Noonan syndrome with multiple lentigines

Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome) is a condition that affects many areas of the body. As the condition name suggests, Noonan syndrome with multiple lentigines is very similar to a condition called Noonan syndrome, and it can be difficult to tell the two disorders apart in early childhood. However, the features of these two conditions differ later in life. The characteristic features of Noonan syndrome with multiple lentigines include brown skin spots called lentigines that are similar to freckles, heart defects, widely spaced eyes (ocular hypertelorism), a sunken chest (pectus excavatum) or protruding chest (pectus carinatum), and short stature. These features vary, however, even among affected individuals in the same family. Not all individuals with Noonan syndrome with multiple lentigines have all the characteristic features of this condition.

The lentigines seen in Noonan syndrome with multiple lentigines typically first appear in mid-childhood, mostly on the face, neck, and upper body. Affected individuals may have thousands of small dark brown skin spots by the time they reach puberty. Unlike freckles, the appearance of lentigines has nothing to do with sun exposure. In addition to lentigines, people with this condition may have lighter brown skin spots called café-au-lait spots. Café-au-lait spots tend to develop before the lentigines, appearing within the first year of life in most affected people.

Of the people with Noonan syndrome with multiple lentigines who have heart defects, about 80 percent have hypertrophic cardiomyopathy, which is a thickening of the heart muscle that forces the heart to work harder to pump blood. The hypertrophic cardiomyopathy most often affects the lower left chamber of the heart (the left ventricle). Up to 20 percent of people with Noonan syndrome with multiple lentigines who have heart problems have a narrowing of the artery from the heart to the lungs (pulmonary stenosis).

People with Noonan syndrome with multiple lentigines can have a distinctive facial appearance. In addition to ocular hypertelorism, affected individuals may have droopy eyelids (ptosis), thick lips, and low-set ears. Affected individuals also usually have an abnormal appearance of the chest; they either have pectus excavatum or pectus carinatum.

At birth, people with Noonan syndrome with multiple lentigines are typically of normal weight and height, but in some, growth slows over time. This slow growth results in affected individuals being shorter than average, although less than half of people with Noonan syndrome with multiple lentigines have significantly short stature.

Other signs and symptoms of Noonan syndrome with multiple lentigines include hearing loss caused by abnormalities in the inner ear (sensorineural deafness), mild intellectual
disability, and extra folds of skin on the back of the neck. Affected males often have genital abnormalities, which can include undescended testes (cryptorchidism) and a urethra that opens on the underside of the penis (hypospadias). These abnormalities may reduce the ability to have biological children (decreased fertility). Females with Noonan syndrome with multiple lentigines may have poorly developed ovaries and delayed puberty.

Noonan syndrome with multiple lentigines 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 with multiple lentigines, the RASopathies include Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome, neurofibromatosis type 1, and Legius syndrome.

Frequency
Noonan syndrome with multiple lentigines is thought to be a rare condition; approximately 200 cases have been reported worldwide.

Causes
Mutations in one of several genes can cause Noonan syndrome with multiple lentigines. Approximately 85 percent of individuals with this condition have mutations in the PTPN11 gene. Another 10 percent have mutations in the RAF1 gene. In rare cases, mutations in the BRAF or MAP2K1 gene have been found to cause this condition. The remaining individuals with Noonan syndrome with multiple lentigines do not have an identified mutation in any of these four genes. In these individuals, the cause of the condition is unknown.

The PTPN11, RAF1, BRAF, and MAP2K1 genes all provide instructions for making proteins that are involved in important signaling pathways needed for the proper formation of several types of tissue during development. These proteins also play roles in the regulation of cell division, cell movement (migration), and cell differentiation (the process by which cells mature to carry out specific functions).

A mutation in the PTPN11, RAF1, BRAF, or MAP2K1 gene leads to the production of a protein that functions abnormally, which impairs the protein's ability to respond to cell signals. A disruption in the regulation of systems that control cell growth and division leads to the characteristic features of Noonan syndrome with multiple lentigines.

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

- cardio-cutaneous syndrome
- cardiomyopathic lentiginosis
- diffuse lentiginosis
- lentiginosis profusa
- LEOPARD syndrome
- Moynahan syndrome
- multiple lentigines syndrome
- NSML
- progressive cardiomyopathic lentiginosis

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  https://primer/testing/genetictesting

- Genetic Testing Registry: LEOPARD syndrome 1

- Genetic Testing Registry: LEOPARD syndrome 2

- Genetic Testing Registry: LEOPARD syndrome 3

- Genetic Testing Registry: Noonan syndrome with multiple lentigines

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Noonan+syndrome+with+multiple+lentigines%22+OR+%22LEOPARD+syndrome%22+OR+%22multiple+lentigines+syndrome%22

Other Diagnosis and Management Resources

- Cincinnati Children's Hospital: Cardiomyopathies
  https://www.cincinnatichildrens.org/health/c/cardiomyopathy

- GeneReview: Noonan Syndrome with Multiple Lentigines
  https://www.ncbi.nlm.nih.gov/books/NBK1383

- MedlinePlus Encyclopedia: Hypertrophic Cardiomyopathy
  https://medlineplus.gov/ency/article/000192.htm
Additional Information & Resources

Health Information from MedlinePlus

• Encyclopedia: Hypertrophic Cardiomyopathy
  https://medlineplus.gov/ency/article/000192.htm

• Encyclopedia: Multiple Lentigines Syndrome
  https://medlineplus.gov/ency/article/001473.htm

• Encyclopedia: Undescended Testicle
  https://medlineplus.gov/ency/article/000973.htm

• Health Topic: Skin Pigmentation Disorders
  https://medlineplus.gov/skinpigmentationdisorders.html

Genetic and Rare Diseases Information Center

• LEOPARD syndrome
  https://rarediseases.info.nih.gov/diseases/1100/leopard-syndrome

Educational Resources

• American Heart Association: Hypertrophic Cardiomyopathy Information Sheet

• Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Kprones/LeopardID10084.html

• Boys Town National Research Hospital: Types of Hearing Loss
  https://www.boystownhospital.org/knowledgeCenter/articles/hearing/Pages/TypesofHearing.aspx

• KidsHealth from Nemours: Growth Disorders

• MalaCards: noonan syndrome with multiple lentigines
  https://www.malacards.org/card/noonan_syndrome_with_multiple_lentigines

• Orphanet: Noonan syndrome with multiple lentigines
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=500

Patient Support and Advocacy Resources

• Alexander Graham Bell Association for the Deaf and Hard of Hearing
  https://www.agbell.org/

• American Heart Association
  https://www.heart.org/en/

• American Society for Deaf Children
  http://deafchildren.org/
• Children's Cardiomyopathy Foundation
  http://www.childrenscardiomyopathy.org/

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

• RASopathiesNet

• The MAGIC Foundation
  https://www.magicfoundation.org/

Clinical Information from GeneReviews
• Noonan Syndrome with Multiple Lentigines
  https://www.ncbi.nlm.nih.gov/books/NBK1383

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Noonan+Syndrome+with+Multiple+Lentigines%5BTIAB%5D%29+OR+%28%28LEOPARD+syndrome%5BTIAB%5D%29+OR+%28multiple+lentigines+syr

Catalog of Genes and Diseases from OMIM
• LEOPARD SYNDROME 1
  http://omim.org/entry/151100

• LEOPARD SYNDROME 2
  http://omim.org/entry/611554

• LEOPARD SYNDROME 3
  http://omim.org/entry/613707

Sources for This Summary
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20883402

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17697839
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25423878

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24767283 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005403/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18505544 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2467408/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27155140

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24935154 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4081049/

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