrome should have an initial evaluation of growth and development, heart, eyes, kidneys, hearing, blood and skeleton. Patients should seek follow up care if a problem is found in any of these areas.

People of any age with Noonan syndrome have a slightly higher risk of cancer. They should monitor their health and adopt healthy 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. At this time there are no standard cancer screening recommendations for people with Noonan syndrome.

Because of the risk of a bleeding disorder, people with Noonan syndrome should avoid taking aspirin or other blood thinners unless recommended by a health care provider who knows this syndrome well.

Other ideas to reduce the risk of cancer include the following:

- Eat a healthy 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, hat and protective clothing when out in the sun

People with Noonan syndrome 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 Noonan syndrome and their families?

Resources about Noonan syndrome:

- Noonan Syndrome Foundation (www.teamnoonan.org/)
  - Links to Noonan syndrome clinics (www.teamnoonan.org/help/#doctors-clinics)
- Noonan Syndrome Association (www.noonansyndrome.org.uk/)
- Genetics Home Reference (ghr.nlm.nih.gov/condition/noonan-syndrome)
- National Organization for Rare Disorders: Noonan Syndrome (rarediseases.org/rare-diseases/noonan-syndrome/)

More resources:

- 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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Sources:

1. Genetics Home Reference - Noonan syndrome
ghr.nlm.nih.gov/condition/noonan-syndrome
2. Gene Reviews – Noonan syndrome
www.ncbi.nlm.nih.gov/books/NBK1124/#_noonan_Differential_Diagnosis_

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