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Noonan Syndrome with Multiple Lentigines

Synonyms: LEOPARD Syndrome, Multiple Lentigines Syndrome

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Summary

Clinical characteristics

Noonan syndrome with multiple lentigines (NSML) is a condition in which the cardinal features consist of lentigines, hypertrophic cardiomyopathy, short stature, pectus deformity, and dysmorphic facial features including widely spaced eyes and ptosis. Multiple lentigines present as dispersed flat, black-brown macules, mostly on the face, neck, and upper part of the trunk with sparing of the mucosa. In general, lentigines do not appear until age four to five years but then increase to the thousands by puberty. Some individuals with NSML do not exhibit lentigines. Approximately 85% of affected individuals have heart defects, including hypertrophic cardiomyopathy (typically appearing during infancy and sometimes progressive) and pulmonary valve stenosis. Postnatal growth restriction resulting in short stature occurs in fewer than 50% of affected persons, although most affected individuals have a height that is less than the 25th centile for age. Sensorineural hearing deficits, present in approximately 20% of affected individuals, are poorly characterized. Intellectual disability, typically mild, is observed in approximately 30% of persons with NSML.

Diagnosis/testing

The clinical diagnosis of Noonan syndrome with multiple lentigines can be established in a proband with multiple lentigines plus two other cardinal features (cardiac abnormalities; poor linear growth / short stature; pectus deformity; and dysmorphic facial features including widely spaced eyes and ptosis) OR, in the absence of lentigines, three of the other cardinal manifestations plus an affected first-degree relative. The molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic variant in one of four genes (*BRAF*, *MAP2K1*, *PTPN11*, and *RAF1*).

Management

Treatment of manifestations: Standard treatment of hypertrophic cardiomyopathy, structural heart defects, eye anomalies / eye movement abnormalities, seizures, cryptorchidism, and developmental issues. Hearing aids may

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be helpful if hearing loss is present. Growth hormone treatment may be considered for those with short stature, but data on use in NSML are lacking, and growth hormone therapy may be contraindicated in those with hypertrophic cardiomyopathy.

Surveillance: Measurement of growth parameters; cardiac auscultation to assess for new heart murmur; clinical assessment for new neurologic manifestations such as seizures; and monitoring of developmental progress and educational needs at each visit. Annual echocardiogram until age three years and then at ages five years and ten years, or as clinically indicated. Audiology evaluation at least annually in infancy and childhood, or as clinically indicated. Ophthalmology evaluation if eye anomalies or eye movement issues are noted.

Agents/circumstances to avoid: For individuals with hypertrophic cardiomyopathy, treatment with growth hormone must be undertaken with great caution (if at all) to avoid exacerbating a cardiac condition, and certain physical activities may be curtailed in order to reduce the risk of sudden cardiac death.

Evaluation of relatives at risk: If the *BRAF*, *MAP2K1*, *PTPN11*, or *RAF1* pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives; if the pathogenic variant in the family is not known, a thorough physical examination with particular attention to the features of NSML may clarify the disease status of at-risk relatives. If NSML is suspected a cardiology evaluation with echocardiogram is recommended.

Pregnancy management: For affected women, cardiac status should be monitored during pregnancy. Those with hypertrophic cardiomyopathy or valve dysfunction may be at risk for the development or exacerbation of heart failure during pregnancy, especially during the second and third trimesters.

Genetic counseling

NSML is inherited in an autosomal dominant manner. A proband with NSML may have the disorder as the result of a *de novo* pathogenic variant; the proportion of cases caused by *de novo* pathogenic variants is unknown. Each child of an individual with NSML has a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for a pregnancy at increased risk is possible if the pathogenic variant in an affected family member is known.

Diagnosis

Suggested clinical diagnostic criteria for Noonan syndrome with multiple lentigines (NSML) have been published [Voron et al 1976, Sarkozy et al 2008].

Suggestive Findings

NSML **should be suspected** in individuals with one or more of the following cardinal features:

- Lentigines
- Cardiac abnormalities, particularly hypertrophic cardiomyopathy
- Poor linear growth / short stature
- Pectus deformity
- Dysmorphic facial features including widely spaced eyes and ptosis

Additional features occurring frequently in NSML:

- Variable degree of cognitive deficits
- Sensorineural hearing loss
- Cryptorchidism

- Skeletal anomalies
- Café au lait macules
- Family history consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations)

  Note: Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The clinical diagnosis of NSML can be established in a proband based on clinical criteria [Voron et al 1976, Sarkozy et al 2008], or the molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in one of four genes (*BRAF*, *MAP2K1*, *PTPN11*, and *RAF1)* listed in Table 1.

Clinical diagnosis

- Multiple lentigines plus two of the other cardinal features, OR
- In the absence of lentigines, three of the other cardinal features plus a first-degree relative with NSML [Sarkozy et al 2008]

Molecular diagnosis. The molecular diagnosis of NSML **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1 identified by molecular genetic testing.

Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of NSML has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and family history findings suggest the diagnosis of NSML, molecular genetic testing approaches can include use of a **multigene panel.** Serial single-gene genetic testing is not frequently used.

A Noonan syndrome, RASopathy, or hypertrophic cardiomyopathy multigene panel that includes *BRAF*, *MAP2K1*, *PTPN11*, *RAF1*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of NSML has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** may be considered. Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Noonan Syndrome with Multiple Lentigines

Gene [1, 2]	Proportion of NSML Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
BRAF	2 individuals	See footnote 6.	Unknown, none reported [7]
MAP2K1	1 individual	See footnote 8.	Unknown, none reported [7]
PTPN11	>95%	Nearly 100% [9]	Unknown, none reported [7]
RAF1	<3%	Nearly 100% [10]	Unknown, none reported [7]
Unknown [11]	<3%	NA	

NA = not applicable

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. See Molecular Genetics for information on variants detected in these genes.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Sequence analysis of all coding exons detected pathogenic missense variants in two individuals with clinical features of NSML [Koudova et al 2009, Sarkozy et al 2009].

7. No exon or whole-gene deletion or duplication involving *BRAF*, *MAP2K1*, *PTPN11*, or *RAF1* has been reported as causative of NSML. Based on the molecular mechanisms implicated in disease pathogenesis, exon or whole-gene deletions or duplications are not expected to cause NSML.

8. Sequence analysis of all coding exons detected pathogenic missense variants in one individual with clinical features of NSML [Nishi et al 2015].

9. Most pathogenic variants causing NSML are identified in exons 7, 12, and 13 [Digilio et al 2002, Legius et al 2002, Sarkozy et al 2009].

10. Sequence analysis of coding exons 6, 13, and 16 detects all reported pathogenic missense variants [Pandit et al 2007].

11. It is likely that one or more additional, as-yet undefined genes, possibly related to RAS signal transduction, are associated with a small proportion of individuals with NSML in whom no pathogenic variant has been identified in *BRAF*, *MAP2K1*, *PTPN11*, or *RAF1*.

Clinical Characteristics

Clinical Description

To date, more than 150 individuals with Noonan syndrome with multiple lentigines (NSML) have been reported.

Table 2. Noonan Syndrome with Multiple Lentigines: Frequency of Select Features

Feature	Frequency			Comment
	Nearly all	Common	Infrequent	
Lentigines	●			Often develop after age 4-5 yrs
Dysmorphic facial features	●			
Hypertrophic cardiomyopathy		●		Up to 70%; may be progressive
Café au lait macules		●		
Short stature		●		>50%, but height in most persons is <25th centile for age & sex
Cryptorchidism		●		~33% of affected males
Intellectual disability		●		~33%; typically in mild range
Pulmonary valve stenosis		●		~25%
EKG abnormalities		●		~25%
Sensorineural hearing loss		●		~20%
Craniosynostosis			●	
Neurofibromata			●	
Malignancies			●	Given rarity of this finding, no consensus tumor screening protocol for NSML currently exists [Villani et al 2017].

NSML = Noonan syndrome with multiple lentigines

Dermatologic. Multiple lentigines present as dispersed flat, black-brown macules, mostly on the face, neck, and upper part of the trunk with sparing of the mucosa. In general, lentigines do not appear until age four to five years but then increase into the thousands by puberty [Coppin & Temple 1997]. Some individuals with NSML do not exhibit lentigines.

- Café au lait macules are also observed in up to 70%-80% of affected individuals [Digilio et al 2006], usually preceding the appearance of lentigines.
- Skin hyperelasticity has also been described.
- Neurofibromas have been described but are rare.

Cardiovascular. Approximately 85% of affected individuals have heart defects similar to those observed in Noonan syndrome (NS) but with different frequencies [Limongelli et al 2007]:

- Hypertrophic cardiomyopathy is detected in up to 70% of individuals with heart defects (compared to 25% in NS). It most commonly appears during infancy and can be progressive.
- Pulmonary valve stenosis is noted in approximately 25% of affected individuals. Abnormalities of the aortic and mitral valves are also observed in a minority of persons with NSML.
- EKG abnormalities, aside from those typically associated with hypertrophic cardiomyopathy, include conduction defects (23%).

Facial features. Dysmorphic facial features are similar to those seen in Noonan syndrome, although usually milder [Digilio et al 2006]. Features include inverted triangular-shaped face, downslanted palpebral fissures, low-set posteriorly rotated ears with thickened helices, and widely spaced eyes. The neck can be short with excess nuchal skin and a low posterior hairline. As in Noonan syndrome, facial features may be less evident or more subtle in adults.

Hearing. Sensorineural hearing deficits are present in approximately 20% of persons with NSML. Minimal information is available about the progression of deafness in those with milder degrees of hearing impairment.

Growth. Birth weight is usually normal but may be above the 97th centile. Postnatal growth restriction resulting in short stature is noted in fewer than 50% of affected individuals, although in most, height is less than the 25th centile for age. Adult height and response to growth hormone therapy have not been studied in this disorder.

Musculoskeletal. Pectus anomalies (either excavatum or carinatum), present in 50% or more of affected individuals, are most often of cosmetic concern only and rarely require medical intervention.

Psychomotor development. Intellectual disability, typically mild, is observed in approximately 30% of persons with NSML. Specific information concerning the deficits typically found in these children is not available.

Genitourinary. Cryptorchidism, unilateral or bilateral, is present in approximately one third of affected males. Other abnormalities including hypospadias, urinary tract defects, and ovarian abnormalities are observed infrequently. Renal anomalies have also (rarely) been reported [Digilio et al 2006].

Eyes. Ophthalmologic involvement in NSML is rare. Described issues include colobomata, stereopsis, and abnormal eye movements [Alfieri et al 2008, Watanabe et al 2011, Van den Heurck et al 2021].

Neurologic. Hypotonia is common in newborns and is associated with psychomotor delays. Seizures and autism spectrum disorder are uncommon manifestations in NSML.

Rare features

- **Craniosynostosis.** An anecdotal association has been reported between NSML and craniosynostosis, although it is unclear whether this represents a true association or whether the reported individuals had co-occurrence of two conditions. However, it has been postulated that an increased risk of craniosynostosis may be related to the functional link between FGF signaling and the RAS-MAPK pathway [McDonald et al 2018, Rodríguez et al 2019].
  - One reported individual with NSML, who had a pathogenic variant in *PTPN11*, had sagittal synostosis that required surgical correction as a result of increased intracranial pressure [McDonald et al 2018].
  - A second affected individual, who had a pathogenic variant in *RAF1*, had multisutural craniosynostosis consistent with a clover-leaf skull that also required surgical correction [Rodríguez et al 2019].
- **Malignancies.** Hematologic malignancies and other tumors have occasionally been reported in individuals with NSML. However, a review of overall tumor risk in individuals with NSML by Villani et al [2017] noted that the risk is low, such that no routine surveillance for individuals with NSML is recommended. Villani et al [2017] suggested that there be an awareness of a potential risk of malignancy and a low threshold for investigating any signs or symptoms suggestive of malignancy.

  Smpokou et al [2015] reported a total of six individuals with NSML and malignancy:
  - Three individuals had leukemia; all 3 had a germline pathogenic variant in *PTPN11* involving amino acid residue 279.
  - One individual had neuroblastoma and one had cerebellar meduloblastoma; both had a germline pathogenic c.1402C>T (p.Thr468Met) *PTPN11* variant.
  - One individual with a clinical diagnosis of NSML had a unilateral corneal choristoma.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *BRAF*, *MAP2K1*, or *RAF1* have been identified in individuals with NSML.

PTPN11. In contrast to what is observed in Noonan syndrome, the NSML-associated pathogenic variants (see Molecular Genetics) are strongly associated with a predisposition to hypertrophic cardiomyopathy [Tartaglia & Gelb 2010, Gelb et al 2015]. This specific correlation results from a differential impact of NS- and NSML-causing *PTPN11* variants on intracellular signalling. In particular, different consequences have been documented on both the MAPK and PI3K-AKT-mTOR pathways [Edouard et al 2010, Marin et al 2011].

Nomenclature

NSML was referred to as cardiomyopathic lentiginosis in the older medical literature. It was also formerly referred to by the acronym LEOPARD syndrome; this designation is no longer considered appropriate.

Prevalence

The population prevalence of NSML is not known.

Genetically Related (Allelic) Disorders

The phenotypic overlap that occurs in individuals with germline pathogenic variants in genes causing Noonan syndrome with multiple lentigines (NSML), Noonan syndrome (NS), and cardiofaciocutaneous syndrome (CFCS) (see Table 3) emphasizes that the three disorders (previously defined as distinct clinical entities) constitute a phenotypic continuum and highlights the usefulness of feature-based management.

Table 3. Allelic Disorders in the Differential Diagnosis of Noonan Syndrome with Multiple Lentigines

NSML Gene(s)	Allelic Disorder	Comment
BRAF *MAP2K1*	Cardiofaciocutaneous syndrome (CFCS)	• CFCS & NSML have similar cardiac findings; however, in CFCS, ID is usually more severe, w/higher likelihood of structural CNS anomalies & seizures; more skin pathology; & more severe & long-lasting GI problems. In CFCS, facial appearance tends to be coarser; dolichocephaly & absent eyebrows are more common; & blue eyes are less common than in NS. • The proportion of CFCS attributed to pathogenic variants in *BRAF* is 50%-75%; in *MAP2K1*, ~10%-15%. See Differential Diagnosis for other genes assoc w/CFCS.
BRAF *MAP2K1* *PTPN11* *RAF1*	Noonan syndrome (NS)	• NS is typically assoc w/short stature, congenital heart defect, broad or webbed neck, pectus deformities, variable DD, cryptorchidism, & characteristic facies. NS shows significant overlap w/NSML, but affected persons are unlikely to be deaf or to have profusion of pigmented lesions, lentigines, & café au lait patches. • The proportion of NS attributed to pathogenic variants in *BRAF* is <2%; in *MAP2K1* <2%; in *PTPN11* 50%; & in *RAF1* 5%. See Differential Diagnosis for other genes assoc w/NS.
PTPN11		The *PTPN11*-related NS phenotypic spectrum encompasses a condition referred to as Noonan-like/multiple giant-cell lesion syndrome (NL/MGCLS). NL/MGCLS is characterized by giant-cell granulomas & bone & joint anomalies that can resemble cherubism, lesions observed in neurofibromatosis (see Neurofibromatosis Type 1), or lesions observed in Ramon syndrome w/juvenile rheumatoid arthritis (polyarticular pigmented villonodular synovitis).

CNS = central nervous system; DD = developmental delay; GI = gastrointestinal; ID = intellectual disability; NSML = Noonan syndrome with multiple lentigines

Other. Germline heterozygous loss-of-function *PTPN11* variants are associated with autosomal dominant metachondromatosis [McFarlane et al 2016].

Sporadic tumors (including leukemia and solid tumors) occurring as single tumors in the absence of any other findings of NSML or NS frequently harbor a somatic pathogenic variant in *BRAF*, *MAP2K1*, *PTPN11*, or *RAF1*

that is **not** present in the germline; thus, predisposition to these tumors is not heritable. For more details see Molecular Genetics.

Differential Diagnosis

Noonan syndrome with multiple lentigines (NSML) should be distinguished from Turner syndrome, Williams syndrome, and monogenic disorders with developmental delay, short stature, congenital heart defects, and distinctive facies (see Table 4).

Turner syndrome, found only in females, is distinguished from NSML by demonstration of an X-chromosome abnormality on cytogenetic studies. The characteristic facial features are also distinct, and in Turner syndrome renal anomalies are more common, developmental delay is much less frequently found, and left-sided heart defects are the rule.

Williams syndrome and NSML are relatively distinct, as they are associated with different facial features, cardiovascular involvement, skin features, and neurodevelopmental profiles. Early in life, however, the facial features may be less distinct, lentigines have not yet emerged for NSML, and both disorders share impaired growth and neurodevelopmental delays. The diagnosis of Williams syndrome requires detection of a recurrent 7q11.23 contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses the elastin gene (*ELN*).

Table 4. Monogenic Disorders of Interest in the Differential Diagnosis of Noonan Syndrome with Multiple Lentigines

Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
BRAF *KRAS* *MAP2K1* *MAP2K2*	Cardiofaciocutaneous syndrome (CFCS)	AD	See Genetically Related Disorders.
BRAF *KRAS* *LZTR1* *MAP2K1* *MRAS* *NRAS* *PTPN11* *RAF1* *RASA2* *RIT1* *RRAS2* *SOS1* *SOS2* *SPRED2* [1]	Noonan syndrome (NS)	AD (AR) [2]	See Genetically Related Disorders.
CBL [3]	NS-like disorder ± JMML (OMIM 613563)	AD	Variable phenotype characterized by relatively high frequency of neurologic features, predisposition to JMML, & low prevalence of cardiac defects, ↓ growth, & cryptorchidism [4]
FGD1	X-linked Aarskog syndrome (OMIM 305400)	XL	Characterized by DD, short stature, congenital heart defects, & distinctive facies
HRAS	Costello syndrome (CS)	AD	CS shares features w/NSML, NS, & CFCS. The typical presentation of CS is characterized by diffuse hypotonia & severe feeding difficulties in infancy; short stature; DD/ID; characteristic facial features; curly or sparse, fine hair; loose soft skin w/deep palmar & plantar creases; papillomata of face & perianal region; joint laxity w/ulnar deviation of wrists & fingers; tight Achilles tendons; & cardiac involvement.

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
MAPK1	*MAPK1*-related neurodevelopmental disorder [5]	AD	Clinically variable neurodevelopmental disorder w/in RASopathy phenotypic spectrum, reminiscent of NS in some persons. Shared features incl postnatally ↓ growth, craniofacial anomalies, short/webbed neck, low posterior hairline, & skin features. [5]
NF1	Watson syndrome (neurofibromatosis 1 variant)	AD	Variably present in both Watson syndrome & NSML are short stature, pulmonary valve stenosis, variable intellectual development, & skin pigment changes incl café au lait macules. Lentigines are not described in Watson syndrome.
PPP1CB *SHOC2* [3]	NS w/loose anagen hair (OMIM PS607721)	AD	Characteristics of NS + loose anagen hair. Skin often has tanned appearance. Abnormalities of mitral valve are more common than in NS. Growth hormone deficiency is also commonly observed.
SPRED1	Legius syndrome	AD	The majority of affected persons have café au lait macules; 30%-50% have skin freckling; 30% have developmental issues; 15% have Noonan-like facial features.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; GI = gastrointestinal; ID = intellectual disability; JMML = juvenile myelomonocytic leukemia; MOI = mode of inheritance; NSML = Noonan syndrome with multiple lentigines; XL = X-linked

1. Motta et al [2021]

2. NS is most often inherited in an autosomal dominant manner. NS caused by pathogenic variants in *LZTR1* can be inherited in an autosomal dominant or autosomal recessive manner. NS caused by pathogenic variants in *SPRED2* is inherited in an autosomal recessive manner.

3. Because of the significant phenotypic overlap with classic NS, most RASopathy diagnostic gene panels include testing for the common *SHOC2* variant and *CBL* gene sequencing.

4. Martinelli et al [2010], Niemeyer et al [2010], Martinelli et al [2015]

5. Motta et al [2020]

Management

No clinical practice guidelines for Noonan syndrome with multiple lentigines (NSML) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with NSML, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Noonan Syndrome with Multiple Lentigines

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	Consider plotting of growth parameters on population-specific growth charts & Noonan syndrome growth charts. [1]
Cardiovascular	Echocardiogram	To assess for congenital heart defects & evidence of hypertrophic cardiomyopathy
	Electrocardiogram	To assess for conduction defects & electrical evidence consistent w/cardiac hypertrophy
Hearing	Audiology eval [2]	To assess for presence & type/degree of hearing loss
Eyes	Ophthalmology eval	To assess for presence of colobomata, stereopsis, & abnormal eye movements [3]
Neurologic	Neurology eval	To incl brain MRI for those w/seizure disorders & (possibly) neurodevelopmental delays

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Genitourinary	Physical exam for cryptorchidism in males	Consider referral to urologist.
	Renal ultrasound	Consider urinalysis if urinary tract anomalies are discovered.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Musculoskeletal	Clinical assessment of spine & rib cage	Consider radiographs & referral to orthopedist if significant scoliosis or rib cage abnormalities are identified.
Genetic counseling	By genetics professionals [4]	To inform affected persons & their families re nature, MOI, & implications of NSML to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; NSML = Noonan syndrome with multiple lentigines
1. Witt et al [1986]; specific growth charts for NSML are not available.
2. Complete assessment of auditory acuity using age-appropriate tests (e.g., ABR testing, auditory steady-state response [ASSR] testing, pure-tone audiometry).
3. Alfieri et al [2008], Van den Heurck et al [2021]
4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Noonan Syndrome with Multiple Lentigines

Manifestation/Concern	Treatment	Considerations/Other
Short stature	Growth hormone therapy may be considered, although no data on use of growth hormone therapy in persons w/NSML exist.	• Growth hormone therapy may be contraindicated in persons w/HCM. • Prior to instituting growth hormone therapy, cardiac eval for HCM is recommended; continued surveillance for development of HCM while on growth hormone therapy is reasonable.
HCM	Standard treatment per cardiologist & cardiovascular surgeon	
Structural heart defects		
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
	Consider cochlear implantation for persons w/ profound deafness.	See Hereditary Hearing Loss and Deafness Overview.
Colobomata, stereopsis, & abnormal eye mvmts	Standard treatment per ophthalmologist	
Seizures	Standard treatment per neurologist	
Cryptorchidism / Genitourinary anomalies	Standard treatment per urologist	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

HCM = hypertrophic cardiomyopathy; NSML = Noonan syndrome with multiple lentigines

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country. Not everyone with NSML will have developmental delay. The following recommendations apply to those in whom neurodevelopmental delays have been noted.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician, where available, is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Communication issues. Speech therapy may be beneficial for those with speech delay.

Surveillance

Table 7. Recommended Surveillance for Individuals with Noonan Syndrome with Multiple Lentigines

System/Concern	Evaluation	Frequency
Growth	Measurement of growth parameters	At each visit
Cardiovascular	Cardiac auscultation to assess for new heart murmur	
	Echocardiogram	Annually until age 3 yrs, then at ages 5 yrs & 10 yrs or as clinically indicated
Hearing	Audiology eval	At least annually in infancy & childhood or as clinically indicated
Eyes	Ophthalmology eval	If nystagmus is noted or as clinically indicated
Neurologic	Assess for new manifestations such as seizure.	At each visit
Development	Monitor developmental progress & educational needs.	
Family/ Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources) & care coordination.	

Agents/Circumstances to Avoid

For individuals with hypertrophic cardiomyopathy:

- Treatment with growth hormone must be undertaken with great caution – if at all – to avoid exacerbating a cardiac condition;
- Certain physical activities may be curtailed in order to reduce the risk of sudden cardiac death.

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those with hypertrophic cardiomyopathy who would benefit from initiation of treatment and preventive measures.

- If the *BRAF*, *MAP2K1*, *PTPN11*, or *RAF1* pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant in the family is not known, a thorough physical examination with particular attention to the features of NSML may clarify the disease status of at-risk relatives. If NSML is suspected, a cardiology evaluation with echocardiogram is recommended.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

For affected women, cardiac status should be monitored during pregnancy. Those with hypertrophic cardiomyopathy or valve dysfunction may be at risk for the development or exacerbation of heart failure during pregnancy, especially during the second and third trimesters.

Some affected pregnant women may be on medications for their cardiovascular issues. See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search Clinical Trials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Noonan syndrome with multiple lentigines (NSML) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with NSML have an affected parent. (Note: Because NSML is associated with variable expressivity and the manifestations of the disorder are frequently subtle, many affected adults are diagnosed only after the birth of a more obviously affected infant.)
- A proband with NSML may have the disorder as the result of a *de novo* *BRAF*, *MAP2K1*, *PTPN11*, or *RAF1* pathogenic variant.
- If the proband is the only family member known to be affected with NSML, recommended evaluations of both parents include:
  - Molecular genetic testing if the NSML-causing pathogenic variant in the proband is known;
  - A thorough physical examination with particular attention to the features of NSML if the NSML-causing pathogenic variant in the proband is not known. If NSML is suspected, a cardiology evaluation with echocardiogram is recommended.
- If the proband has an NSML-related pathogenic variant that is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present only in the germ cells.
- The family history of some individuals diagnosed with NSML may appear to be negative because of failure to recognize the disorder in affected family members. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic

testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.

  Because there can be significant intrafamilial variability, sibs may not have the same phenotypic findings as other affected family members.

- If the proband has a known NSML-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

- If the parents are clinically unaffected (based on appropriate clinical evaluation) but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with NSML has a 50% chance of inheriting the NSML-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or is known to have the familial pathogenic variant, members of the parent's family may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the NSML-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Noonan syndrome with multiple lentigines
- **RASopathies Network**
  Email: info@rasopathiesnet.org
  www.rasopathiesnet.org
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **Noonan Syndrome Foundation**
  Email: info@teamnoonan.org
  www.teamnoonan.org
- **The Children's Heart Foundation**
  Phone: 847-634-6474
  Email: info@childrensheartfoundation.org
  www.childrensheartfoundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Noonan Syndrome with Multiple Lentigines: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BRAF	7q34	Serine/threonine-protein kinase B-raf	BRAF database NSEuroNet database - BRAF	BRAF	BRAF
MAP2K1	15q22.31	Dual specificity mitogen-activated protein kinase kinase 1	MAP2K1 @ LOVD NSEuroNet database - MAP2K1	MAP2K1	MAP2K1
PTPN11	12q24.13	Tyrosine-protein phosphatase non-receptor type 11	PTPN11 database PTPN11base: Database for pathogenic mutations in the SHP-2 SH2 domain NSEuroNet database - PTPN11	PTPN11	PTPN11

Table A. continued from previous page.

RAF1	3p25.2	RAF proto-oncogene serine/threonine-protein kinase	NSEuroNet database - RAF1	RAF1	RAF1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Noonan Syndrome with Multiple Lentigines (View All in OMIM)

151100	LEOPARD SYNDROME 1; LPRD1
164757	B-RAF PROTOONCOGENE, SERINE/THREONINE KINASE; BRAF
164760	RAF1 PROTOONCOGENE, SERINE/THREONINE KINASE; RAF1
176872	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1; MAP2K1
176876	PROTEIN-TYROSINE PHOSPHATASE, NONRECEPTOR-TYPE, 11; PTPN11
611554	LEOPARD SYNDROME 2; LPRD2
613707	LEOPARD SYNDROME 3; LPRD3

Molecular Pathogenesis

Noonan syndrome with multiple lentigines (NSML) is a RASopathy, a class of disorders for which genetic variation alters proteins belonging to the RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway. The pathogenic variants in *PTPN11* that cause NSML are all pathogenic missense variants. These pathogenic variants are distinct from the pathogenic missense variants in *PTPN11* that cause Noonan syndrome (NS). The NS-associated pathogenic variants are gain of function, with increased activity of the protein tyrosine phosphatase, SHP-2, encoded by *PTPN11*. For NSML-associated *PTPN11* pathogenic variants, however, the effects are different. The altered SHP-2 proteins have reduced, but not eliminated, phosphatase activities. Biochemical studies have suggested both dominant-negative effects and gain-of-function effects, the latter through liquid-liquid phase separation. Efforts to definitively understand how *PTPN11* pathogenic variants cause NSML are ongoing. NS- and NSML-causing *PTPN11* pathogenic variants have different effects on the MAPK and PI3k-AKT-mTOR signaling pathways. The other NSML-related genes, *BRAF*, *MAP2K1*, and *RAF1*, encode kinases that phosphorylate proteins in the RAS-MAPK pathway, with positive regulatory functions. The precise mechanism(s) through which alterations in those proteins could mediate NSML have not been well studied.

Table 8. Noonan Syndrome with Multiple Lentigines: Mechanism of Disease Causation

Gene [1]	Mechanism	Comment/Reference
BRAF	Gain of function	Sarkozy et al [2009]
MAP2K1	Gain of function	Nishi et al [2015]
PTPN11	Mixed loss-of-function & dominant-negative effects	Kontaridis et al [2006], Zhu et al [2020]
RAF1	Gain of function	Pandit et al [2007], Razzaque et al [2007]

1. Genes from Table 1 in alphabetic order

Table 9. Noonan Syndrome with Multiple Lentigines: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
BRAF	NM_004333.6 NP_004324.2	c.721A>C	p.Thr241Pro	
		c.735A>T	p.Leu245Phe	FDA-recognized variant

Table 9. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
MAP2K1	NM_002755.4 NP_002746.1	c.199G>A	p.Asp67Asn	FDA-recognized variant
		c.305A>G	p.Glu102Gly	
PTPN11	NM_002834.5 NP_002825.3	c.836A>G	p.Tyr279Cys	
		c.1381G>A	p.Ala461Thr	
		c.1391G>C	p.Gly464Met	
		c.1402C>T	p.Thr468Met	Assoc w/malignancy in a small case series [Smpokou et al 2015]
		c.1507G>C	p.Gly503Arg	
		c.1510A>G	p.Met504Val	FDA-recognized variant
		c.1517A>C	p.Gln506Pro	
		c.1529A>C	p.Gln510Pro	FDA-recognized variant
RAF1	NM_002880.4 NP_002871.1	c.770C>T	p.Ser257Leu	FDA-recognized variant
		c.1837C>G	p.Leu613Val	FDA-recognized variant

1. Genes from Table 1 in alphabetic order

Cancer and Benign Tumors

Sporadic tumors (including leukemia and solid tumors) occurring as single tumors in the absence of any other findings of NSML may harbor somatic nucleotide variants in *BRAF*, *MAP2K1*, *PTPN11*, or *RAF1* that are not present in the germline; thus, predisposition to these tumors is not heritable. See Catalogue of Somatic Mutations in Cancer.

- **Solid tumors.** *BRAF* variants mutated in solid tumors, such as p.Asp594Gly and p.Thr599Ile, alter the functional activation segment [Pandit et al 2007]. However, no occurrence of the common *BRAF* oncogenic somatic p.Val600Glu amino acid substitution has been documented to occur as a germline event associated with cardiofaciocutaneous syndrome (CFCS), NS, or NSML.
- **Leukemia.** Juvenile myelomonocytic leukemia (JMML) accounts for one third of childhood cases of myelodysplastic syndrome (MDS) and about 2% of leukemia. Somatic pathogenic variants in exons 3 and 13 of *PTPN11* have been demonstrated in 34% of a cohort with JMML [Tartaglia et al 2003b]. Pathogenic variants in exon 3 were also found in 19% of children with MDS with an excess of blast cells, which often evolves into acute myeloid leukemia (AML) and is associated with poor prognosis. Nonsyndromic AML, especially the monocyte subtype FAB-M5, has been shown to be caused by *PTPN11* pathogenic variants. All these pathogenic variants result in a gain of function of the protein tyrosine phosphatase non-receptor type 11 (SHP-2), likely leading to an early initiating lesion in JMML oncogenesis with increased cell proliferation attributable (in part) to prolonged activation of the RAS/MAPK pathway.

  The spectrum of leukemogenesis associated with *PTPN11* pathogenic variants has been extended to include childhood acute lymphoblastic leukemia (ALL). Pathogenic variants were observed in 8% of B-cell precursor ALL cases, but not among children with T-lineage ALL [Tartaglia et al 2004b]. Additionally, SHP-2-activating *PTPN11* pathogenic variants have been found rarely in solid tumors, including breast, lung, and gastric neoplasms and neuroblastoma [Bentires-Alj et al 2004].

Chapter Notes

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References

Literature Cited

Alfieri P, Cesarini L, Zampino G, Pantaleoni F, Selicorni A, Salerni A, Vasta I, Cerutti M, Dickmann A, Colitto F, Staccioli S, Leoni C, Ricci D, Brogna C, Tartaglia M, Mercuri E. Visual function in Noonan and LEOPARD syndrome. Neuropediatrics. 2008;39:335–40. PubMed PMID: 19568997.

Bentires-Alj M, Paez JG, David FS, Keilhack H, Halmos B, Naoki K, Maris JM, Richardson A, Bardelli A, Sugarbaker DJ, Richards WG, Du J, Girard L, Minna JD, Loh ML, Fisher DE, Velculescu VE, Vogelstein B, Meyerson M, Sellers WR, Neel BG. Activating mutations of the noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. Cancer Res. 2004;64:8816–20. PubMed PMID: 15604238.

Coppin BD, Temple IK. Multiple lentigines syndrome (LEOPARD syndrome or progressive cardiomyopathic lentiginosis). J Med Genet. 1997;34:582–6. PubMed PMID: 9222968.

Digilio MC, Conti E, Sarkozy A, Mingarelli R, Dottorini T, Marino B, Pizzuti A, Dallapiccola B. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. Am J Hum Genet. 2002;71:389–94. PubMed PMID: 12058348.

Digilio MC, Sarkozy A, de Zorzi A, Pacileo G, Limongelli G, Mingarelli R, Calabro R, Marino B, Dallapiccola B. LEOPARD syndrome: clinical diagnosis in the first year of life. Am J Med Genet A. 2006;140:740–6. PubMed PMID: 16523510.

Edouard T, Combier JP, Nédélec A, Bel-Vialar S, Métrich M, Conte-Auriol F, Lyonnet S, Parfait B, Tauber M, Salles JP, Lezoualc'h F, Yart A, Raynal P. Functional effects of PTPN11 (SHP2) mutations causing LEOPARD syndrome on epidermal growth factor-induced phosphoinositide 3-kinase/AKT/glycogen synthase kinase 3beta signaling. Mol Cell Biol. 2010;30:2498–507. PubMed PMID: 20308328.

Gelb BD, Roberts AE, Tartaglia M. Cardiomyopathies in Noonan syndrome and the other RASopathies. Prog Pediatr Cardiol. 2015;39:13–19. PubMed PMID: 26380542.

Kontaridis MI, Swanson KD, David FS, Barford D, Neel BG. PTPN11 (Shp2) mutations in LEOPARD syndrome have dominant negative, not activating, effects. J Biol Chem. 2006;281:6785–92. PubMed PMID: 16377799.

Koudova M, Seemanova E, Zenker M. Novel BRAF mutation in a patient with LEOPARD syndrome and normal intelligence. Eur J Med Genet. 2009;52:337–40. PubMed PMID: 19416762.

Legius E, Schrander-Stumpel C, Schollen E, Pulles-Heintzberger C, Gewillig M, Fryns JP. PTPN11 mutations in LEOPARD syndrome. J Med Genet. 2002;39:571–4. PubMed PMID: 12161596.

Limongelli G, Pacileo G, Marino B, Digilio MC, Sarkozy A, Elliott P, Versacci P, Calabro P, De Zorzi A, Di Salvo G, Syrris P, Patton M, McKenna WJ, Dallapiccola B, Calabro R. Prevalence and clinical significance of cardiovascular abnormalities in patients with the LEOPARD syndrome. Am J Cardiol. 2007;100:736–41. PubMed PMID: 17697839.

Marin TM, Keith K, Davies B, Conner DA, Guha P, Kalaitzidis D, Wu X, Lauriol J, Wang B, Bauer M, Bronson R, Franchini KG, Neel BG, Kontaridis MI. Rapamycin reverses hypertrophic cardiomyopathy in a mouse model of LEOPARD syndrome-associated PTPN11 mutation. J Clin Invest. 2011;121:1026–43. PubMed PMID: 21339643.

Martinelli S, De Luca A, Stellacci E, Rossi C, Checquolo S, Lepri F, Caputo V, Silvano M, Buscherini F, Consoli F, Ferrara G, Digilio MC, Cavaliere ML, van Hagen JM, Zampino G, van der Burgt I, Ferrero GB, Mazzanti L, Screpanti I, Yntema HG, Nillesen WM, Savarirayan R, Zenker M, Dallapiccola B, Gelb BD, Tartaglia M. Heterozygous germline mutations in the CBL tumor-suppressor gene cause a Noonan syndrome-like phenotype. Am J Hum Genet. 2010;87:250–7. PubMed PMID: 20619386.

Martinelli S, Stellacci E, Pannone L, D'Agostino D, Consoli F, Lissewski C, Silvano M, Cencelli G, Lepri F, Maitz S, Pauli S, Rauch A, Zampino G, Selicorni A, Melançon S, Digilio MC, Gelb BD, De Luca A, Dallapiccola B, Zenker M, Tartaglia M. Molecular diversity and associated phenotypic spectrum of germline CBL mutations. Hum Mutat. 2015;36:787–96. PubMed PMID: 25952305.

McDonald BS, Pigors M, Kelsell DP, O'Toole EA, Burkitt-Wright E, Kerr B, Batta K. Noonan syndrome with multiple lentigines and associated craniosynostosis. Clin Exp Dermatol. 2018;43:357–9. PubMed PMID: 29356064.

McFarlane J, Knight T, Sinha A, Cole T, Kiely N, Freeman R. Exostoses, enchondromatosis and metachondromatosis; diagnosis and management. Acta Orthop Belg. 2016;82:102–5. PubMed PMID: 26984661.

Motta M, Fasano G, Gredy S, Brinkmann J, Bonnard AA, Simsek-Kiper PO, Gulec EY, Essaddam L, Utine GE, Guarnetti Prandi I, Venditti M, Pantaleoni F, Radio FC, Ciolfi A, Petrini S, Consoli F, Vignal C, Hepbasli D,

Ullrich M, de Boer E, Vissers LELM, Gritli S, Rossi C, De Luca A, Ben Becher S, Gelb BD, Dallapiccola B, Lauri A, Chillemi G, Schuh K, Cavé H, Zenker M, Tartaglia M. SPRED2 loss-of-function causes a recessive Noonan syndrome-like phenotype. Am J Hum Genet. 2021;108:2112–29. PubMed PMID: 34626534.

Motta M, Pannone L, Pantaleoni F, Bocchinfuso G, Radio FC, Cecchetti S, Ciolfi A, Di Rocco M, Elting MW, Brilstra EH, Boni S, Mazzanti L, Tamburrino F, Walsh L, Payne K, Fernández-Jaén A, Ganapathi M, Chung WK, Grange DK, Dave-Wala A, Reshmi SC, Bartholomew DW, Mouhlas D, Carpentieri G, Bruselles A, Pizzi S, Bellacchio E, Piceci-Sparascio F, Lißewski C, Brinkmann J, Waclaw RR, Waisfisz Q, van Gassen K, Wentzensen IM, Morrow MM, Álvarez S, Martínez-García M, De Luca A, Memo L, Zampino G, Rossi C, Seri M, Gelb BD, Zenker M, Dallapiccola B, Stella L, Prada CE, Martinelli S, Flex E, Tartaglia M. Enhanced MAPK1 function causes a neurodevelopmental disorder within the RASopathy clinical spectrum. Am J Hum Genet. 2020;107:499–513. PubMed PMID: 32721402.

Niemeyer CM, Kang MW, Shin DH, Furlan I, Erlacher M, Bunin NJ, Bunda S, Finklestein JZ, Sakamoto KM, Gorr TA, Mehta P, Schmid I, Kropshofer G, Corbacioglu S, Lang PJ, Klein C, Schlegel PG, Heinzmann A, Schneider M, Starý J, van den Heuvel-Eibrink MM, Hasle H, Locatelli F, Sakai D, Archambeault S, Chen L, Russell RC, Sybingco SS, Ohh M, Braun BS, Flotho C, Loh ML. Germline CBL mutations cause developmental abnormalities and predispose to juvenile myelomonocytic leukemia. Nat Genet. 2010;42:794–800. PubMed PMID: 20694012.

Nishi E, Mizuno S, Nanjo Y, Niihori T, Fukushima Y, Matsubara Y, Aoki Y, Kosho T. A novel heterozygous MAP2K1 mutation in a patient with Noonan syndrome with multiple lentigines. Am J Med Genet A. 2015;167A:407–11. PubMed PMID: 25423878.

Pandit B, Sarkozy A, Pennacchio LA, Carta C, Oishi K, Martinelli S, Pogna EA, Schackwitz W, Ustaszewska A, Landstrom A, Bos JM, Ommen SR, Esposito G, Lepri F, Faul C, Mundel P, Lopez Siguero JP, Tenconi R, Selicorni A, Rossi C, Mazzanti L, Torrente I, Marino B, Digilio MC, Zampino G, Ackerman MJ, Dallapiccola B, Tartaglia M, Gelb BD. Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. Nat Genet. 2007;39:1007–12. PubMed PMID: 17603483.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Razzaque MA, Nishizawa T, Komoike Y, Yagi H, Furutani M, Amo R, Kamisago M, Momma K, Katayama H, Nakagawa M, Fujiwara Y, Matsushima M, Mizuno K, Tokuyama M, Hirota H, Muneuchi J, Higashinakagawa T, Matsuoka R. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. Nat Genet. 2007;39:1013–7. PubMed PMID: 17603482.

Rodríguez F, Ponce D, Berward FJ, Lopetegui B, Cassorla F, Aracena M. RAF1 variant in a patient with Noonan syndrome with multiple lentigines and craniosynostosis. Am J Med Genet A. 2019;179:1598–602. PubMed PMID: 31145547.

Sarkozy A, Carta C, Moretti S, Zampino G, Digilio MC, Pantaleoni F, Scioletti AP, Esposito G, Cordeddu V, Lepri F, Petrangeli V, Dentici ML, Mancini GM, Selicorni A, Rossi C, Mazzanti L, Marino B, Ferrero GB, Silengo MC, Memo L, Stanzial F, Faravelli F, Stuppia L, Puxeddu E, Gelb BD, Dallapiccola B, Tartaglia M. Germline BRAF mutations in Noonan, LEOPARD, and cardiofaciocutaneous syndromes: molecular diversity and associated phenotypic spectrum. Hum Mutat. 2009;30:695–702. PubMed PMID: 19206169.

Sarkozy A, Digilio MC, Dallapiccola B. Leopard syndrome. Orphanet J Rare Dis. 2008;3:13. PubMed PMID: 18505544.

Smpokou P, Zand DJ, Rosenbaum KN, Summar ML. Malignancy in Noonan syndrome and related disorders. Clin Genet. 2015;88:516–22. PubMed PMID: 25683281.

Tartaglia M, Gelb BD. Disorders of dysregulated signal traffic through the RAS-MAPK pathway: phenotypic spectrum and molecular mechanisms. Ann N Y Acad Sci. 2010;1214:99–121. PubMed PMID: 20958325.

Tartaglia M, Martinelli S, Cazzaniga G, Cordeddu V, Iavarone I, Spinelli M, Palmi C, Carta C, Pession A, Arico M, Masera G, Basso G, Sorcini M, Gelb BD, Biondi A. Genetic evidence for lineage-related and differentiation stage-related contribution of somatic PTPN11 mutations to leukemogenesis in childhood acute leukemia. Blood. 2004b;104:307–13. PubMed PMID: 14982869.

Tartaglia M, Niemeyer CM, Fragale A, Song X, Buechner J, Jung A, Hahlen K, Hasle H, Licht JD, Gelb BD. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nat Genet. 2003b;34:148–50. PubMed PMID: 12717436.

Van den Heurck JJ, Boven KB, Claes CC. Optic disc coloboma and contralateral optic disc pit maculopathy treated by vitrectomy in a patient with Noonan syndrome with multiple lentigines. Retin Cases Brief Rep. 2021. Epub ahead of print. PubMed PMID: 34009903.

Villani A, Greer MC, Kalish JM, Nakagawara A, Nathanson KL, Pajtler KW, Pfister SM, Walsh MF, Wasserman JD, Zelley K, Kratz CP. Recommendations for cancer surveillance in individuals with RASopathies and other rare genetic conditions with increased cancer risk. Clin Cancer Res. 2017;23:e83–e90. PubMed PMID: 28620009.

Voron DA, Hatfield HH, Kalkhoff RK. Multiple lentigines syndrome. Case report and review of the literature. Am J Med. 1976;60:447–56. PubMed PMID: 1258892.

Watanabe Y, Yano S, Niihori T, Aoki Y, Matsubara Y, Yoshino M, Matsuishi T. A familial case of LEOPARD syndrome associated with a high-functioning autism spectrum disorder. Brain Dev. 2011;33:576–9. PubMed PMID: 21093184.

Witt DR, Keena BA, Hall JG, Allanson JE. Growth curves for height in Noonan syndrome. Clin Genet. 1986;30:150–3. PubMed PMID: 3780030.

Zhu G, Xie J, Kong W, Xie J, Li Y, Du L, Zheng Q, Sun L, Guan M, Li H, Zhu T, He H, Liu Z, Xia X, Kan C, Tao Y, Shen HC, Li D, Wang S, Yu Y, Yu ZH, Zhang ZY, Liu C, Zhu J. Phase separation of disease-associated SHP2 mutants underlies MAPK hyperactivation. Cell. 2020;183:490–502.e18. PubMed PMID: 33002410.

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