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Noonan Syndrome

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Summary

Disease characteristics. Noonan syndrome (NS) is characterized by short stature; congenital heart defect; broad or webbed neck; unusual chest shape with superior pectus carinatum, inferior pectus excavatum, and apparently low-set nipples; developmental delay of variable degree; cryptorchidism; and characteristic facies. Varied coagulation defects and lymphatic dysplasias are frequently observed. 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 appear in infancy or childhood. Other structural defects frequently observed include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Length at birth is usually normal. Final adult height approaches the lower limit of normal. Mild mental retardation is seen in up to one-third of individuals. Ocular abnormalities, including strabismus, refractive errors, amblyopia, and nystagmus, occur in up to 95% of individuals.

Diagnosis/testing. Diagnosis of NS is made on clinical grounds, by observation of key features. Affected individuals have normal chromosome studies. *PTPN11*, *KRAS*, *SOS1*, and *RAF1* are the only genes known to be associated with Noonan syndrome. Molecular genetic testing identifies mutations in the *PTPN11* gene in 50% of affected individuals and is available on a clinical basis. Molecular genetic testing identifies mutations in the *RAF1* gene in 3%-17% of affected individuals and is available on a clinical basis. Molecular genetic testing identifies mutations in the *KRAS* gene in fewer than 5% of affected individuals and is available on a clinical basis. Molecular genetic testing identifies mutation in the *SOS1* gene in about 10% of individuals with Noonan syndrome and is available on a clinical basis.

Management. Treatment of cardiovascular anomalies in NS is generally the same as in the general population. Developmental disabilities are addressed by early intervention programs and individualized education strategies. The bleeding diathesis in NS can have a variety of causes and the specific treatment for serious bleeding may be guided by knowledge of a factor deficiency or platelet aggregation anomaly. Growth velocity increases with growth hormone (GH) treatment. Surveillance includes monitoring of anomalies found in any system, especially cardiovascular abnormalities.

Genetic counseling. NS is inherited in an autosomal dominant manner. Many affected individuals have *de novo* mutations; however, an affected parent is recognized in 30%-75% of families. The risk to the sibs of a proband depends upon 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 Noonan syndrome has a 50% chance of inheriting the mutation. Prenatal testing is available if the disease-causing allele has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Diagnosis of Noonan syndrome (NS) is made on clinical grounds, by observation of key features. Despite a lack of defined diagnostic criteria, the cardinal features of NS are well delineated [Allanson 1987]:

- Short stature
- Congenital heart defect
- Broad or webbed neck
- Unusual chest shape with superior pectus carinatum, inferior pectus excavatum
- Apparently low-set nipples
- Developmental delay of variable degree
- Cryptorchidism in males
- Characteristic facies. The facial appearance of NS shows considerable change with age, being most striking in the newborn period and middle childhood, and most subtle in the adult [Allanson et al 1985]. Key features found irrespective of age include low-set, posteriorly rotated ears with fleshy helices; vivid blue or blue-green irides; and eyes that are often wide-spaced, with epicanthal folds and thick or droopy eyelids.
- Others:
  - Varied coagulation defects. Coagulation screens such as prothrombin time, activated partial thromboplastin time, platelet count, and bleeding time often show abnormalities. Specific testing should identify the particular coagulation defect. Laboratory findings include von Willebrand disease, thrombocytopenia, varied coagulation factor defects (factors V, VIII, XI, XII, protein C), and platelet dysfunction.
  - Lymphatic dysplasias

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Four genes are known to be associated with Noonan syndrome:

- ***PTPN11***mutations are observed in about 50% of individuals with Noonan syndrome.
- ***KRAS***mutations are observed in fewer than 5% of individuals with Noonan syndrome [Schubbert et al 2006].
- ***SOS1***mutations are identified in about 13% of individuals with Noonan syndrome. About 16%-20% of individuals with a clinical diagnosis of Noonan syndrome who do not have an identified *PTPN11* mutation are found to have an *SOS1* mutation [Roberts et al 2006; Tartaglia, Pennacchio et al 2006].
- ***RAF1***mutations are observed in 3%-17% of individuals with Noonan syndrome [Pandit et al 2007, Razzaque et al 2007].

Other loci. Absence of linkage to 12q (the location of the *PTPN11* gene) in some families from the original report suggested locus heterogeneity. It is unclear whether any of these families may have had *KRAS* mutations. It is presumed that additional loci may be identified.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

Sequence analysis

- ***PTPN11.*** Sequence analysis of all exons of *PTPN11* detects missense mutations in about 50% of individuals tested [Tartaglia et al 2001, Tartaglia et al 2002, Jongmans et al 2004].
- ***KRAS.*** Isolation of genomic DNA and direct, bidirectional sequencing of all exons of *KRAS* detects mutations in fewer than 5% of individuals with Noonan syndrome [Schubbert et al 2006].
- ***SOS1.*** Sequence analysis of exons 1-23 detects all reported missense mutations [Roberts et al 2006].
- ***RAF1.*** Sequence analysis of exons 1-17 detects all reported missense mutations [Pandit et al 2007, Razzaque et al 2007].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Noonan Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*PTPN11* mutations	50%	Clinical Testing
FISH (genomic microarray) analysis	*PTPN11* deletions	<1% [2]	
Sequence analysis	*KRAS* mutations	<5%	Clinical Testing
Sequence analysis	*SOS1* mutations	10%-13%	Clinical Testing
Sequence analysis	*RAF1* mutations	3%-17%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene and test method
2. The only reported deletion in *PTPN11* was a 3-bp deletion in exon 3 in a female infant with severe features of Noonan syndrome, including hydrops fetalis and juvenile myelomonocytic leukemia [Yoshida et al 2004]; thus, the use of FISH (genomic microarray analysis) seems unlikely to detect/diagnose Noonan syndrome.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

1. *PTPN11* sequence analysis of exons 3, 8, 9, and 13
2. If no mutation is identified, sequence analysis of *SOS1* exons 1-23
3. If no mutation identified in *PTPN11* or *SOS1*, sequence analysis of remaining 11 exons of *PTPN11* and of *RAF1* exons 7, 14, and 17
4. If no mutation is identified, sequence analysis of remaining *RAF1* exons and exons 1-6 of *KRAS*

Genetically Related (Allelic) Disorders

PTPN11

- **LEOPARD syndrome** (**l**entigines, **E**CG abnormalities, **o**cular hypertelorism, **p**ulmonary stenosis, **a**bnormalities of genitalia, **r**etardation of growth, **d**eafness) is an autosomal dominant condition with variable expression. It shows significant overlap with Noonan syndrome, in which pigmentary differences such as nevi (25%), café au lait patches (10%), and lentigines (3%) are reported. Recently, mutations in exons 7 and 12 of *PTPN11* have been reported in LEOPARD syndrome [Digilio et al 2002, Legius et al 2002]. These reports suggest that Noonan syndrome and LEOPARD syndrome are allelic conditions, or that a particular genotype-phenotype correlation exists with certain mutations in *PTPN11* leading to the pigmentary changes observed. It is interesting to note that some families with LEOPARD syndrome show no *PTPN11* mutation or linkage to chromosome 12q; thus this condition, like Noonan syndrome, is genetically heterogeneous.

- **Leukemia and solid tumors.** Juvenile myelomonocytic leukemia (JMML) constitutes one-third of childhood cases of myelodysplastic syndrome (MDS) and about 2% of leukemia. Mutations in *NRAS*, *KRAS2*, and *NF1* have been shown to deregulate the RAS/MAPK pathway leading to JMML in about 40% of cases. Recently, somatic mutations in exons 3 and 13 of *PTPN11* have been demonstrated in 34% of a cohort of individuals with JMML [Tartaglia, Niemeyer et al 2003]. Mutations 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-MD, has been shown to be caused by *PTPN11* mutations. All of these mutations cause 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.

  More recently, the spectrum of leukemogenesis associated with *PTPN11* mutations has been extended to include childhood acute lymphoblastic leukemia (ALL). Mutations were observed in 8% of B-cell precursor ALL cases, but not among children with T-lineage ALL [Tartaglia, Martinelli et al 2004]. Additionally, Bentires-Alj and colleagues (2004) have described SHP-2-activating *PTPN11* mutations in solid tumors such as breast, lung, and gastric neoplasms, and neuroblastoma.

- **Noonan-like/multiple giant-cell lesion syndrome** is said to be characterized by some cardinal features of Noonan syndrome in association with giant cell lesions of bone and soft tissues (cherubism). *PTPN11* mutations have been described in both familial and simplex (i.e., a single occurrence in a family) cases.

  Sarkozy et al (2004) reported a girl whose early phenotype was typical of Noonan syndrome, but who, over time, developed the hearing loss and lentigines characteristic of LEOPARD syndrome. Thus, Noonan-like/multiple giant-cell lesion syndrome may be too limited and inaccurate a term; a variety of *PTPN11* mutations, some of them programming the phenotype of Noonan syndrome and others the phenotype of LEOPARD syndrome, may also program the development of giant cell lesions.

  One family with Noonan-like/multiple giant-cell lesion syndrome has a *PTPN11* mutation that has been 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.

KRAS. Mutations in *KRAS* are rarely associated with cardio-facial-cutaneous syndrome (see Differential Diagnosis).

SOS1. A frameshift mutation in *SOS1* has been reported in a single four-generation family with hereditary gingival fibromatosis [Hart et al 2002]. This condition is a rare form of gingival overgrowth characterized by benign slowly progressive fibrous enlargement of the maxillary and mandibular keratinized gingiva. *SOS1* mutations have not been reported in other families with this disorder.

RAF1. LEOPARD syndrome is also caused by gain-of-function mutations in *RAF1*. About one-third of the families without *PTPN11* mutations will have a mutation in *RAF1*.

RAF1 missense mutations are observed rarely in somatic cancer (see Pandit et al 2007, references).

Clinical Description

Natural History

Females and males are equally likely to be affected.

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

- **In the neonate,** tall forehead, hypertelorism with downslanting palpebral fissures, low-set, posteriorly rotated ears with a thickened helix, a deeply grooved philtrum with high, wide peaks to the vermillion 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 fissures, hypertelorism, and thickened or ptotic lids. The nose has a depressed root, wide base, and bulbous tip.
- **In childhood,** facial appearance is often lacking in affect or expression, resembling an individual with a myopathy.
- **By adolescence,** facial shape is an inverted triangle, wide at the forehead, 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.

Cardiovascular. Significant bias in the frequency of congenital heart disease may exist because many clinicians require the presence of cardiac anomalies for diagnosis of NS. The frequency of congenital heart disease is estimated to be between 50% and 80% [Allanson 1987, Patton 1994]. An electrocardiographic abnormality is documented in about 90% of individuals with NS [Sharland, Burch et al 1992], and may be present without concomitant structural defects.

- **Pulmonary valve** stenosis, often with dysplasia, is the most common anomaly in NS, found in 20%-50% of affected individuals [Allanson 1987; Sharland, Burch et al 1992; Ishizawa et al 1996]; it may be isolated or associated with other cardiovascular defects.
- **Hypertrophic cardiomyopathy** is found in 20% to 30% of affected individuals [Allanson 1987; Sharland, Burch et al 1992; Patton 1994; Ishizawa et al 1996]. It may present at birth, in infancy, or in childhood.
- **Other structural defects** frequently observed include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot [Allanson 1987,

Ishizawa et al 1996]. Coarctation of the aorta is more common than previously thought [Digilio et al 1998].

Growth. Birth weight is usually normal, although edema may cause a transient increase [Allanson 1987, Patton 1994]. Infants with NS frequently have feeding difficulties [Sharland, Burch et al 1992]. 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. Mean height follows the third centile until puberty, when below-average growth velocity and attenuated adolescent growth spurt tend to occur. As bone maturity is usually delayed, prolonged growth potential into the 20s is possible [Allanson 1987; Sharland, Burch et al 1992]. Final adult height approaches the lower limit of normal: 161 cm in males and 150-152 cm in females [Witt et al 1986]. Growth curves have been developed from these cross-sectional retrospective data [Witt et al 1986]. A recent 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 [Noonan et al 2003].

Decreased IGF1 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 axis, in some affected persons. Mild growth hormone resistance related to a postreceptor signalling defect, which may be partially compensated for by elevated growth hormone secretion, is reported in individuals with Noonan syndrome and a *PTPN11* mutation [Binder et al 2005].

Psychomotor development. Early developmental milestones may be delayed, likely as a result, in part, of the combination of joint hyperextensibility and hypotonia.

Most school-age children perform well in a normal educational setting, but 25% have learning disabilities [Lee et al 2005] and 10% to 15% require special education [Sharland, Burch et al 1992; van der Burgt et al 1999]. Mild mental retardation is observed in up to one-third of individuals [Mendez & Opitz 1985, Allanson 1987]. Verbal performance is frequently lower than nonverbal performance. 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 intervention therapy. Language delay may be related to hearing loss, perceptual motor disabilities, or articulation deficiencies [Allanson 1987].

No particular syndrome of behavioral disability or psychopathology is observed and self-esteem is comparable to age-related peers [Lee et al 2005].

Ocular. Ocular abnormalities occur in up to 95% of individuals. They include strabismus, refractive errors, amblyopia, and nystagmus. Anterior segment and fundus changes are less frequent [Lee et al 1992; Sharland, Burch et al 1992].

Bleeding diathesis. Most persons with NS have a history of abnormal bleeding or bruising [Sharland, Patton et al 1992]. About one-third of all individuals with NS have one or more coagulation defects [Witt et al 1988]. The coagulopathy may manifest as severe surgical hemorrhage, clinically mild bruising, or laboratory abnormalities with no clinical consequences.

Lymphatic. Varied lymphatic abnormalities are described in individuals with NS [Mendez & Opitz 1985, Witt et al 1987]. 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.

Prenatal features suggestive of Noonan syndrome, likely of a lymphatic nature, include transient or persistent cystic hygroma, polyhydramnios and, rarely, hydrops fetalis [Gandhi et al 2004, Yoshida et al 2004, Joo et al 2005].

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 [George et al 1993].

Male pubertal development and subsequent fertility may be normal, delayed, or inadequate [Mendez & Opitz 1985; Sharland, Burch et al 1992]. Deficient spermatogenesis may be related to cryptorchidism, which is noted in 60% to 80% of males [Patton 1994, personal data].

Puberty may be delayed in females, with a mean age at menarche of 14.6±1.17 years [Sharland, Burch et al 1992]. Normal fertility is the rule.

Dermatologic. Skin differences, particularly follicular keratosis over extensor surfaces and face, are relatively common and may occasionally be as severe as those found in cardio-facio-cutaneous syndrome (see Differential Diagnosis) [Pierini & Pierini 1979; Sharland, Burch et al 1992].

Scalp hair may be curly, thick, and wooly, or sparse and poor growing with easy breakage.

Café-au-lait spots and lentigines are described in NS more frequently than in the general population [Allanson 1987; Sharland, Burch et al 1992] (see LEOPARD syndrome discussion in Allelic Disorders).

Other

- **Arnold-Chiari I malformation** has been reported several times [Holder-Espinasse & Winter 2003] and the author is aware of at least three other individuals with this anomaly [Author, personal observation].
- **Hepatosplenomegaly** is frequent; the cause is unknown [Sharland, Burch et al 1992] but may be related to subclinical myelodysplasia.
- **Juvenile myelomonocytic leukemia (JMML)** is often caused by somatic mutations in *PTPN11* (see Genetically Related Disorders) [Tartaglia, Niemeyer et al 2003; Tartaglia, Martinelli et al 2004]. Additionally, individuals with Noonan syndrome and a germline mutation in *PTPN11* have a predisposition to this unusual childhood leukemia. In general, JMML in Noonan syndrome runs a more benign course, a finding that may be related to the higher gain-of-function effect of somatic mutations leading to leukemogenesis [Tartaglia, Martinelli et al 2006].
- **Myeloproliferative disorders,** either transient or more fulminant, can also occur in infants with Noonan syndrome [Kratz et al 2005].

Genotype-Phenotype Correlations

PTPN11. Analysis of a large cohort of individuals with Noonan syndrome [Tartaglia et al 2001, Tartaglia et al 2002] has suggested that *PTPN11* mutations are more likely to be found when pulmonary stenosis is present, whereas hypertrophic cardiomyopathy is less prevalent among individuals with Noonan syndrome caused by *PTPN11* abnormalities.

Additional cohort analyses have linked *PTPN11* mutations to short stature, pectus deformity, easy bruising, characteristic facial appearance [Zenker et al 2004], and cryptorchidism [Jongmans et al 2004].

The likelihood of developmental delay does not differ in mutation-positive and -negative groups, although individuals with the N308D mutation are said to be more likely to receive normal education [Jongmans et al 2004].

Mutations at codons 61, 71, 72, and 76 are significantly associated with leukemogenesis, and identify a subgroup of individuals with Noonan syndrome at risk for JMML [Niihori et al 2005].

Knowledge of the postreceptor signalling defect causing mild growth hormone resistance in individuals with Noonan syndrome and a *PTPN11* mutation [Binder et al 2005] might suggest reduced efficacy of growth hormone treatment in mutation-positive individuals. One published study supports this hypothesis [Ferreira et al 2005].

KRAS. No data are currently available as too few cases have been reported.

SOS1. In a study of 22 individuals with Noonan syndrome who were found to have *SOS1* mutations, Tartaglia, Pennacchio et al (2006) concluded that the phenotype in this cohort fell within the spectrum of Noonan syndrome but emphasized the more frequent occurrence of ectodermal abnormalities and a greater likelihood of normal development and stature. In a companion paper, Roberts et al (2006) reported 14 individuals with Noonan syndrome who were found to have *SOS1* mutations. This cohort did not differ in development and stature from other individuals with Noonan syndrome. Cardiac septal defects were found more frequently than in individuals with Noonan syndrome and mutations in *PTPN11*. The study did not make specific mention of ectodermal findings.

RAF1. The studies reported to date emphasize a striking correlation with hypertrophic cardiomyopathy, with 95% of affected individuals showing this feature, in comparison with the usual prevalence of 18%. This suggests that pathologic cardiomyocyte hypertrophy occurs because of increased Ras signaling.

Penetrance

Penetrance of Noonan syndrome is difficult to determine because of ascertainment bias and variable expressivity with frequent subtlety of features. Many affected adults are only diagnosed after the birth of a more obviously affected infant.

Anticipation

Anticipation has not been described in Noonan syndrome.

Nomenclature

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

Ullrich, in 1949, reported a series of 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

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

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Turner syndrome, found only in females, is differentiated from NS by demonstration of a sex chromosome abnormality on cytogenetic studies in individuals with Turner syndrome. The phenotype of Turner syndrome is actually quite different, 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.

The **Watson syndrome** phenotype also overlaps with that of neurofibromatosis type 1 and the two are now known to be allelic. Like Noonan syndrome, features of Watson syndrome include short stature, pulmonary valve stenosis, variable intellectual development, and skin pigment changes, such as café au lait patches [Allanson et al 1991].

Cardiofaciocutaneous (CFC) syndrome and Noonan syndrome have the greatest overlap in features. CFC syndrome has similar cardiac and lymphatic findings [Noonan 2001]. In CFC syndrome, mental deficiency is usually more severe, with a higher likelihood of structural central nervous system anomalies; skin pathology is more florid; gastrointestinal problems are more severe and long lasting; and bleeding diathesis is rare. Facial appearance tends to be more coarse, dolichocephaly and absent eyebrows are more frequently seen, and blue eyes are less commonly seen. CFC syndrome occurs sporadically. *PTPN11* mutations were not found in a cohort of 28 affected individuals [Ion et al 2002]. Recently, Rodriguez-Viciana et al (2006) studied 23 individuals with CFC syndrome and demonstrated mutations in three genes in the MAPK pathway. In the majority (18 of 23) a *BRAF* mutation was found, while more rarely a mutation in *MEK1* or *MEK2* was found.

Costello syndrome shares features with both NS and CFC [Noonan, personal observations]. Two series of individuals with Costello syndrome have been studied molecularly and no *PTPN11* mutation has been identified [Tartaglia, Cotter et al 2003; Troger et al 2003]. Recently, germline mutations occurring exclusively in exon 2 of the *HRAS* proto-oncogene have been shown to cause Costello syndrome [Aoki et al 2005].

Other. NS should be distinguished from other syndromes with developmental delay, short stature, congenital heart defects, and distinctive facies, especially Williams syndrome, Aarskog syndrome, and in utero exposure to alcohol or primidone.

Management

Evaluations Following Initial Diagnosis

At the time of initial diagnosis of Noonan syndrome (NS), a series of evaluations is recommended to appropriately guide medical management:

- Complete physical and neurologic examination
- Plotting of growth parameters on NS growth charts [Witt et al 1986]
- Cardiologic evaluation with echocardiography and electrocardiography
- Ophthalmologic evaluation

- Hearing evaluation
- Coagulation screen
- Renal ultrasound examination with urinalysis if the urinary tract is anomalous
- Clinical and radiographic assessment of spine and rib cage
- Brain and cervical spine MRI, if neurologic symptoms are present
- Multidisciplinary developmental evaluation
- Genetics consultation

Treatment of Manifestations

Treatment of cardiovascular anomalies is generally the same as in the general population.

Any developmental disability should be addressed by early intervention programs and individualized education strategies.

The bleeding diathesis in Noonan syndrome can have a variety of causes. Specific treatment for serious bleeding may be guided by knowledge of a factor deficiency or platelet aggregation anomaly. Factor VIIa has been successfully used to control bleeding caused by hemophilia, von Willebrand disease, thrombocytopenia, and thrombasthenia. It has also been used in an infant with Noonan syndrome whose platelet count and prothrombin and partial thromboplastin times were normal to control severe post-operative blood loss resulting from gastritis [Tofil et al 2005].

Results of growth hormone (GH) treatment studies from the US, UK and Japan [Ogawa et al 2004] and aggregated European data are expected shortly. Data show that growth velocity increases with GH treatment, at least over the first three years, with maximum gain in the first year or two. Only a small number of study participants have reached final adult height. In some individuals, bone age appeared to advance disproportionately, but this phenomenon is not unique to treatment of Noonan syndrome. No abnormal impact on ventricular wall size was noted. As a result of these studies, enthusiasm for GH treatment is considerable in the US while in other countries such treatment is not initiated without a documented deficiency of GH (see review of treatment in Allanson 2005). Dutch data [K Noordam, personal communication] suggest a 1.3 standard deviation gain in final height (7 cm), leading endocrinologists in Holland to reserve use of growth hormone for affected individuals whose expected final height would be less than the mean for Noonan syndrome.

Surveillance

If anomalies are found in any system, periodic follow-up should be planned and lifelong monitoring may be necessary, especially of cardiovascular abnormalities.

Agents/Circumstances to Avoid

Aspirin therapy should be avoided.

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Noonan syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many affected individuals have *de novo* mutations; however, an affected parent is recognized in 30%-75% of families [Mendez & Opitz 1985, Allanson 1987]. In simplex cases (i.e., those with no known family history), paternal origin of the mutation has been found universally to date [Tartaglia, Cordeddu et al 2004]. In this cohort, advanced paternal age was observed along with a significant sex-ratio bias favoring transmission to males, which is thus far unexplained.
- It is appropriate to evaluate both parents, including a thorough physical examination with particular attention to the features of NS; echo- and electrocardiography; coagulation screening; and review of photographs of the face at all ages, searching for characteristic features of NS. Molecular genetic testing of parents is available on a clinical basis if the proband has an identified disease-causing mutation.

Sibs of a proband

- The risk to the sibs of a proband depends upon the genetic status of the parents.
- If a parent is affected or has the disease-causing mutation that was identified in the proband, the risk to the sibs is 50%.

- When the parents are clinically unaffected and do not have the disease-causing mutation found in the proband, the risk to the sibs of a proband appears to be low (<1%). No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband. Each child of an individual with NS has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

High-risk pregnancy

- **Molecular genetic testing.** Prenatal diagnosis for pregnancies at increased risk for Noonan syndrome is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

  Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

- **Ultrasound examination.** For pregnancies at 50% risk, high-resolution ultrasound examination is also available. A common prenatal indicator of NS, caused by lymphatic dysfunction or abnormality, is a cystic hygroma, which 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, although a recent study has pointed out how infrequently such a defect will be detected prenatally [Menashe et al 2002].

Low-risk pregnancy. Although the ultrasonographic findings described above suggest the diagnosis of Noonan syndrome in high-risk pregnancies, they are nonspecific and may be associated with cardiovascular defects or other chromosomal and non-chromosomal syndromes.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Noonan Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
KRAS	12p12.1	GTPase KRas
PTPN11	12q24.1	Tyrosine-protein phosphatase non-receptor type 11
RAF1	3p25	RAF proto-oncogene serine/threonine-protein kinase
SOS1	2p22-p21	Son of sevenless homolog 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Noonan Syndrome

163950	NOONAN SYNDROME 1; NS1
164760	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1; RAF1
176876	PROTEIN-TYROSINE PHOSPHATASE, NONRECEPTOR-TYPE, 11; PTPN11
182530	SON OF SEVENLESS, DROSOPHILA, HOMOLOG 1; SOS1
190070	V-KI-RAS2 KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG; KRAS
609942	NOONAN SYNDROME 3
610733	NOONAN SYNDROME 4; NS4

Table C. Genomic Databases for Noonan Syndrome

Gene Symbol	Entrez Gene	HGMD
KRAS	3845 (MIM No. 190070)	
PTPN11	5781 (MIM No. 163950)	PTPN11
RAF1	5894 (MIM No. 164760)	RAF1
SOS1	6654 (MIM No. 182530)	SOS1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

PTPN11

Normal allelic variants: Tartaglia et al (2001) identified the *PTPN11* gene as causative of Noonan syndrome. The gene comprises 15 exons, with two tandemly arranged SRC-2 homology 2 (SH2) domains at the N terminus (N-SH2 and C-SH2), a single catalytic protein tyrosine phosphatase (PTP) domain, and a carbody tail with two TP sites and a proline-rich stretch. The SH2-PTP interaction maintains TP sites and a proline-rich stretch. The SH2-PTP interaction maintains the protein in an inactive state.

Pathologic allelic variants: Missense mutations in *PTPN11* were identified in 50% of individuals examined. Ninety-five percent of mutations alter residues at or close to the SH2-PTP interacting surfaces, which are involved in switching between active and inactive

conformations of the protein and cause catalytic activation and gain of function. Five percent of the mutations alter sensitivity to activation from binding partners. One 3-bp deletion has been described [Tartaglia et al 2002; Fragale et al 2004].

Normal gene product: *PTPN11* encodes tyrosine-protein phosphatase non-receptor type II (SHP-2), a widely expressed extra-cellular protein. The protein is a key molecule in the cellular response to growth factors, hormones, cytokines and cell adhesion molecules. It is required in several intracellular signal transduction pathways that control diverse developmental processes (including cardiac semilunar valvulogenesis and blood cell progenitor commitment and differentiation) and has a role in modulating cellular proliferation, differentiation, migration, and apoptosis [Tartaglia et al 2002, Fragale et al 2004].

Abnormal gene product: Activation of tyrosine-protein phosphatase non-receptor type II stimulates epidermal growth factor-mediated RAS/ERK/MAPK activation, increasing cell proliferation [Tartaglia et al 2002, Fragale et al 2004].

KRAS

Normal allelic variants: The gene has four exons spanning 45 kb. Alternative splicing results in two isoforms (4a and 4b) that differ at the C terminus. In 98% of transcripts, exon 4a is spliced out and only exon 4b is available for translation into protein. The effector or switch domains are part of exons 1 and 2, while binding to guanine nucleotide exchange factors occurs in exon 3.

Pathologic allelic variants: Somatic *KRAS* and *NRAS* mutations have been found in myeloid malignancies and other cancers. The association between abnormal Kras and Noonan syndrome is the first evidence of a role in embryonic development. These gain-of-function mutations confer similar biochemical and cellular phenotypes as Noonan syndrome-associated SHP-2 mutations.

Normal gene product: Ras proteins regulate cell fates by cycling between active guanosine triphosphate (GTP)-bound and inactive guanosine diphosphate (GDP)-bound conformations. They are key regulators of the RAS-RAF-MEK-ERK pathway, which is important for proliferation, growth and death of cells.

Abnormal gene product: The abnormal K-Ras protein induces hypersensitivity of primary hematopoietic progenitor cells to growth factors and deregulates signal transduction in a cell lineage-specific manner. Strong gain-of-function *KRAS* mutations may be incompatible with life.

SOS1

Normal allelic variants: Human *SOS1* comprises 23 exons and encodes a 150-kd multidomain protein. The gene contains a RAS-GEF (guanine nucleotide exchange factor) domain, a conserved histone-like fold, Dbl homology (DH) and plekstrin homology (PH) domains, a helical linker, a RAS exchange motif (REM) and a proline-rich region. The Dbl homology domain may act as a guanine nucleotide exchange factor (GEF) for the RAC family small G proteins (RAC-GEF). *SOS1* has two RAS binding sites: an effector site in the Cdc25 domain and an allosteric site formed by the REM and Cdc25 domains. RAS binding to the allosteric site enhances RAS-GEF activity. The DH-PH module controls RAS binding at this site and likely acts as an intramolecular inhibitor of RAS-GEF activity. The entire N terminus functions as an integrated unit to inhibit the REM-Cdc25 domain.

Pathologic allelic variants: Noonan syndrome-associatred *SOS1* missense mutations are hypermorphic. The vast majority are located in highly conserved sites. They cluster at codons encoding residues implicated in the maintenance of *SOS1* in its autoinhibited form. One such cluster is found in the PH domain and may disrupt the autoinhibited conformation by destabilizing the conformation of the DH domain. Another cluster resides in the helical linker between the DH and REM domains. A third cluster affects residues that mediate the interaction between the DH and Rem domains.

Normal gene product: SOS1 is a RAS-specific guanine nucleotide exchange factor (GEF). The protein is autoinhibited owing to complex regulatory intra- and intermolecular interactions. After receptor tyrosine kinase (RTK) stimulation, SOS1 is recruited to the plasma membrane, where it acquires a catalytically active conformation. It then, in turn, catalyses activation of the RAS-MAPK pathway by conversion of RAS-GDP to RAS-GTP.

Abnormal gene product: Noonan syndrome-associated *SOS1* mutations abrogate autoinhibition, increasing and prolonging RAS activation and downstream signaling through enhanced RAS-GEF activity. Somatic *SOS1* mutations have not been found in cancer.

RAF1

Normal allelic variants: Human *RAF1* comprises 17 exons. It has three conserved regions (CR). CR1, exons 2-5, contains a RAS-binding domain (RBD) and a cysteine-rich domain (CRD). CR2 lies in exon 7, while CR3, which spans exons 10-17, contains an activation segment. The gene is highly regulated with numerous serine and threonine residues that can be phosphorylated, resulting in activation or inactivation. Ser259, which is in CR2, is particularly important. In the inactive state, the N terminus of *RAF1* interacts with and inactivates the kinase domain at the C terminus. This conformation is stabilized by 14-3-3 protein dimers that bind to phosphorylated Ser259 and Ser261. Dephosphorylation of Ser259 facilitates binding of *RAF1* to RAS-GTP and propagation of the signal through the RAS-MAPK cascade via *RAF1MEK* kinase activity.

Pathologic allelic variants: The consensus 14-3-3 recognition site includes Arg256, Ser257, Ser259, and Pro261 in exon 7. Many of the mutations identified in Noonan syndrome cluster in this CR2 domain, interfere with 14-3-3 binding, and cause greater kinase activity than wild-type protein, both basally and after EGF stimulation. Other mutations reside in the RAF activation segment in CR3 and show reduced or absent kinase activity. However, they still result in constitutive ERK activation. Somatic *RAF1* mutations have only rarely been found in cancer. Most of these cancer-causing mutations do not cluster in the CR2 and CR3 hot spots.

Normal gene product: *RAF1* is ubiquitously expressed and encodes a protein of 648 amino acids with three domains. CR1 contains a Ras-binding domain, CR2 is a site of regulatory phosphorylation and association with the 14-3-3 protein. CR1 and CR2 both have negative regulatory function, removal of which results in oncogenic activity. The kinase domain, CR3, also associates with 14-3-3.

Abnormal gene product: Noonan syndrome-associated *RAF1* mutations increase and prolong RAS activation and downstream signaling through enhanced RAS-GEF activity and reduced 14-3-3 binding and autoinhibition.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Noonan syndrome

The Noonan Syndrome Support Group
PO Box 145
Upperco MD 21155
Phone: 888-686-2224; 410-374-5245
Email: info@noonansyndrome.org
www.noonansyndrome.org

Human Growth Foundation
997 Glen Cove Avenue Suite 5
Glen Head NY 11545
Phone: 800-451-6434
Fax: 516-671-4055
Email: hgf1@hgfound.org
www.hgfound.org

The MAGIC Foundation
6645 West North Avenue
Oak Park IL 60302
Phone: 800-362-4423; 708-383-0808
Fax: 708-383-0899
Email: info@magicfoundation.org
www.magicfoundation.org

Genetic Alliance BioBank
A centralized biological and data [consent/clinical/environmental] repository to enable translational genomic research on rare genetic diseases.
Phone: 202-966-5557
Email: sterry@geneticalliance.org
www.biobank.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

Tartaglia M, Gelb BD. Noonan syndrome. Atlas of Genetics and Cytogenetics Oncology and Haematology. atlasgeneticsoncology.org. 2005

Chapter Notes

Revision History

- 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 to live Web site
- 17 December 2003 (me) Comprehensive update posted to live Web site
- 15 November 2001 (me) Review posted to live Web site
- 2 August 2001 (ja) Original submission