



## Noonan Syndrome

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### Summary

#### Clinical characteristics

Noonan syndrome (NS) is characterized by characteristic facies, short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one fourth of affected individuals have mild intellectual disability, and language impairments in general are more common in NS than in the general population.

#### Diagnosis/testing

The diagnosis of Noonan is established in a proband with suggestive findings and a heterozygous pathogenic variant in *BRAF*, *KRAS*, *MAP2K1*, *MRAS*, *NRAS*, *PTPN11*, *RAF1*, *RASA2*, *RIT1*, *RRAS2*, *SOS1*, or *SOS2* or either a heterozygous variant or biallelic pathogenic variants in *LZTR1* identified by molecular genetic testing. Several additional genes associated with a Noonan syndrome-like phenotype in fewer than ten individuals have been identified.

#### Management

*Treatment of manifestations:* Cardiovascular anomalies in NS are usually treated as in the general population. Developmental disabilities are addressed by early intervention programs and individualized education strategies. Treatment for serious bleeding is guided by knowledge of the specific factor deficiency or platelet aggregation anomaly. Growth hormone (GH) treatment increases growth velocity. Standard treatment for juvenile

myelomonocytic leukemia (JMML) and other malignancies, feeding difficulties, ADHD, behavioral problems, cryptorchidism in males, renal anomalies / hydronephrosis, strabismus, hearing loss, and Chiari malformation.

*Surveillance:* At each visit: measurement of growth parameters; evaluation of nutritional status in infants and toddlers; monitor for evidence of new neurologic manifestations (chronic headache, neck pain, changes in tone, dizziness, or obstructive sleep apnea); monitor developmental progress; assessment of behavioral issues, as age appropriate; skin examination. Annually in childhood or as clinically indicated: ophthalmology and audiology evaluations.

- In children age <5 years: if initial cardiac evaluation is normal, at least annual cardiac evaluations until age 5 years.
- In children age >5 years through adulthood, cardiac evaluation at least every 5 years, or as clinically indicated.
- Prior to any surgical procedure or in those with clinical bleeding: assessment of bleeding history, CBC with differential, and consideration of measurement of coagulation factors.
- For those with pathogenic *PTPN11* or *KRAS* variants: consider physical examination with assessment of spleen size & CBC every 3-6 months until age 5 years to assess for concerns about JMML/malignancy.

*Agents/circumstances to avoid:* Aspirin therapy should be avoided because it may exacerbate a bleeding diathesis.

*Pregnancy management:* Consider referral to an adult congenital heart program for peripartum evaluation and management; consider a hematology referral if the affected pregnant woman has a history of bleeding abnormalities and/or has not undergone previous screening for coagulopathy.

## Genetic counseling

NS is most often inherited in an autosomal dominant manner. While many individuals with autosomal dominant NS have a *de novo* pathogenic variant, an affected parent is recognized in 30%-75% of families. The risk to sibs of a proband with autosomal dominant NS depends on the genetic status of the parents: if a parent is affected, the risk is 50%; when the parents are clinically unaffected, the risk to the sibs of a proband appears to be low (<1%). Each child of an individual with autosomal dominant NS has a 50% chance of inheriting the pathogenic variant.

NS caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner. The parents of an individual with autosomal recessive NS are typically heterozygotes (i.e., have one *LZTR1* pathogenic variant), and may either be asymptomatic or have mild features of NS. If both parents are heterozygous for one *LZTR1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of having one *LZTR1* pathogenic variant (which can be associated with mild NS features), and a 25% chance of being unaffected and not a carrier.

Prenatal testing and preimplantation genetic testing are possible if the NS-related pathogenic variant(s) have been identified in an affected family member.

## Diagnosis

No consensus clinical diagnostic criteria for Noonan syndrome have been published. Diagnostic scoring systems, most recently published in van der Burgt [2007] and embedded in the [management guidelines](#) developed by DYSCERNE in the United Kingdom [Noonan Syndrome Guideline Development Group 2010], have been proposed but have not been used extensively in North America.

## Suggestive Findings

Noonan syndrome (NS) **should be suspected** in individuals with the following clinical, laboratory, and family history findings.

### Clinical findings

- Characteristic facies. The facial appearance of NS shows considerable change with age, being most striking in young and middle childhood, and most subtle in adulthood. Key features found regardless of age include the following:
  - Low-set, posteriorly rotated ears with fleshy helices
  - Vivid blue or blue-green irises
  - Widely spaced and downslanted palpebral fissures
  - Epicanthal folds
  - Fullness or droopiness of the upper eyelids (ptosis)

**Note:** See the National Human Genome Research Institute (NHGRI) [Atlas of Human Malformation Syndromes](#) (scroll to **ATLAS IMAGES**) for photographs of individuals with Noonan syndrome from diverse ethnic backgrounds.

- Short stature for sex and family background
- Congenital heart defects, most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy
- Developmental delay of variable degree
- Broad or webbed neck
- Unusual chest shape with superior pectus carinatum and inferior pectus excavatum
- Widely spaced nipples
- Cryptorchidism in males
- Lymphatic dysplasia of the lungs, intestines, and/or lower extremities

### Suggestive laboratory findings. Coagulation defects:

- Coagulation screens (e.g., prothrombin time, activated partial thromboplastin time, platelet count, and platelet aggregation testing) may show abnormalities.
- Specific testing should identify the particular coagulation defect, such as von Willebrand disease, thrombocytopenia, varied coagulation factor defects (factors V, VIII, XI, XII, protein C), and platelet dysfunction.

**Family history** is consistent with autosomal dominant (e.g., affected males and females in multiple generations) or - rarely - autosomal recessive inheritance (see Genetic Counseling). Absence of a known family history of Noonan syndrome does not preclude the diagnosis.

## Establishing the Diagnosis

The molecular diagnosis of NS 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 or biallelic pathogenic (or likely pathogenic) variants in *LZTR1*.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis. (3) As up to 20% of individuals meeting the proposed clinical diagnostic criteria [van der Burgt 2007] for NS do not have an identifiable molecular genetic etiology, nondiagnostic genetic testing does not rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing or 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 Noonan syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

## Option 1

When the phenotypic findings suggest the diagnosis of Noonan syndrome, molecular genetic testing approaches usually include the use of a multigene panel. A **Noonan syndrome multigene panel** that includes some or all of the genes listed in Table 1 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. Since Noonan syndrome occurs through a gain-of-function mechanism and large intragenic deletions or duplications have not been reported, testing for intragenic deletions or duplications is unlikely to result in a diagnosis; however, rare cases have been reported for some genes (see Table 1).

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

Note: **Serial single-gene testing** can be considered if panel testing is not feasible. Approximately 50% of individuals with NS have a pathogenic missense variant in *PTPN11*; therefore, single-gene testing starting with *PTPN11* would be the next best first test. Appropriate serial single-gene testing if *PTPN11* testing is not diagnostic can be determined by the individual's phenotype (e.g., *RIT1* if there is hypertrophic cardiomyopathy, *LZTR1* if autosomal recessive inheritance is suspected); however, continued sequential single-gene testing is not recommended as it is less efficient and more costly than panel testing.

## Option 2

When the diagnosis of Noonan syndrome has not been considered because an individual has atypical phenotypic features or if some but not all characteristic phenotypic features are present (e.g., a "Noonan-like" phenotype), **comprehensive genomic testing**, which does not require the clinical to determine which gene is likely involved, may be used. **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 (NS)

Gene <sup>1, 2</sup>	Proportion of NS Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant <sup>3</sup> Detected by Method	
		Sequence analysis <sup>4</sup>	Gene-targeted deletion/duplication analysis <sup>5</sup>
<i>BRAF</i>	<2% <sup>6</sup>	100%	Unknown <sup>7</sup>
<i>KRAS</i>	<5% <sup>8</sup>	100%	Unknown <sup>7</sup>
<i>LZTR1</i>	~8% <sup>9</sup>	100%	Unknown <sup>7</sup>
<i>MAP2K1</i>	<2% <sup>10</sup>	100%	Unknown <sup>7</sup>
<i>MRAS</i>	<1% <sup>11</sup>	100%	Unknown <sup>7</sup>
<i>NRAS</i>	<1% <sup>12</sup>	100%	Unknown <sup>7</sup>
<i>PTPN11</i>	50% <sup>13</sup>	Nearly 100%	Rare duplication, <sup>14</sup> diagnosis of NS questioned <sup>15</sup>
<i>RAF1</i>	5% <sup>16</sup>	Nearly 100%	1 reported case w/a duplication, <sup>17</sup> diagnosis of NS questioned <sup>15</sup> ; 1 reported case of a deletion <sup>18</sup>
<i>RASA2</i>	Unknown <sup>19</sup>	100%	Unknown <sup>7</sup>
<i>RIT1</i>	5% <sup>16</sup>	100%	Unknown <sup>7</sup>
<i>RRAS2</i>	<1% <sup>20</sup>	100%	Unknown <sup>7</sup>
<i>SOS1</i>	10%-13% <sup>21</sup>	100%	Unknown <sup>7</sup>
<i>SOS2</i>	~4% <sup>22</sup>	100%	Unknown <sup>7</sup>

Table 1. continued from previous page.

Gene <sup>1, 2</sup>	Proportion of NS Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant <sup>3</sup> Detected by Method	
		Sequence analysis <sup>4</sup>	Gene-targeted deletion/duplication analysis <sup>5</sup>
Others <sup>23</sup>	NA		

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. Sarkozy et al [2009]

7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

8. Schubert et al [2006], Brasil et al [2010]

9. Chen et al [2014b], Yamamoto et al [2015]

10. Nava et al [2007]

11. Higgins et al [2017], Motta et al [2019], Suzuki et al [2019], Pires et al [2021]

12. Altmüller et al [2017], Garren et al [2020]

13. Tartaglia et al [2002]

14. Shchelochkov et al [2008], Graham et al [2009], Chen et al [2014a]

15. Lisowski et al [2015]

16. Aoki et al [2016]

17. Luo et al [2012]

18. Sana et al [2014]

19. Chen et al [2014b]

20. Capri et al [2019], Niihori et al [2019]

21. Approximately 16%-20% of individuals with a clinical diagnosis of Noonan syndrome who do not have an identified *PTPN11* pathogenic variant are found to have an *SOS1* pathogenic variant [Roberts et al 2007, Tartaglia et al 2007].

22. Chen et al [2014b], Cordeddu et al [2015], Yamamoto et al [2015], Lisowski et al [2021]

23. Recent reports have implicated additional genes associated with a Noonan syndrome-like phenotype in fewer than ten individuals each, including *RRAS* (2 probands) [Flex et al 2014] and *A2ML1* (3 probands) [Vissers et al 2015].

## Clinical Characteristics

### Clinical Description

To date, including those with a clinical and a molecular genetic diagnosis and with an estimated incidence of 1:1000-1:2500, several thousand individuals have been identified with Noonan syndrome (NS) [Roberts et al 2013]. The following description of the phenotypic features associated with this condition is based on these reports.

**Table 2.** Noonan Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Eye anomalies	95%	
Short stature	50%-70%	For age, sex, & family background
Hypotonia	Majority	Can contribute to feeding problems, speech articulation issues, & delayed attainment of gross motor milestones
Joint hyperextensibility	Majority	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Pectus anomaly	Majority	Characteristic pectus deformity of the chest: pectus carinatum superiorly & pectus excavatum inferiorly
Cryptorchidism in males	60%-80%	
Congenital heart disease	50%-80%	25%-71% of affected persons have pulmonary valve stenosis, often w/ pulmonary valve dysplasia.
Hearing loss	40%	May be sensorineural, conductive, or mixed
Hypertrophic cardiomyopathy	10%-29%	Half of those w/hypertrophic cardiomyopathy are diagnosed by age 6 mos.
Learning disability	25%	~10%-15% of those w/NS require special education.
Intellectual disability <sup>1</sup>	6%-23%	
Renal anomalies	11%	Most commonly dilatation of the renal pelvis
Abnormal bleeding or bruising	Bleeding: 6%-10%; bruising: majority	

1. Defined as IQ <70

**Prenatal features.** Advanced paternal age has been observed in cohorts with simplex NS. Common perinatal findings [Stuurman et al 2019]:

- Polyhydramnios
- Lymphatic dysplasia including increased distended jugular lymphatic sacs, nuchal translucency, cystic hygroma, pleural effusion, and ascites
- Relative macrocephaly
- Cardiac and renal anomalies

In chromosomally normal fetuses with increased nuchal translucency, it is estimated that 3%-15% have *PTPN11*-associated NS [Stuurman et al 2019].

**Growth.** Birth weight is usually normal, although edema may cause a transient increase. Infants with NS frequently have feeding difficulties. This period of failure to thrive is self limited, although poor weight gain may persist for up to 18 months.

Length at birth is usually normal. Postnatal growth failure is often obvious from the first year of life [Seo & Yoo 2018]. Mean height then follows the third centile from ages two to four years until puberty, when below-average growth velocity and an attenuated adolescent growth spurt tend to occur. As bone maturity is usually delayed, prolonged growth into the 20s is possible.

Final adult height approaches the lower limit of normal: 161-167 cm in males and 150-155 cm in females. Growth curves have been developed from these cross-sectional retrospective data. One study suggests that 30% of affected individuals have height within the normal adult range, while more than 50% of females and nearly 40% of males have an adult height below the third centile [Seo & Yoo 2018].

In many affected persons, decreased IGF-I- and IGF-binding protein 3, together with low responses to provocation, suggest impaired growth hormone release or disturbance of the growth hormone / insulin-like growth factor I axis. Mild growth hormone resistance related to a post-receptor signaling defect (which may be partially compensated for by elevated growth hormone secretion) is reported in individuals with NS and a *PTPN11* pathogenic variant [Seo & Yoo 2018].

Growth hormone (GH) therapy has been used in individuals with NS (see Management):

- In Europe, GH treatment is the standard of care for children with abnormalities of the GH-IGF-I axis and could be used when GH physiology is normal.
- Short- and long-term studies of GH treatment have been published [Ogawa et al 2004, Osio et al 2005, Noordam 2007, Noordam et al 2008, Romano et al 2009, Rohrer et al 2020] and demonstrate a consistent and significant increase in height velocity in children with Noonan syndrome who have been treated.
- The increase in height standard deviation (SD) varies from 0.6 to 1.8 SD and may depend on age at start of treatment, duration of study, age at onset of puberty, and/or GH sensitivity [Seo & Yoo 2018].
- Studies have shown that children with prepubertal NS growth hormone deficiency have increased their growth rate with GH therapy at a rate equivalent to girls with Turner syndrome but at a lower rate than that seen in idiopathic GH deficiency [Lee et al 2015, Zavras et al 2015].

**Cardiovascular.** Significant bias in the frequency of congenital heart disease may exist because many clinicians have in the past required the presence of cardiac anomalies for diagnosis of NS. The frequency of congenital heart disease is estimated at between 50% and 80%.

- **Pulmonary valve stenosis**, often with dysplasia, is the most common anomaly in NS, found in 25%-71% of affected individuals; it may be isolated or associated with other cardiovascular defects.
- **Hypertrophic cardiomyopathy** is found in 10%-29% of individuals with NS. It usually presents early in life: the median age at diagnosis is five months and more than 50% of individuals with NS and hypertrophic cardiomyopathy are diagnosed by age six months [Hickey et al 2011, Wilkinson et al 2012].
- **Other structural defects** frequently observed include atrial septal defects (4%-57%), ventricular septal defects (1%-14%), atrioventricular canal defects (1%-13%), mitral valve abnormalities (2%-17%), aortic coarctation (2%-9%), patent ductus arteriosus (1%-6%), and tetralogy of Fallot (1%-4%) [Linglart & Gelb 2020].
- **An electrocardiographic abnormality** is documented in approximately 90% of individuals with NS and may be present without concomitant structural defects. Extreme right axis deviation with superior counterclockwise frontal QRS loop, superior or left axis deviation, left anterior hemiblock, or an RSR' pattern in lead V1 (of no clinical consequence) are common findings [Sharland et al 1992].

**Psychomotor development.** Early developmental milestones may be delayed, likely in part as a result of the combination of joint hyperextensibility and hypotonia. The average age for sitting unsupported is around ten months and for walking is 21 months [Pierpont 2016]. About 50% of school-age children meet diagnostic criteria for a developmental coordination disorder [Lee et al 2005a] and impaired manual dexterity is significantly correlated with verbal and nonverbal intellectual functioning [Pierpont et al 2015].

Most school-age children perform well in a normal educational setting, but 25% have learning disabilities [Lee et al 2005a] and 10%-15% require special education [van der Burgt et al 1999]. Intellectual abilities are in general mildly lowered in children with NS. IQ scores below 70 are seen in 6%-23% across studies [Pierpont et al 2015]. Studies conflict with regard to strength in verbal vs nonverbal performance and no clear pattern has emerged [Pierpont et al 2015]. There may be a specific cognitive disability, either in verbal or praxic reasoning, requiring a special academic strategy and school placement.

Articulation deficiency is common (72%) but usually responds well to speech therapy. Language delay may be related to hearing loss, perceptual motor disabilities, or articulation deficiencies. The average age at first words is around 15 months and simple two-word phrases emerge on average from age 31 to 32 months [Pierpont et al 2015].

A study of the language phenotype of children and adults with NS showed that language impairments in general are more common in NS than in the general population and a majority of children (70%) receive speech and language therapy. When language issues are present, there is a higher risk for reading and spelling difficulties



[Pierpont et al 2015]. Language is significantly correlated with nonverbal cognition, hearing ability, articulation, motor dexterity, and phonologic memory. No specific aspect of language was selectively affected in those with NS.

There is emerging evidence that impairment in attention and executive functioning is one of the most common neuropsychological challenges for children with NS [Pierpont et al 2015]. Studies that rely on screening measures rather than comprehensive diagnostic assessments suggest that children with NS are at heightened risk for autism spectrum disorders; however, further research is needed [Pierpont 2016].

**Psychological health.** Few details of psychological health in Noonan syndrome are reported. No particular syndrome of behavioral disability or psychopathology is observed, and self-esteem is comparable to age-related peers [Lee et al 2005a]. A study of 37 individuals with a molecular genetic diagnosis of Noonan syndrome demonstrated a higher incidence of emotional dysregulation, irritability, and anxiety symptomatology compared to the general population [Alfieri et al 2021]. Noonan [2005a] documented problems in a cohort of 51 adults: depression was found in 23%, and occasional substance abuse and bipolar disease were reported. Similar findings were not reported in a large UK cohort followed over many years [Shaw et al 2007]. In one study of adults with NS, 49% reported that they had been diagnosed and treated for depression and/or anxiety [Smpokou et al 2012].

**Genitourinary.** Renal abnormalities, generally mild, are present in 11% of individuals with NS. Dilatation of the renal pelvis is most common. Duplex collecting systems, minor rotational anomalies, distal ureteric stenosis, renal hypoplasia, unilateral renal agenesis, unilateral renal ectopia, and bilateral cysts with scarring are reported less commonly.

Male pubertal development and subsequent fertility may be normal, delayed, or inadequate. Deficient spermatogenesis may be related to cryptorchidism, which is noted in 60%-80% of males; however, a study of male gonadal function identified Sertoli cell dysfunction both in males with cryptorchidism and those with normal testicular descent, suggesting an intrinsic defect leading to hypergonadotropic hypogonadism [Moniez et al 2018].

Puberty may be delayed in females, with a mean age at menarche of  $14.6 \pm 1.17$  years. Normal fertility is the rule.

**Facial features.** Differences in facial appearance, albeit subtle at certain ages, are a key clinical feature:

- **In the neonate**, tall forehead, widely spaced eyes with downslanted palpebral fissures, low-set, posteriorly rotated ears with a thickened helix, a deeply grooved philtrum with high, wide peaks to the vermilion border of the upper lip, and a short neck with excess nuchal skin and low posterior hairline are found.
- **In infancy**, eyes are prominent, with horizontal palpebral fissures, widely spaced eyes, and full or ptotic upper eyelids. The nose has a depressed nasal bridge, wide base, and bulbous tip.
- **In childhood**, facial appearance is often lacking in affect or expression, as in an individual with a myopathy.
- **By adolescence**, facial shape is an inverted triangle, wide at the forehead and tapering to a pointed chin. Eyes are less prominent and features are sharper. The neck lengthens, accentuating skin webbing or prominence of the trapezius muscle.
- **In the older adult**, nasolabial folds are prominent, and the skin appears transparent and wrinkled.

### Skeletal features

- Thoracic scoliosis is reported in 13%-30% of individuals diagnosed at a mean age of nine years.
- Estimates of the frequency of the characteristic appearance of the chest (superior pectus carinatum and inferior pectus excavatum with a broad chest and increased inter-nipple distance) range from 28% to 95% [Rodríguez et al 2020].
- Vertebral defects have also been reported.

- Reported upper limb anomalies include cubitus valgus, radioulnar synostosis, brachydactyly, and fifth finger clinodactyly.
- Common maxillofacial features include micrognathia, high arched palate, and dental crowding [Rodríguez et al 2020].
- Small studies have suggested lower bone mineral density in children and osteopenia in adults [Fowlkes et al 2021].
- Multiple giant cell lesions of the jaw, joints (pigmented villonodular synovitis), and/or soft tissue have been reported in association with *PTPN11*-, *SOS1*-, and *RAF1*-associated cases of Noonan syndrome [Miri et al 2018, Rodríguez et al 2020].

**Bleeding diathesis.** Most persons with NS have a history of abnormal bleeding or bruising. Early studies reported that about one third of all individuals with NS have one or more coagulation defects, with subsequent studies suggesting a lower rate of coagulopathy [Derbent et al 2010]. The coagulopathy may manifest as severe surgical hemorrhage, clinically mild bruising, or laboratory abnormalities with no clinical consequences. A variety of small studies have shown that while 50%-89% of those with NS have either a history of bleeding and/or abnormal hemostatic lab results, only 10%-42% have both (reviewed in Briggs & Dickerman [2012]). A study of 70 individuals with NS who had not had preoperative evaluation for coagulopathy demonstrated a 6.2% risk of perioperative bleeding complications [Briggs et al 2020].

**Lymphatic.** Varied lymphatic abnormalities are described in individuals with NS. They may be localized or widespread, prenatal, and/or postnatal. Dorsal limb (top of the foot and back of the hand) lymphedema is most common. Less common findings include: intestinal, pulmonary, or testicular lymphangiectasia; chylous effusions of the pleural space and/or peritoneum; and localized lymphedema of the scrotum or vulva.

**Ocular.** Ocular abnormalities including ptosis, strabismus, refractive errors, amblyopia, and nystagmus occur in up to 95% of affected individuals. Anterior segment and fundus changes are less common. There are case reports of keratoconus and Axenfeld anomaly [Lee & Sakhalkar 2014, Guerin et al 2015, van Trier et al 2018].

**Ears/hearing.** Hearing impairment has an estimated incidence of 40%. Some individuals have sensorineural hearing loss, others have a secondary conductive hearing loss due to chronic otitis media or middle ear effusion, and some have mixed conductive and sensorineural hearing loss [van Nierop et al 2017].

**Dermatologic.** Skin differences, particularly follicular keratosis over extensor surfaces and face, are relatively common and may occasionally be as severe as those found in [cardiofaciocutaneous syndrome](#) (see Differential Diagnosis).

Café au lait spots and lentigines are described in NS more frequently than in the general population (see Noonan syndrome with multiple lentigines discussion in Genetically Related Disorders).

## Other

- **Arnold-Chiari I malformation.** Eleven cases of Arnold-Chiari malformation have been reported in the medical literature; the true incidence in NS is not known [Smpokou et al 2012, Keh et al 2013, Mitsuhara et al 2014, Zarate et al 2014, Ejarque et al 2015].
- **Hepatosplenomegaly** is frequent; the cause is likely related to subclinical myelodysplasia.
- **Juvenile myelomonocytic leukemia (JMML).** The most common hematologic disorder in NS is transient myeloproliferative disorder, typically diagnosed in the neonatal period or early infancy. An estimated 10% of these cases progress to JMML [Niemeyer 2014]. Individuals with Noonan syndrome and a germline pathogenic variant in *PTPN11* have a predisposition to this unusual childhood leukemia. In general, JMML in Noonan syndrome runs a more benign course. The associated variants are different from the

somatic pathogenic variants in *PTPN11*-associated JMML, which - when present as germline variants - are associated with neonatal-lethal NS [Mason-Suares et al 2017].

- **Other malignancies.** One study of individuals with Noonan syndrome caused by a pathogenic variant in *PTPN11* supports a threefold increased risk of malignancy [Jongmans et al 2011].
  - Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are found at higher frequency in Noonan syndrome than in the general population [Hasle 2009, Jongmans et al 2011].
  - Solid tumors, such as rhabdomyosarcoma and neuroblastoma, are described [Denayer et al 2010, Jongmans et al 2010]. Three embryonal rhabdomyosarcomas (ERMS) caused by a germline *SOS1* pathogenic variant have been reported [Denayer et al 2010, Hastings et al 2010, Jongmans et al 2010]. One with obstructive jaundice involved the biliary ampulla/duodenum; one the bladder; and one the urachus. Three additional cases of ERMS and NS (of the orbit, vagina, and abdomen) were reported; genotype was not determined [Khan et al 1995, Jung et al 2003, Moschovi et al 2007].
  - A recent review of the literature yielded 30 cases of individuals with *PTPN11*-associated NS yielded 28 cases of brain tumors, 24 of which were low-grade gliomas and glioneuronal tumors [Lodi et al 2020].
- **Noonan-like / multiple giant-cell lesion syndrome.** The giant-cell granulomas and bone and joint anomalies in Noonan-like / multiple giant-cell lesion syndrome are recognized to be part of the Noonan syndrome spectrum. They can resemble cherubism (an autosomal dominant disorder caused by pathogenic variants in *SH3BP2*; see [Cherubism](#)), lesions observed in neurofibromatosis (see [Neurofibromatosis Type 1](#)), or lesions observed in the Ramon syndrome with juvenile rheumatoid arthritis (polyarticular pigmented villonodular synovitis).

Noonan-like / multiple giant-cell lesion syndrome is caused by pathogenic variants in *PTPN11* [Jafarov et al 2005, Wolvius et al 2006] and *SOS1* [Beneteau et al 2009, Neumann et al 2009]. One family with Noonan-like / multiple giant-cell lesion syndrome has a *PTPN11* pathogenic variant that was also reported in Noonan syndrome without giant-cell lesions [Tartaglia et al 2002]; thus, additional genetic factors may be necessary for the giant-cell proliferation to occur.

- These multiple giant cell lesions are also recognized in persons with [cardiofaciocutaneous syndrome](#), caused by mutation of *BRAF* and *MEK1* [Neumann et al 2009]. Thus, dysregulation of the RAS-MAPK pathway represents the common and basic molecular event predisposing to giant-cell lesion formation, arguing against the existence of Noonan-like / multiple giant-cell lesion syndrome as a separate entity.
- **Overall risk of malignancy.** Kratz et al [2015] reported on a cohort of 632 individuals with molecularly confirmed NS (inclusive of Noonan syndrome with multiple lentigines) and found four individuals with JMML, two with brain tumor, two with ALL, and one with neuroblastoma; they calculated a childhood cancer standardized incidence ratio of 8.1 [Kratz et al 2015]. Individuals with NS are at an eightfold greater risk of developing a childhood cancer than are those without NS. The overall cancer risk by age 20 years is estimated to be 4% [Lodi et al 2020].

An international meeting of the American Association for Cancer Research was held to propose consensus surveillance recommendations for RASopathies and other genetic disorders associated with increased childhood cancer risk. Overall, because the cancer risk falls below 5%, routine cancer surveillance was not recommended. However, for those with *PTPN11* or *KRAS* variants known to be associated with myeloproliferative disorder or JMML, physical examination every three to six months with spleen size assessment and complete blood count from birth/time of diagnosis to age five years was recommended for consideration - though there is not yet evidence that this strategy leads to survival advantage [Villani et al 2017].

## Phenotype Correlations by Gene

There are no known phenotype correlations for *RASA2* or *RRAS2*.

**Table 3.** Noonan Syndrome Phenotype Correlations by Gene

Gene <sup>1</sup>	Phenotypic Feature				
	HCM	Ectodermal findings	ID	Pulmonary stenosis	Other
<i>BRAF</i>		+++ <sup>2</sup>			Typically classic features
<i>KRAS</i>			+++ <sup>3</sup>		Craniosynostosis reported in 2 persons <sup>4</sup>
<i>LZTR1</i>	++ <sup>5</sup>				
<i>MAP2K1</i>		+++ <sup>2</sup>			Typically classic features
<i>MRAS</i>	+++				6 of 6 reported persons <sup>6</sup>
<i>PTPN11</i>	- <sup>7</sup>			+++	Persons are also more likely to have short stature, pectus anomaly, easy bruising, cryptorchidism, & characteristic facial features.
<i>RAF1</i>	+++ <sup>8</sup>	++ <sup>9</sup>			
<i>RIT1</i>	++ <sup>10</sup>	++ <sup>11</sup>	- <sup>12</sup>		Persons are less likely to have short stature & pectus anomalies & more likely to have perinatal abnormalities, high birth weight, & relative macrocephaly.
<i>SOS1</i>		++	-		Persons are more likely to have normal stature & cardiac septal defects.
<i>SOS2</i>		++	-		Infrequent short stature; lymphatic abnormalities in >50% <sup>13</sup>

+, ++, +++ = degree of likelihood that a given feature is present (i.e., more +s = more likely); - = a feature that is less likely to be present. Blank cells indicate that there is no known correlation between the likelihood of having a particular feature when a person has a pathogenic variant in that gene.

HCM = hypertrophic cardiomyopathy; ID = intellectual disability

1. Genes are listed in alphabetic order.

2. Nava et al [2007], Nyström et al [2008], Sarkozy et al [2009]

3. Those with pathogenic variants in *KRAS* tend to have a greater likelihood and severity of intellectual disability [Zenker et al 2007].

4. Kratz et al [2009]

5. In one study, 5/26 persons with a heterozygous pathogenic variant in *LZTR1* and 19/26 with biallelic pathogenic variants in *LZTR1* had hypertrophic cardiomyopathy.

6. Pires et al [2021]

7. Those with a pathogenic variant in *PTPN11* are less likely to have hypertrophic cardiomyopathy compared to those with Noonan syndrome of other genetic causes.

8. The chance of having hypertrophic cardiomyopathy in persons with Noonan syndrome caused by a heterozygous pathogenic variant in *RAF1* is ~85% compared to 18% for those with Noonan syndrome in general [Gelb et al 2015].

9. Multiple nevi, lentigenes, and/or café au lait spots were reported in one third of those with *RAF1*-associated NS.

10. Hypertrophic cardiomyopathy is present in 70%-75% of persons with *RIT1*-associated NS [Aoki et al 2013, Yaoita et al 2016].

11. Including curly hair, hyperpigmentation, and wrinkled palms and soles

12. Those with *RIT1*-NS are less likely to have intellectual disability [Bertola et al 2014, Yaoita et al 2016].

13. Lisowski et al [2021]

## Genotype-Phenotype Correlations

No genotype-phenotype correlations for *BRAF*, *KRAS*, *LZTR1*, *MAP2K1*, *MRAS*, *NRAS*, *RAF1*, *RASA2*, *RIT1*, *RRAS2*, *SOS1*, or *SOS2* have been identified.

### *PTPN11*

- Germline pathogenic variants at codons 61, 71, 72, and 76 are significantly associated with leukemogenesis and identify a subgroup of individuals with NS at risk for JMML [Niihori et al 2005].
- Individuals with the p.Asn308Asp pathogenic variant are said to be more likely to receive a typical education [Jongmans et al 2004].
- An in-frame three-nucleotide *PTPN11* deletion (p.Gly60del) in a female infant with severe features of Noonan syndrome, including hydrops fetalis and juvenile myelomonocytic leukemia [Yoshida et al 2004], has been reported. The p.Asp61del three-nucleotide *PTPN11* deletion has also been reported in a child with typical rather than severe NS [Lee et al 2005b].

## Nomenclature

An early term for NS, "male Turner syndrome," incorrectly implied that the condition would not be found in females.

In 1949, Otto Ullrich reported affected individuals and noted a similarity between their features and those in a strain of mice bred by Bonnevie (webbed neck and lymphedema). The term "Bonnevie-Ullrich syndrome" became popular, particularly in Europe.

## Prevalence

NS is common and reported to occur in between 1:1,000 and 1:2,500 persons. Mild expression is likely to be overlooked.

## Genetically Related (Allelic) Disorders

The autosomal dominant allelic disorders summarized in Table 4 have clinical features overlapping those associated with Noonan syndrome and should be considered in the differential diagnosis.

**Table 4.** Allelic Disorders to Consider in the Differential Diagnosis of Noonan Syndrome

Genes	Disorder	Comment
<i>BRAF</i> <i>KRAS</i> <i>MAP2K1</i> <i>MAP2K2</i> <sup>2</sup>	CFC syndrome	CFC syndrome & NS have the greatest overlap in features. CFC syndrome has similar cardiac & lymphatic findings <sup>1</sup> but more severe ID, w/higher likelihood of structural CNS anomalies; skin pathology is more florid; GI problems are more severe & long lasting; bleeding diathesis is rare. Facial appearance tends to be coarser, dolichocephaly & absent eyebrows are more frequent, blue eyes less common.
<i>BRAF</i> <i>MAP2K1</i> <i>PTPN11</i> <i>RAF1</i>	Noonan syndrome w/multiple lentiginos	Formerly referred to as LEOPARD syndrome. NSML is assoc w/variable expression & shows significant overlap w/NS. In early childhood the NSML phenotype can be typical of NS; w/age, other characteristic features (incl lentiginos & hearing loss) develop.

AD = autosomal dominant; CFC = cardiofaciocutaneous; GI = gastrointestinal; ID = intellectual disability; LEOPARD = *l*entiginos, *E*KG abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of genitalia, *r*etardation of growth, *d*eafness; MOI = mode of inheritance; NS = Noonan syndrome; NMSL = Noonan syndrome with multiple lentiginos

1. Noonan [2001], Armour & Allanson [2008]

2. Pathogenic variants in *BRAF* account for ~75% of CFC syndrome; *MAP2K1* and *MAP2K2* account for ~25%; *KRAS* <2%.

### Other allelic disorders

- Heterozygous germline pathogenic variants in *LZTR1* are also known to be associated with [schwannomatosis](#) type 2.
- Heterozygous germline pathogenic variants in *SOS1* are also known to be associated with hereditary gingival fibromatosis (OMIM [135300](#)).
- *PTPN11* intragenic deletion and splice site variants are associated with autosomal dominant metachondromatosis [McFarlane et al 2016].

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *MRAS*, *NRAS*, *RASA2*, *RIT1*, *RRAS2*, or *SOS2*.

Mosaic activating pathogenic variants in *KRAS* are associated with [encephalocraniocutaneous lipomatosis](#) (ECCL). The pathogenic variants reported in ECCL are of postzygotic origin but arise early during development. ECCL comprises a spectrum of predominantly congenital anomalies. In its typical form, ECCL is characterized by congenital skin, eye, and brain anomalies, in particular intracranial and spinal lipomas.

**Sporadic tumors** (including leukemia and solid tumors) occurring as single tumors in the absence of any other findings of Noonan syndrome may contain a somatic pathogenic nucleotide variant in *BRAF*, *KRAS*, *LZTR1*, *MAP2K1*, *MRAS*, *NRAS*, *PTPN11*, *RAF1*, or *RRAS2* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. See Molecular Genetics, Cancer and Benign Tumors.

## Differential Diagnosis

**Turner syndrome**, typically seen in females, is differentiated from Noonan syndrome (NS) by demonstration of a sex chromosome abnormality on cytogenetic studies in affected individuals. The phenotype of Turner syndrome is quite different from that of NS, when one considers face, heart, development, and kidneys. In Turner syndrome, renal anomalies are more common, developmental delay is much less frequently found, and left-sided heart defects are the rule.

Genes of interest in the differential diagnosis of NS are summarized in Table 5.

**Table 5.** Genes of Interest in the Differential Diagnosis of Noonan Syndrome

Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
<i>BRAF</i> <i>KRAS</i> <i>MAP2K1</i> <i>MAP2K2</i> <sup>1</sup>	<a href="#">Cardiofaciocutaneous syndrome</a>	AD	See Genetically Related Disorders.
<i>BRAF</i> <i>MAP2K1</i> <i>PTPN11</i> <i>RAF1</i>	<a href="#">Noonan syndrome w/multiple lentigines</a> (previously referred to as LEOPARD syndrome)	AD	See Genetically Related Disorders.
<i>CBL</i> <sup>2</sup>	Noonan syndrome-like disorder ± juvenile myelomonocytic leukemia (OMIM <a href="#">613563</a> )	AD	Variable phenotype characterized by relatively high frequency of neurologic features, predisposition to JMML, low prevalence of cardiac defects, ↓ growth, & cryptorchidism <sup>3</sup>
<i>FGD1</i>	X-linked Aarskog syndrome (OMIM <a href="#">305400</a> )	XL	Characterized by DD, short stature, congenital heart defects, & distinctive facies
<i>HRAS</i>	<a href="#">Costello syndrome</a>	AD	Typically characterized by failure to thrive in infancy due to severe postnatal feeding difficulties; short stature; DD or ID; coarse facial features; curly or sparse, fine hair; loose, soft skin w/deep palmar & plantar creases; papillomata of the face & perianal region; diffuse hypotonia & joint laxity w/ulnar deviation of wrists & fingers; tight Achilles tendons; & cardiac involvement. Relative or absolute macrocephaly is typical.

Table 5. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
<i>NF1</i>	Neurofibromatosis 1 (NF1)	AD	NF1 shares some features w/NS, incl short stature, learning difficulties, & café au lait patches. Rare affected persons may have a NS-like facial appearance. <sup>4</sup> Watson syndrome, an NF1 variant, is characterized by multiple café au lait spots, pulmonic stenosis, ID, & short stature.
<i>PPP1CB</i> <i>SHOC2</i> <sup>2</sup>	Noonan syndrome w/loose anagen hair (OMIM PS607721)	AD	NS-like features or, in a small proportion of affected persons, the classic NS phenotype. <sup>5</sup> The recurrent pathogenic missense <i>SHOC2</i> variant 4A>G has been found in a subgroup w/features of NS but also GH deficiency; distinctive hyperactive behavior that improves w/age in most; hair anomalies; darkly pigmented skin w/eczema or ichthyosis; hypernasal voice; & overrepresentation of mitral valve dysplasia & septal defects in comparison w/classic NS <sup>1,6</sup>
<i>SPRED1</i>	Legius syndrome	AD	Majority: café au lait macules, 30%-50% skin freckling, 30% developmental issues, 15% Noonan-like facial features

AD = autosomal dominant; DD = developmental delay; GH = growth hormone; GI = gastrointestinal; ID = intellectual disability; JMML = juvenile myelomonocytic leukemia; MOI = mode of inheritance; NS = Noonan syndrome; XL = X-linked

1. Cordeddu et al [2009]

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

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

4. This could be caused by chance concurrence of NS and NF1 [Colley et al 1996, Bertola et al 2005]. However, most often it appears to be a NS-like facial appearance in a person with a pathogenic variant in *NF1*, sometimes in the presence of a variant NF1 phenotype [Stevenson et al 2006, Nyström et al 2009].

5. B Kerr, personal observation

6. Gripp et al [2016], Huckstadt et al [2021]

**Other.** NS should be distinguished from other syndromes/conditions with developmental delay, short stature, congenital heart defects, and distinctive facies, especially the following:

- Autosomal dominant Aarskog syndrome of unknown genetic cause (OMIM 100050)
- In utero exposure to alcohol or primidone

## Management

Management guidelines have been developed by DYSCERNE, a European consortium [Noonan Syndrome Guideline Development Group 2010] ([full text](#)); a separate set has been published by an American consortium working with the Noonan Syndrome Support Group [Romano et al 2010] and in the *Lancet* [Roberts et al 2013].

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Noonan syndrome, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 6.** Recommended Evaluations Following Initial Diagnosis in Individuals with Noonan Syndrome

System/Concern	Evaluation	Comment
<b>Constitutional</b>	Measurements of growth parameters	<ul style="list-style-type: none"> <li>• On NS-specific growth charts</li> <li>• To identify those w/failure to thrive &amp;/or short stature</li> </ul>
<b>Endocrine</b>	Bone age, growth hormone & thyroid function studies <sup>1</sup>	In children w/short stature (height >2 SD below standard growth curve or crossing 2 major height %iles)

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
<b>Gastrointestinal/ Feeding</b>	Gastroenterology / nutrition / feeding team eval	<ul style="list-style-type: none"> <li>In infants w/poor weight gain, dysphagia</li> <li>Eval for malrotation if persistent unexplained vomiting</li> </ul>
<b>Development</b>	Developmental assessment	<p>To incl:</p> <ul style="list-style-type: none"> <li>Motor, adaptive, cognitive, &amp; speech-language eval</li> <li>Eval for early intervention / special education</li> </ul>
<b>Psychiatric/ Behavioral</b>	Neuropsychiatric eval may be considered.	For those age >12 mos: screen for behavior concerns, autism, depression, ADHD, & anxiety (some symptoms may not be present until adulthood).
<b>Cardiovascular</b>	Echocardiogram & EKG	To identify congenital heart defects, cardiomyopathy, &/or cardiac conduction abnormalities
<b>Genitourinary</b>	Kidney ultrasound	To assess for renal anomalies; if present, referral to urologist
	Assessment for cryptorchidism in males	Referral to urologist if cryptorchidism is present
<b>Musculoskeletal</b>	PT/OT eval	<p>To incl:</p> <ul style="list-style-type: none"> <li>Assessment of gross motor &amp; fine motor skills</li> <li>Need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> </ul>
	Consider radiographs of the spine if asymmetry or scoliosis is present on physical exam.	Consider referral to orthopedist.
<b>Hematologic/ Lymphatic</b>	In consultation w/hematologist: bleeding history, CBC w/differential, PT/aPTT, factor XI, XII, IX, VIII, vWf, & platelet aggregation testing	If initial screening was performed before age 12 mos, repeat after age 12 mos. <sup>2</sup>
<b>Eyes</b>	Ophthalmologic eval	To assess for amblyopia, refractive error, nystagmus, strabismus, & clinically significant ptosis
<b>Hearing</b>	Audiologic eval	Assess for hearing loss & middle ear effusion.
<b>Integument</b>	Full skin exam	Consider referral to dermatologist in those w/multiple lentigines requiring monitoring or significant xeroderma. <sup>3</sup>
<b>Neurologic</b>	Neurologic eval	To incl brain & spine MRI if signs or symptoms consistent w/ possible Chiari malformation
<b>Genetic counseling</b>	By genetics professionals <sup>4</sup>	To inform affected persons & their families re nature, MOI, & implications of NS in order to facilitate medical & personal decision making



Table 6. continued from previous page.

System/Concern	Evaluation	Comment
<b>Family support &amp; resources</b>	Assess need for: <ul style="list-style-type: none"> <li>Community or online resources such as <a href="#">Parent to Parent</a>;</li> <li>Social work involvement for parental support;</li> <li>Home nursing referral.</li> </ul>	

ADHD = attention-deficit/hyperactivity disorder; MOI = mode of inheritance; NS = Noonan syndrome; OT = occupational therapy; PT = physical therapy; PT/aPTT = prothrombin/activated partial thromboplastin time; vWF = von Willebrand factor

1. Thyroid function tests may include TSH and free T4.

2. Romano et al [2010], Roberts et al [2013]

3. Quaio et al [2013]

4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

Table 7. Treatment of Manifestations in Individuals with Noonan Syndrome

Manifestation/Concern	Treatment	Considerations/Other
<b>Short stature</b>	GH therapy may be considered.	<ul style="list-style-type: none"> <li>No standard dose has been established.</li> <li>No apparent correlation between dosage used &amp; final height, though earlier age at initiation of GH therapy is assoc w/↑ final adult height.</li> <li>Short stature due to NS is an FDA-approved indication for GH treatment.</li> <li>No evidence supports ↑ prevalence of neoplasm, cardiac, or other comorbidities in those treated w/ GH. <sup>1</sup></li> </ul>
<b>Feeding difficulties</b>	Consideration of nasogastric tube feedings in infants w/poor growth, esp if they have a congenital heart defect or cardiomyopathy	Invasive intervention (i.e., placement of gastrostomy tube) may be needed, though feeding issues are often self-limited.
<b>DD/ID</b>	See Developmental Delay / Intellectual Disability Management Issues.	
<b>Psychiatric/Behavioral</b>	Standard treatment for ADHD & any neuropsychiatric features &/or behavioral problems	Referral to a neurodevelopmental specialist or psychiatrist, depending on age, may be considered.
<b>Congenital heart defects</b>	Standard treatment per cardiologist	Pulmonary valve stenosis treated w/percutaneous balloon pulmonary valvuloplasty has a higher reintervention rate vs pulmonary valve stenosis w/o NS but is still considered 1st-line treatment. <sup>2</sup>
<b>HCM</b>	Standard treatment per cardiologist	HCM is assoc w/substantial early mortality; infants presenting before age 6 mos in congestive heart failure have worst prognosis (2-yr survival of 30%). <sup>3</sup>
<b>Cryptorchidism</b>	Standard treatment per urologist	
<b>Renal anomalies / Hydronephrosis</b>	Standard treatment per urologist &/or nephrologist	

Table 7. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
<b>Bleeding diathesis</b>	Standard treatment per hematologist	<ul style="list-style-type: none"> <li>• Specific treatment for serious bleeding may be guided by knowledge of a factor deficiency or platelet aggregation anomaly.</li> <li>• Factor VIIa has also been used in an infant w/NS who had normal platelet count &amp; prothrombin &amp; partial thromboplastin times to control severe postoperative blood loss due to gastritis.<sup>4</sup></li> </ul>
<b>Abnormal vision &amp;/or strabismus</b>	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
<b>Hearing</b>	Hearing aids may be helpful; as per otolaryngologist.	Community hearing services through early intervention or school district
<b>Chiari malformation</b>	Standard treatment per neurosurgeon	
<b>Juvenile myelomonocytic leukemia &amp; other malignancies</b>	Standard treatment per oncologist	
<b>Family/Community</b>	<ul style="list-style-type: none"> <li>• Ensure appropriate social work involvement to connect families w/ local resources, respite, &amp; support.</li> <li>• Coordinate care to manage multiple subspecialty appointments, equipment, medications, &amp; supplies.</li> </ul>	<ul style="list-style-type: none"> <li>• Ongoing assessment of need for palliative care involvement &amp;/or home nursing</li> <li>• Consider involvement in adaptive sports or <a href="#">Special Olympics</a>.</li> </ul>

ADHD = attention-deficit/hyperactivity disorder; DD/ID = developmental delay / intellectual disability; GH = growth hormone; HCM = hypertrophic cardiomyopathy; NS = Noonan syndrome

1. Romano et al [2010], Rohrer et al [2020]

2. Prendiville et al [2014], Linglart & Gelb [2020]

3. Hickey et al [2011], Wilkinson et al [2012]

4. Tofil et al [2005]

## 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.

**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 available for those who qualify. 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.

**All ages.** Consultation with a developmental pediatrician may be considered 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 needed.
  - 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 may be considered. 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.

## Surveillance

**Table 8.** Recommended Surveillance for Individuals with Noonan Syndrome

System/Concern	Evaluation	Frequency
<b>Constitutional</b>	<ul style="list-style-type: none"> <li>• Measurement of growth parameters on NS-specific growth charts</li> <li>• Eval of nutritional status in infants &amp; toddlers</li> </ul>	At each visit
<b>Development</b>	Monitor developmental progress & educational needs.	
<b>Neurologic</b>	Assess for new manifestations, e.g., chronic headache, neck pain, changes in tone, dizziness, or signs/symptoms of OSA that may indicate a Chiari malformation. <sup>1</sup>	
<b>Integument</b>	Skin exam	
<b>Family/Community</b>	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	
<b>Psychiatric/Behavioral</b>	Behavioral assessment for anxiety, attention, & depression	At each visit starting in early childhood, as age appropriate
<b>Cardiovascular</b>	In children <5 yrs: if initial cardiac eval is normal	At least annual cardiac eval until age 5 yrs or as clinically indicated
	In children >5 yrs through adulthood	At least every 5 yrs or as clinically indicated
<b>Eyes</b>	Ophthalmology eval	Annually in childhood & adolescence or as clinically indicated
<b>Hearing</b>	Audiology eval	Annually in early childhood or as clinically indicated

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
<b>Malignancy/ JMML</b> <sup>2</sup>	For those w/pathogenic <i>PTPN11</i> or <i>KRAS</i> variants <sup>3</sup> : consider physical exam w/assessment of spleen size & CBC.	Every 3-6 mos until age 5 yrs
<b>Coagulation/ Bleeding</b>	In consultation w/hematologist: bleeding history, CBC w/differential, PT/aPTT, factor XI, XII, IX, VIII, vWf, & platelet aggregation testing	Prior to any surgical procedure or if there is a bleeding history

CBC = complete blood count; PT/aPTT = prothrombin/activated partial thromboplastin time; vWF = von Willebrand factor; JMML = juvenile myelomonocytic leukemia; OSA = obstructive sleep apnea

1. With referral to neurologist and consideration of head MRI to include sections through the base of the skull to assess for Chiari malformation
2. Despite the apparent increased incidence of hematologic and solid tumor malignancies, no consensus surveillance strategies have been evaluated or recommended.
3. Villani et al [2017]

## Agents/Circumstances to Avoid

Aspirin therapy should be avoided because it may exacerbate a bleeding diathesis.

## Evaluation of Relatives at Risk

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

## Pregnancy Management

For affected women who are pregnant, consider referral to an adult congenital heart program for peripartum evaluation and management.

Pregnancy is generally a time of increased coagulation, but consider a hematology referral if the pregnant woman has a history of bleeding abnormalities and/or has not undergone previous screening for coagulopathy.

## Therapies Under Investigation

The MEK inhibitor trametinib was given under compassionate use to two infants with pathogenic variants in *RIT1* and progressive, congenital hypertrophic cardiomyopathy. Trametinib is a highly selective reversible allosteric inhibitor of MEK1/2 activity. In both cases, there was reversal of progressive myocardial hypertrophy and valvar obstruction along with a catch-up pattern of somatic growth [Andelfinger et al 2019].

Dori et al [2020] reported an individual age 14 years with *SOS1*-related NS who had resolution of mesenteric and retroperitoneal lymphangiectasia and chylothorax after treatment with trametinib, with complete remodeling of the lymphatic system.

Andrew Dauber, MD, Children's National Research Institute, is enrolling children with genetic causes of short stature, including Noonan syndrome, for a vosoritide treatment trial. Vosoritide is a selective NPR-B agonist that targets the growth plate. See [Clinical Trials](#).

Search [ClinicalTrials.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.

## 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 (NS) caused by pathogenic variants in *BRAF*, *KRAS*, *MAP2K1*, *MRAS*, *NRAS*, *PTPN11*, *RAF1*, *RASA2*, *RIT1*, *RRAS2*, *SOS1*, or *SOS2* is inherited in an autosomal dominant manner.

NS caused by pathogenic variants in *LZTR1* can be inherited in an autosomal dominant or autosomal recessive manner.

## Autosomal Dominant Inheritance – Risk to Family Members

### Parents of a proband

- 30%-75% of individuals diagnosed with NS have an affected parent. (Note: Because NS 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 NS may have the disorder as the result of a *de novo* pathogenic variant in an NS-related gene.
- In simplex cases (i.e., those with no known family history), paternal origin of the *de novo* pathogenic variant has been found universally to date [Yoon et al 2013]. In this cohort, advanced paternal age was observed along with a significant sex-ratio bias favoring transmission to males, a finding that is thus far unexplained.
- If the proband is the only family member known to have NS, recommended evaluations of both parents include the following:
  - A thorough physical examination with particular attention to the features of NS; echo- and electrocardiography; coagulation screening; and examination of photographs of the face at all ages for characteristic features of NS
  - Molecular genetic testing if the NS-causing pathogenic variant in the proband is known
- If the proband has an NS-causing 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 in the germ cells only.
- The family history of some individuals diagnosed with NS 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 a proband depends on the clinical/genetic status of the proband's parents:

- If a parent 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 the proband.
- If the parents are clinically unaffected and the proband has an NS-causing pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that

of the general population because of the possibility of parental germline mosaicism (germline mosaicism for the *PTPN11* c.922A>G pathogenic variant has been reported [Yoon et al 2013]).

**Offspring of a proband.** Each child of an individual with NS has a 50% chance of inheriting the NS-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, the parent's family members may be at risk.

## Autosomal Recessive Inheritance – Risk to Family Members

### Parents of a proband

- The parents of an affected child are presumed to be heterozygous for one *LZTR1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *LZTR1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes may be asymptomatic [Johnston et al 2018] or may have mild features of NS [Jenkins et al 2020].

### Sibs of a proband

- If both parents are known to be heterozygous for an *LZTR1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting two pathogenic variants and being affected, a 50% chance of inheriting one *LZTR1* pathogenic variant and being heterozygous, and a 25% chance of inheriting neither familial pathogenic variant.
- Heterozygotes may be asymptomatic [Johnston et al 2018] or may have mild features of NS [Jenkins et al 2020].

**Offspring of a proband.** The offspring of an individual with NS are obligate heterozygotes for a pathogenic variant in *LZTR1*.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being heterozygous for an *LZTR1* pathogenic variant.

### Heterozygote Detection

Heterozygote detection for at-risk relatives requires prior identification of the *LZTR1* pathogenic variants in the family.

## Related Genetic Counseling Issues

### 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 or at risk.

**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). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

### High a priori-risk pregnancy

- **Molecular genetic testing.** Once the NS-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.
- **Ultrasound examination.** For a pregnancy at 50% risk, high-resolution ultrasound examination is also possible. Prenatal features are nonspecific but may include polyhydramnios, hydronephrosis, pleural effusion, edema, cardiac defects, distended jugular lymphatic sacs, cystic hygroma, and increased nuchal translucency [Myers et al 2014]. Cystic hygroma may be accompanied by scalp edema, polyhydramnios, pleural and pericardial effusions, ascites, and/or frank hydrops fetalis. The presence of these findings should suggest the diagnosis of NS. In addition, a search for a cardiac defect should be made; congenital heart disease is diagnosed prenatally in about 20% of cases [Myers et al 2014]. Treatment of these pregnancy complications is the same as that in the general population.

**Low a priori-risk pregnancy** (i.e., a fetus at no known increased risk of NS). Although the ultrasonographic findings described suggest the diagnosis of NS in high-risk pregnancies, they are nonspecific and may be associated with cardiovascular defects or other chromosome and non-chromosome syndromes. In a retrospective analysis of 309 pregnancies with isolated increased nuchal translucency (>99%ile) and no other reported ultrasound findings, four pregnancies were subsequently diagnosed with NS [Pauta et al 2022]. Of 44 pregnancies with nonimmune hydrops fetalis enrolled in the Hydrops-Yielding Diagnostic Results of Prenatal Sequencing (HYDROPS) study, four were diagnosed with NS by trio exome analysis [Al-Kouatly et al 2021].

## 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](#).*

- **New England Regional Genetics Network**  
**Phone:** 603-862-4320  
**Email:** [info.negenetics@unh.edu](mailto:info.negenetics@unh.edu)  
[Noonan Syndrome](#)
- **MedlinePlus**  
[Noonan syndrome](#)
- **Noonan Syndrome Foundation**  
**Email:** [info@teamnoonan.org](mailto:info@teamnoonan.org)  
[www.teamnoonan.org](http://www.teamnoonan.org)
- **RASopathies Network**  
**Email:** [info@rasopathiesnet.org](mailto:info@rasopathiesnet.org)  
[www.rasopathiesnet.org](http://www.rasopathiesnet.org)
- **Human Growth Foundation**  
[www.hgfound.org](http://www.hgfound.org)

- **MAGIC Foundation**  
**Phone:** 800-362-4423  
**Email:** [contactus@magicfoundation.org](mailto:contactus@magicfoundation.org)  
[www.magicfoundation.org](http://www.magicfoundation.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: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>BRAF</i>	7q34	Serine/threonine-protein kinase B-raf	BRAF database NSEuroNet database - BRAF	BRAF	BRAF
<i>KRAS</i>	12p12.1	GTPase KRas	KRAS database NSEuroNet database - KRAS	KRAS	KRAS
<i>LZTR1</i>	22q11.21	Leucine-zipper-like transcriptional regulator 1	LZTR1 @ LOVD	LZTR1	LZTR1
<i>MAP2K1</i>	15q22.31	Dual specificity mitogen-activated protein kinase kinase 1	MAP2K1 @ LOVD NSEuroNet database - MAP2K1	MAP2K1	MAP2K1
<i>MRAS</i>	3q22.3	Ras-related protein M-Ras		MRAS	MRAS
<i>NRAS</i>	1p13.2	GTPase NRas	NRAS database NRASbase: Mutation registry for Autoimmune lymphoproliferative syndrome type IV NSEuroNet database - NRAS	NRAS	NRAS
<i>PTPN11</i>	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
<i>RAF1</i>	3p25.2	RAF proto-oncogene serine/threonine-protein kinase	NSEuroNet database - RAF1	RAF1	RAF1
<i>RASA2</i>	3q23	Ras GTPase-activating protein 2		RASA2	RASA2
<i>RIT1</i>	1q22	GTP-binding protein Rit1	NSEuroNet database - RIT1	RIT1	RIT1
<i>RRAS2</i>	11p15.2	Ras-related protein R-Ras2	RRAS2 database	RRAS2	RRAS2
<i>SOS1</i>	2p22.1	Son of sevenless homolog 1	SOS1 database NSEuroNet database - SOS1	SOS1	SOS1
<i>SOS2</i>	14q21.3	Son of sevenless homolog 2		SOS2	SOS2

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 ([View All in OMIM](#))

163950	NOONAN SYNDROME 1; NS1
164757	B-RAF PROTOONCOGENE, SERINE/THREONINE KINASE; BRAF
164760	RAF1 PROTOONCOGENE, SERINE/THREONINE KINASE; RAF1
164790	NRAS PROTOONCOGENE, GTPase; NRAS
176872	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1; MAP2K1
176876	PROTEIN-TYROSINE PHOSPHATASE, NONRECEPTOR-TYPE, 11; PTPN11
182530	SOS RAS/RAC GUANINE NUCLEOTIDE EXCHANGE FACTOR 1; SOS1
190070	KRAS PROTOONCOGENE, GTPase; KRAS
600098	RELATED RAS VIRAL ONCOGENE HOMOLOG 2; RRAS2
600574	LEUCINE ZIPPER-LIKE TRANSCRIPTIONAL REGULATOR 1; LZTR1
601247	SOS RAS/RAC GUANINE NUCLEOTIDE EXCHANGE FACTOR 2; SOS2
601589	RAS p21 PROTEIN ACTIVATOR 2; RASA2
605275	NOONAN SYNDROME 2; NS2
608435	MUSCLE RAS VIRAL ONCOGENE HOMOLOG; MRAS
609591	RIC-LIKE PROTEIN WITHOUT CAAX MOTIF 1; RIT1
609942	NOONAN SYNDROME 3; NS3
610733	NOONAN SYNDROME 4; NS4
611553	NOONAN SYNDROME 5; NS5
613224	NOONAN SYNDROME 6; NS6
613706	NOONAN SYNDROME 7; NS7
615355	NOONAN SYNDROME 8; NS8
616559	NOONAN SYNDROME 9; NS9
616564	NOONAN SYNDROME 10; NS10
618499	NOONAN SYNDROME 11; NS11
618624	NOONAN SYNDROME 12; NS12

## Molecular Pathogenesis

The genes implicated in Noonan syndrome are part of or interact with the Ras/MAPK pathway. This pathway is a widely important signal transduction pathway. Growth factors, cytokines, hormones, and other extracellular ligands stimulate cell differentiation, proliferation, metabolism, and survival. Adaptor proteins are recruited and form a complex that converts inactive, GDP-bound RAS to its active GTP-bound form. This leads to downstream activation of the RAF-MEK-ERK pathway via sequential phosphorylation, culminating in activated ERK entering the nucleus and altering gene transcription. Noonan syndrome pathogenic variants usually enhance signal flow through this pathway [Roberts et al 2013].

**Table 9.** Noonan Syndrome: Mechanism of Disease Causation

Gene <sup>1</sup>	Mechanism	Comment/Reference
<i>BRAF</i>	Gain of function	Sarkozy et al [2009]
<i>KRAS</i>		

Table 9. continued from previous page.

Gene <sup>1</sup>	Mechanism	Comment/Reference
<i>LZTR1</i>	Gain of function	For heterozygous pathogenic variants that lead to autosomal dominant <i>LZTR1</i> -related Noonan syndrome [Motta et al 2019]
	Loss of function	Recessive variants typically influence protein synthesis/stability or subcellular localization [Motta et al 2019].
<i>MAP2K1</i>	Gain of function	Cirstea et al [2010], Runtuwene et al [2011]
<i>MRAS</i>		Higgins et al [2017], Motta et al [2020]
<i>NRAS</i>		
<i>PTPN11</i>		
<i>RAF1</i>		Pandit et al [2007]
<i>RASA2</i>		Chen et al [2014b]
<i>RIT1</i>		Aoki et al [2013]
<i>RRAS</i>		Chen et al [2014b], Flex et al [2014]
<i>SOS1</i>		Roberts et al [2007]
<i>SOS2</i>		Chen et al [2014b], Yamamoto et al [2015], Lissewski et al [2021]

1. Genes from Table 1 in alphabetic order

Table 10. Noonan Syndrome: Notable Pathogenic Variants by Gene

Gene <sup>1</sup>	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
<i>PTPN11</i>	NM_002834.3 NP_002825.3	c.179_181delGTG	p.Gly60del	Yoshida et al [2004]
		c.181_183delGAT	p.Asp61del	Lee et al [2005b]
	NM_002834.5 NP_002825.3	c.172A>G	p.Asn58Asp	NS & JMML <sup>2</sup>
		c.174C>G	p.Asn58Lys	
		c.182A>G	p.Asp61Gly	
		c.184T>G	p.Tyr62Asp	
		c.188A>G	p.Tyr63Cys	
		c.214G>A	p.Ala72Thr	
		c.214G>T	p.Ala72Ser	
		c.215C>G	p.Ala72Gly	
		c.218C>T	p.Thr73Ile	
		c.227A>T	p.Glu76Val	
		c.228G>T	p.Glu76Asp	
		c.236A>G	p.Gln79Arg	
		c.417G>C	p.Glu139Asp	
		c.417G>T	p.Glu139Asp	
		c.794G>A	p.Arg265Gln	
		c.836A>C	p.Tyr279Ser	
		c.853T>C	p.Phe285Leu	
c.922A>G <sup>3</sup>	p.Asn308Asp <sup>3</sup>			

Table 10. continued from previous page.

Gene <sup>1</sup>	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
		c.923A>G	p.Asn308Ser	
		c.1403C>T	p.Thr468Met	
		c.1504T>G	p.Ser502Ala	
		c.1504T>A	p.Ser502Thr	
		c.1507G>A	p.Gly503Arg	
		c.1507G>C	p.Gly503Arg	
		c.1510A>G	p.Met504Val	
<i>RAF1</i>	<a href="#">NM_002880.4</a> <a href="#">NP_002871.1</a>	c.770C>T	p.Ser257Leu	2 persons w/infantile fatal pulmonary hypertension <sup>4</sup>

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

JMML = juvenile myelomonocytic leukemia; NS = Noonan syndrome

1. Genes from Table 1 in alphabetic order

2. Curated from Clinvar; included variants are those classified as pathogenic or likely pathogenic with both Noonan syndrome and JMML as listed conditions for the variant [Grant et al 2018].

3. Less likely to be associated with learning issues [Jongmans et al 2004]

4. Hopper et al [2015]

## Cancer and Benign Tumors

Sporadic tumors (including leukemia and solid tumors) occurring as single tumors in the absence of any other findings of Noonan syndrome may contain a somatic nucleotide variant in *PTPN11*, *KRAS*, *LZTR1*, *MRAS*, *NRAS*, *BRAF*, or *MAP2K1* that is not present in the germline; thus, predisposition to these tumors is not heritable. See [Catalogue of Somatic Mutations in Cancer](#).

- Leukemia and solid tumors. Juvenile myelomonocytic leukemia (JMML) accounts for one third of myelodysplastic syndrome (MDS) and about 2% of leukemia. Pathogenic variants in *NRAS*, *KRAS*, and *NF1* have been shown to deregulate the RAS-MAPK pathway leading to JMML in about 40% of affected individuals. Somatic pathogenic variants in exons 3 and 13 of *PTPN11* have been demonstrated in 34% of individuals with JMML in one cohort [Tartaglia et al 2003, Tartaglia et al 2004, Hasle 2009].
- Pathogenic variants in *PTPN11* 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-MD, can be caused by *PTPN11* pathogenic variants. These pathogenic variants cause a gain of function in tyrosine-protein phosphatase non-receptor type II (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 individuals with B-cell precursor ALL, but not among children with T-lineage ALL [Tartaglia et al 2004]. Additionally, Bentires-Alj et al [2004] described SHP-2-activating *PTPN11* pathogenic variants in solid tumors including breast, lung, and gastric neoplasms and neuroblastoma.
- Somatic *RAF1* nucleotide variants have only rarely been found in cancer; most of these cancer-causing variants do not cluster in the regions that are germline mutational hot spots in Noonan syndrome [Pandit et al 2007].

- *NRAS* variants are commonly observed in somatic cancer; they occur in regions different from germline *NRAS* variants that cause Noonan syndrome.
- *MAP2K1* somatic variants have been reported in ovarian cancer [Estep et al 2007] and lung cancer [Marks et al 2008].
- Somatic *SOS1* pathogenic variants have not been found in cancer.
- Recent studies have identified somatic *RIT1* pathogenic variants in lung adenocarcinoma and myeloproliferative or mixed myelodysplastic/myeloproliferative neoplasms [Berger et al 2014, Cancer Genome Atlas Research Network 2014].
- The somatic p.Gly248Arg pathogenic variant in *LZTR1* has been identified in melanoma, glioblastoma, and colorectal cancers (COSMIC database).

## Chapter Notes

### Author Notes

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### Author History

Judith E Allanson, MD; Children's Hospital of Eastern Ontario (2001-2021)

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### Revision History

- 17 February 2022 (aa) Revision: [encephalocraniocutaneous lipomatosis](#) added to Genetically Related Disorders
- 16 December 2021 (ma) Comprehensive update posted live
- 8 August 2019 (ma) Revision: pathogenic variants in *LZTR1* associated with autosomal dominant and autosomal recessive Noonan syndrome

- 25 February 2016 (ha) Comprehensive update posted live
- 4 August 2011 (me) Comprehensive update posted live
- 7 October 2008 (me) Comprehensive update posted live
- 6 September 2007 (cd) Revision: mutations in *RAF1* associated with Noonan syndrome
- 22 December 2006 (cd) Revision: *SOS1* mutations responsible for some cases of Noonan syndrome; clinical testing available
- 22 May 2006 (cd) Revision: prenatal testing for Noonan syndrome caused by *KRAS* mutations clinically available
- 16 May 2006 (cd) Revision: *KRAS* testing clinically available
- 1 May 2006 (ja) Revision: mutations in *KRAS* cause Noonan syndrome
- 9 March 2006 (me) Comprehensive update posted live
- 17 December 2003 (me) Comprehensive update posted live
- 15 November 2001 (me) Review posted live
- 2 August 2001 (ja) Original submission

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