Noonan syndrome

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 \textit{PTPN11} gene cause about half of all cases. \textit{SOS1} gene mutations cause an additional 10 to 15 percent, and \textit{RAF1} and \textit{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 \textit{PTPN11}, \textit{SOS1}, \textit{RAF1}, and \textit{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.

Inheritance Pattern

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

Diagnosis & Management

Formal Diagnostic Criteria

Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, Roberts AE, Robinson W, Takemoto CM, Noonan JA. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010 Oct;126(4):746-59. doi: 10.1542/peds.2009-3207. Epub 2010 Sep 27. Review.

Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20876176

Formal Treatment/Management Guidelines

Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, Roberts AE, Robinson W, Takemoto CM, Noonan JA. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010 Oct;126(4):746-59. doi: 10.1542/peds.2009-3207. Epub 2010 Sep 27. Review.

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Genetic Testing Information

What is genetic testing?/primer/testing/genetictesting

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 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 Testing Registry: Noonan syndrome 10  
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225280/

Research Studies from ClinicalTrials.gov
• ClinicalTrials.gov  
  https://clinicaltrials.gov/ct2/results?cond=%22noonan+syndrome%22

Other Diagnosis and Management Resources
• GeneReview: Noonan Syndrome  
  https://www.ncbi.nlm.nih.gov/books/NBK1124

• MedlinePlus Encyclopedia: Noonan Syndrome  
  https://medlineplus.gov/ency/article/001656.htm

• The Children's Hospital of Philadelphia  
  https://www.chop.edu/conditions-diseases/noonan-syndrome

Additional Information & Resources
Health Information from MedlinePlus
• Encyclopedia: Noonan Syndrome  
  https://medlineplus.gov/ency/article/001656.htm

• Encyclopedia: Pulmonary Valve Stenosis  
  https://medlineplus.gov/ency/article/001096.htm

• Encyclopedia: Undescended Testicle  
  https://medlineplus.gov/ency/article/000973.htm
• Health Topic: Bleeding Disorders
  https://medlineplus.gov/bleedingdisorders.html
• Health Topic: Cardiomyopathy
  https://medlineplus.gov/cardiomyopathy.html
• Health Topic: Congenital Heart Defects
  https://medlineplus.gov/congenitalheartdefects.html
• Health Topic: Craniofacial Abnormalities
  https://medlineplus.gov/craniofacialabnormalities.html
• Health Topic: Growth Disorders
  https://medlineplus.gov/growthdisorders.html

Genetic and Rare Diseases Information Center
• Noonan syndrome
  https://rarediseases.info.nih.gov/diseases/10955/noonan-syndrome

Additional NIH Resources
• National Human Genome Research Institute
  https://www.genome.gov/Genetic-Disorders/Noonan-Syndrome

Educational Resources
• Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Kprones/NoonanID10085.html
• MalaCards: noonan syndrome 1
  https://www.malacards.org/card/noonan_syndrome_1
• Merck Manual Consumer Version
  https://www.merckmanuals.com/home/children-s-health-issues/chromosome-and-gene-abnormalities/noonan-syndrome
• National Health Service (UK)
  https://www.nhs.uk/conditions/noonan-syndrome/
• Nemours Teens Health: Delayed Puberty
  https://kidshealth.org/en/teens/delayed-puberty.html
• Orphanet: Noonan syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=648
• RASopathiesNet
  https://rasopathiesnet.org/
• St. Jude Children's Research Hospital
  https://www.stjude.org/disease/noonan-syndrome.html
• The University of Arizona Health Sciences Hereditary Ocular Disease Database: Noonan Syndrome
  https://disorders.eyes.arizona.edu/disorders/noonan-syndrome

• University of California, Davis Children's Hospital
  https://health.ucdavis.edu/children/clinical_services/cleft_craniofacial/anomalies/noonan.html

Patient Support and Advocacy Resources
• American Heart Association
  https://www.heart.org/

• Children's Cardiomyopathy Foundation
  https://dev.childrenscardiomyopathy.org/

• National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/noonan-syndrome/

Clinical Information from GeneReviews
• Noonan Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1124

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?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

Catalog of Genes and Diseases from OMIM
• NOONAN SYNDROME 1
  http://omim.org/entry/163950

• NOONAN SYNDROME 2
  http://omim.org/entry/605275

• NOONAN SYNDROME 3
  http://omim.org/entry/609942

• NOONAN SYNDROME 4
  http://omim.org/entry/610733

• NOONAN SYNDROME 5
  http://omim.org/entry/611553

• NOONAN SYNDROME 6
  http://omim.org/entry/613224

• NOONAN SYNDROME 7
  http://omim.org/entry/613706
Medical Genetics Database from MedGen

• Noonan syndrome
  https://www.ncbi.nlm.nih.gov/medgen/18073

Sources for This Summary

• Chen PC, Yin J, Yu HW, Yuan T, Fernandez M, Yung CK, Trinh QM, Peltekova VD, Reid JG, Tworog-Dube E, Morgan MB, Muzny DM, Stein L, McPherson JD, Roberts AE, Gibbs RA, Neel BG, Kucherlapati R. Next-generation sequencing identifies rare variants associated with Noonan syndrome. Proc Natl Acad Sci U S A. 2014 Aug 5;111(31):11473-8. doi: 10.1073/pnas.1324128111. Epub 2014 Jul 21. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25049390 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4128129/

• Cordeddu V, Yin JC, Gunnarsson C, Virtanen C, Drunat S, Lepri F, De Luca A, Rossi C, Ciolfi A, Pugh TJ, Bruselles A, Priest JR, Pennacchio LA, Lu Z, Danesh A, Quevedo R, Hamid A, Martinelli S, Pantaleoni F, Gnazzo M, Daniele P, Lisewski C, Bocchinfuso G, Stella L, Odent S, Philip N, Faivre L, Vickova M, Seemanova E, Digilio C, Zerken M, Zampino G, Verloes A, Dallapiccola B, Roberts AE, Cavé H, Gelb BD, Neel BG, Tartaglia M. Activating Mutations Affecting the Dbl Homology Domain of SOS2 Cause Noonan Syndrome. Hum Mutat. 2015 Nov;36(11):1080-7. doi: 10.1002/humu.22834. Epub 2015 Aug 3. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26173643 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604019/

• Flex E, Jaiswal M, Pantaleoni F, Martinelli S, Strullu M, Fansa EK, Caye A, De Luca A, Lepri F, Dvorsky R, Pannone L, Paolacci S, Zhang SC, Fodale V, Bocchinfuso G, Rossi C, Burkitt-Wright EM, Farrotti A, Stellacci E, Cecchetti S, Ferese R, Bottero L, Castro S, Finnennetou O, Brethon B, Sanchez M, Roberts AE, Yntema HG, Van Der Burgt I, Cianci P, Bondeson ML, Cristina Digilio M, Zampino G, Kerr B, Aoki Y, Loh ML, Palleschi A, Di Schiavi E, Carè A, Selicorni A, Dallapiccola B, Cirstea IC, Stella L, Zerken M, Gelb BD, Cavé H, Ahmadian MR, Tartaglia M. Activating mutations in RRAS underlie a phenotype within the RASopathy spectrum and contribute to leukaemogenesis. Hum Mol Genet. 2014 Aug 15;23(16):4315-27. doi: 10.1093/hmg/ddu148. Epub 2014 Apr 4. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24705357 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103678/

• Kouz K, Lisewski C, Spranger S, Mitter D, Riess A, Lopez-Gonzalez V, Lütgten S, Aydin H, von Deimling F, Evers C, Hahn A, Hempel M, Issa U, Kahler AK, Lieb A, Villavicencio-Lorini P, Ballesta-Martinez MJ, Nampoothiri S, Owens-Raeder A, Puchmajerová A, Satanovskij R, Seidel H, Unkelbach S, Zabel B, Kutsche K, Zerken M. Genotype and phenotype in patients with Noonan syndrome and a RIT1 mutation. Genet Med. 2016 Apr 21. doi: 10.1038/gim.2016.32. [Epub ahead of print] Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27101134
Yamamoto GL, Aguena M, Gos M, Hung C, Pinch J, Fahiminiya S, Abramowicz A, Cristian I, Buscarilli M, Naslavsky MS, Malaquias AC, Zatz M, Bodamer O, Majewski J, Jorge AA, Pereira AC, Kim CA, Passos-Bueno MR, Bertola DR. Rare variants in SOS2 and LZTR1 are associated with Noonan syndrome. J Med Genet. 2015 Jun;52(6):413-21. doi: 10.1136/jmedgenet-2015-103018. Epub 2015 Mar 20. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25795793

van der Burgt I. Noonan syndrome. Orphanet J Rare Dis. 2007 Jan 14;2:4. Review. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17222357
Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1781428/

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