

Noonan syndrome

Description

Noonan syndrome is a condition that affects many areas of the body. It is characterized by mildly unusual facial features, short stature, heart defects, bleeding problems, skeletal malformations, and many other signs and symptoms.

People with Noonan syndrome have distinctive facial features such as a deep groove in the area between the nose and mouth (philtrum), widely spaced eyes that are usually pale blue or blue-green in color, and low-set ears that are rotated backward. Affected individuals may have a high arch in the roof of the mouth (high-arched palate), poor teeth alignment, and a small lower jaw (micrognathia). Many children with Noonan syndrome have a short neck, and both children and adults may have excess neck skin (also called webbing) and a low hairline at the back of the neck.

Between 50 and 70 percent of individuals with Noonan syndrome have short stature. At birth, they are usually a normal length and weight, but growth slows over time. Abnormal levels of growth hormone, a protein that is necessary for the normal growth of the body's bones and tissues, may contribute to the slow growth.

Individuals with Noonan syndrome often have either a sunken chest (pectus excavatum) or a protruding chest (pectus carinatum). Some affected people may also have an abnormal side-to-side curvature of the spine (scoliosis).

Most people with Noonan syndrome have some form of critical congenital heart disease. The most common heart defect in these individuals is a narrowing of the valve that controls blood flow from the heart to the lungs (pulmonary valve stenosis). Some have hypertrophic cardiomyopathy, which enlarges and weakens the heart muscle.

A variety of bleeding disorders have been associated with Noonan syndrome. Some affected individuals have excessive bruising, nosebleeds, or prolonged bleeding following injury or surgery. Rarely, women with Noonan syndrome who have a bleeding disorder have excessive bleeding during menstruation (menorrhagia) or childbirth.

Adolescent males with Noonan syndrome typically experience delayed puberty. They go through puberty starting at age 13 or 14 and have a reduced pubertal growth spurt that results in shortened stature. Most males with Noonan syndrome have undescended testes (cryptorchidism), which may contribute to infertility (inability to father a child) later in life. Females with Noonan syndrome can experience delayed puberty but most have

normal puberty and fertility.

Noonan syndrome can cause a variety of other signs and symptoms. Most children diagnosed with Noonan syndrome have normal intelligence, but a few have special educational needs, and some have intellectual disability. Some affected individuals have vision or hearing problems. Affected infants may have feeding problems, which typically get better by age 1 or 2 years. Infants with Noonan syndrome may be born with puffy hands and feet caused by a buildup of fluid (lymphedema), which can go away on its own. Older individuals can also develop lymphedema, usually in the ankles and lower legs.

Some people with Noonan syndrome develop cancer, particularly those involving the blood-forming cells (leukemia). It has been estimated that children with Noonan syndrome have an eightfold increased risk of developing leukemia or other cancers over age-matched peers.

Noonan syndrome is one of a group of related conditions, collectively known as RASopathies. These conditions all have similar signs and symptoms and are caused by changes in the same cell signaling pathway. In addition to Noonan syndrome, the RASopathies include cardiofaciocutaneous syndrome, Costello syndrome, neurofibromatosis type 1, Legius syndrome, and Noonan syndrome with multiple lentigines.

Frequency

Noonan syndrome occurs in approximately 1 in 1,000 to 2,500 people.

Causes

Mutations in multiple genes can cause Noonan syndrome. Mutations in the *PTPN11* gene cause about half of all cases. *SOS1* gene mutations cause an additional 10 to 15 percent, and *RAF1* and *RIT1* genes each account for about 5 percent of cases. Mutations in other genes each account for a small number of cases. The cause of Noonan syndrome in 15 to 20 percent of people with this disorder is unknown.

The *PTPN11*, *SOS1*, *RAF1*, and *RIT1* genes all provide instructions for making proteins that are important in the RAS/MAPK cell signaling pathway, which is needed for cell division and growth (proliferation), the process by which cells mature to carry out specific functions (differentiation), and cell movement (migration). Many of the mutations in the genes associated with Noonan syndrome cause the resulting protein to be turned on (active) longer than normal, rather than promptly switching on and off in response to cell signals. This prolonged activation alters normal RAS/MAPK signaling, which disrupts the regulation of cell growth and division, leading to the characteristic features of Noonan syndrome.

Rarely, Noonan syndrome is associated with genes that are not involved in the RAS/MAPK cell signaling pathway. Researchers are working to determine how mutations in these genes can lead to the signs and symptoms of Noonan syndrome.

Learn more about the genes associated with Noonan syndrome

- BRAF
- KRAS
- LZTR1
- MAP2K1
- NRAS
- PTPN11
- RAF1
- RIT1
- SOS1

Additional Information from NCBI Gene:

- A2ML1
- RASA2
- RRAS
- SOS2

Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Other Names for This Condition

- Familial Turner syndrome
- Female pseudo-Turner syndrome
- Male Turner syndrome
- Noonan's syndrome
- Noonan-Ehmke syndrome
- NS
- Pseudo-Ullrich-Turner syndrome
- Turner phenotype with normal karyotype
- Turner syndrome in female with X chromosome
- Turner-like syndrome
- Ullrich-Noonan syndrome

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Noonan syndrome (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0028326/>)
- Genetic Testing Registry: Noonan syndrome 1 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4551602/>)
- Genetic Testing Registry: Noonan syndrome 10 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225280/>)
- Genetic Testing Registry: Noonan syndrome 2 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1854469/>)
- Genetic Testing Registry: Noonan syndrome 3 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1860991/>)
- Genetic Testing Registry: Noonan syndrome 4 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1853120/>)
- Genetic Testing Registry: Noonan syndrome 5 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1969057/>)
- Genetic Testing Registry: Noonan syndrome 6 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2750732/>)
- Genetic Testing Registry: Noonan syndrome 7 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3150970/>)
- Genetic Testing Registry: Noonan syndrome 8 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3809233/>)
- Genetic Testing Registry: Noonan syndrome 9 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225282/>)

Genetic and Rare Diseases Information Center

- Noonan syndrome (<https://rarediseases.info.nih.gov/diseases/10955/index>)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (<https://rarediseases.org/>)

Clinical Trials

- ClinicalTrials.gov ([https://clinicaltrials.gov/search?cond=%22Noonan syndrome%22](https://clinicaltrials.gov/search?cond=%22Noonan%20syndrome%22))

Catalog of Genes and Diseases from OMIM

- NOONAN SYNDROME 1; NS1 (<https://omim.org/entry/163950>)
- NOONAN SYNDROME 2; NS2 (<https://omim.org/entry/605275>)
- NOONAN SYNDROME 4; NS4 (<https://omim.org/entry/610733>)
- NOONAN SYNDROME 3; NS3 (<https://omim.org/entry/609942>)
- NOONAN SYNDROME 5; NS5 (<https://omim.org/entry/611553>)
- NOONAN SYNDROME 8; NS8 (<https://omim.org/entry/615355>)
- NOONAN SYNDROME 7; NS7 (<https://omim.org/entry/613706>)
- NOONAN SYNDROME 6; NS6 (<https://omim.org/entry/613224>)
- NOONAN SYNDROME 9; NS9 (<https://omim.org/entry/616559>)
- NOONAN SYNDROME 10; NS10 (<https://omim.org/entry/616564>)

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28Noonan+Syndrome%5BMAJR%5D%29+AND+%28Noonan+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>)

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