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.

Genetic Changes
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

- 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

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

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
• Genetic Counseling  
  https://medlineplus.gov/geneticcounseling.html

• Palliative Care  
  https://medlineplus.gov/palliativecare.html

• Surgery and Rehabilitation  
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

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  
  http://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_312225.pdf

• 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

• Disease InfoSearch: LEOPARD syndrome  
  http://www.diseaseinfosearch.org/LEOPARD+syndrome/4176

• KidsHealth from Nemours: Growth Disorders  

• MalaCards: noonan syndrome with multiple lentigines  
  http://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
  http://www.heart.org/HEARTORG/
- 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/

GeneReviews

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

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

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Noonan+Syndrome+with+Multiple+Lentigines%5BTIAB%5D+OR+%28LEOPARD+syndrome%5BTIAB%5D+OR+%28multiple+lentigines+syndrome%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22+AND+human%5Bdp%5D
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/