# Noonan syndrome – a new survey

Alireza Tafazoli[1], Peyman Eshraghi[2], Zahra Kamel Koleti[3], Mohammadreza Abbaszadegan[4]

[1]Medical Genetics Research Center, Medical School, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Pediatrics, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Pathology and Medical laboratory, Shohada Hospital, Mazandaran University of Medical Sciences, Sari, Iran
[4]Division of Human Genetics, Immunology Research Center, Avicenna Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran

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**Corresponding author:**
Prof. Mohammadreza Abbaszadegan
Division of Human Genetics
Immunology Research Center
Avicenna Research Institute
Mashhad University of Medical Sciences
Vakil abad Blv.
9177948988 Mashhad, Iran
Phone: +98 9151156121
E-mail: Abbaszadeganmr@mums.ac.ir

## Abstract

Noonan syndrome (NS) is an autosomal dominant disorder with vast heterogeneity in clinical and genetic features. Various symptoms have been reported for this abnormality such as short stature, unusual facial characteristics, congenital heart abnormalities, developmental complications, and an elevated tumor incidence rate. Noonan syndrome shares clinical features with other rare conditions, including LEOPARD syndrome, cardio-facio-cutaneous syndrome, Noonan-like syndrome with loose anagen hair, and Costello syndrome. Germline mutations in the RAS-MAPK (mitogen-activated protein kinase) signal transduction pathway are responsible for NS and other related disorders. Noonan syndrome diagnosis is primarily based on clinical features, but molecular testing should be performed to confirm it in patients. Due to the high number of genes associated with NS and other RASopathy disorders, next-generation sequencing is the best choice for diagnostic testing. Patients with NS also have higher risk for leukemia and specific solid tumors. Age-specific guidelines for the management of NS are available.

**Key words:** Noonan syndrome, RAS-MAPK signaling pathways, germline mutation.

## Introduction

Noonan syndrome (NS, OMIM 163950) is known as a multisystem disease with a wide spectrum of heterogeneity regarding the genetic and clinical characteristics. Despite the autosomal dominant traits of the majority of NS cases, autosomal recessive transmission has also been reported in a few cases. Sporadic and familial types of transmission have been reported in NS cases, but most cases follow a sporadic pattern which is suggested to be the consequence of new mutations [1–5]. Noonan syndrome is characterized by reduced postnatal growth, distinctive facial dysmorphism, a wide spectrum of congenital heart defects (CHDs), learning difficulties, short stature, renal anomalies, lymphatic malformations, bleeding disorders, and skeletal malformations [2, 6, 7]. Due to the extensive diversity of phenotypic properties in NS, clinical overlaps have been detected between Noonan and other autosomal dominant disorders such as LEOPARD syndrome, cardio-facio-cutaneous syndrome,

NS-like syndrome with loose anagen hair, and Costello syndrome [8]. The prevalence and global frequency of NS at live birth almost all over the world has been reported as one in 1000–2500 individuals, which makes it the second cause of congenital heart disease next to trisomy 21 [2, 9, 10].

Noonan syndrome was first introduced by Jacqueline Noonan following her investigations on 9 patients with pulmonic stenosis (PS), chest deformities and unique facial dysmorphic features such as hypertelorism, ptosis, low-set ears, and webbed neck [11]. Figure 1 shows NS patients with these symptoms and clinical manifestations. Germline mutations in the RAS-MAPK (mitogen-activated protein kinase) pathway are responsible for NS and other related disorders. Genes in this pathway include *PTPN11*, *SOS1*, *RAF1*, *BRAF*, *HRAS*, *KRAS*, *NRAS*, *SHOC*, *MAP2K1*, *MAP2K2*, and *CBL*. Recently, mutations in *RIT1*, *RASA2*, and *A2ML1* have also been shown to cause NS. Therefore, NS is referred to as a heterogeneous condition [3, 8, 12]. Because *PTPN11* and other genes such as *KRAS*, *HRAS*, *NRAS*, and *BRAF* have essential roles in the RAS-MAPK pathway, patients with NS are predisposed to leukemia and certain solid tumors [13].

## Clinical features and symptoms

Noonan syndrome has several medical and developmental features that can be detected both pre- and postnatally. According to previous studies, there are various unusual prenatal presentations which should be regarded as risk factors of NS. In some cases the karyotype of the fetus might be normal but symptoms such as polyhydramnios, hydronephrosis, pleural effusion, edema, cardiac abnormalities, distended jugular, lymphatic sacs, cystic hygroma, and elevated nuchal are other possible signs of the NS. These prenatal features can be identified during the first or second trimester [14–18]. After birth, Noonan patients show a wide range of observable and internal symptoms through the lifetime including hearing and digestive problems, abnormal height and skin pigmentation, unilateral or bilateral cryptorchidism in up to 80% of boys, hematological disorders, lymphatic abnormalities, multiple giant cell lesions, spinal and chest deformities, joint, tendon, and bursa lesions, widely spaced nipples, webbed neck, cubitus valgus, genu valgum, mild intellectual impairment, social cognition difficulties, language impairments including reading and spelling difficulties, and eyes abnormalities including ptosis and hypertelorism, excess nuchal skin, and swollen edematous dorsa of hands and feet. Wispy hair, thickly hooded prominent eyes, wide-based depressed nose with bulbous, high-arched palate, upturned lips, and a cupid-bow appearance of the upper lips are more frequently seen in infants than older children with NS [7]. Patients are also predisposed to cancers such as juvenile myelomonocytic leukemia and neuroblastoma [19–26]. The main facial presentations of NS are proposed to be head size relative to face, tall forehead, hypertelorism, down-slanting palpebral fissures, epicanthal folds, short wide nose with depressed nasal root and full tip, severely grooved philtrum, wide peaks of the vermilion border of the upper lip, small jaw and short neck, and low-set and posteriorly rotated ears with oval-shaped and thick helixes [7, 27]. Heart defects are present in more than 80% of patients, and timely diagnosis of the NS will positively affect the treatment of choice, outcome, and prognosis [21, 28]. The most prevalent congenital heart defects are pulmonary valve stenosis, atrial septal defect, ostium secundum type, and stenosis of the peripheral pulmonary arteries which is related to *PTPN11* gene mutation. Ventricular septal defect and most left-sided heart defects show a trend toward overrepresentation in patients with other mutations [14, 29]. It has been observed that specific gene mutations lead to specific heart problems; for example, *RAF1* mutations are usually related to hy-


**Figure 1.** Noonan syndrome at different ages

pertrophic cardiomyopathy rather than other cardiac problems [21]. Table I lists clinical symptoms of patients with NS.

## Genetics of Noonan syndrome

Autosomal dominant abnormalities called RASopathies are the results of germline mutations in the intracellular RAS/mitogen-activated protein kinase (MAPK) pathway which can lead to NS and the associated abnormalities.

The RAS-MAPK pathway is known as the principal signal transduction cascade involved in cell cycle differentiation, growth, and senescence through adjusting morphology determination, organogenesis, and synaptic plasticity (Figure 2) [1, 8, 30]. Both downstream and upstream gene mutations in the RAS-MAPK pathway are related to specific complications which can cause a wide range of possible developmental abnormalities in NS [31]. Also recent studies indicated that mutations in three other genes – *RIT1*, *RASA2* and *A2ML1* – result in NS and related disorders. Investigations on new mutations in *A2ML1*, a gene responsible for protease inhibitor α2-macroglobulin (A2M)-like-1 expression, led to the development of a syndrome clinically related to Noonan disorder [12]. The other RASopathy disorders show mutations in specific genes. LEOPARD syndrome (LS, OMIM 151100) is associated with *PTPN11*, *RAF1* and *BRAF* gene mutations, Noonan-like syndrome with loose anagen hair (NS/LAH, OMIM 607721) with *SHOC2* gene mutations, cardio-facial-cutaneous syndrome (CFCS, OMIM 115150) with *KRAS*, *BRAF*, *MEK1* and *MEK2* gene mutations and Costello syndrome (CS, OMIM 218040) with *HRAS* gene mutations [32–46].

Mutations in *PTPN11,* which is involved in protein tyrosine phosphatase SHP-2 expression, on chromosome 12 (12q24), account for up to 50% of NS patients. *PTPN11* is expressed in various tissues and is involved in adjusting the eukaryotic cells' reflexes to multiple extracellular stimuli, such as hormones, cytokines, and growth factors. Activation of SHP-2 results from binding of the N-terminal-SH2 (N-SH2) domains to short amino acid motifs containing a phosphotyrosyl residue. Most of the mutations are the missense type and occur in exons 3, 8, and 13, which contain the N-SH2 domain and PTP domains. Gain-of-function is the effect of the mutations, resulting in over-activation of RAS-MAPK pathway molecules [32, 47–49]. Other associated genes include *SOS1* (approximately 10%), *RAF1* (approximately 10%), *MEK1* (less than 4%), *KRAS* (less than 2%) and *NRAS* (less than 1%) [2, 50]. However, there are no distinct statistical data for the role of novel genes related to NS. In one study the investigators found that *RIT1* is involved in 9% of Noonan cases, but this number may be different in other populations [33]. Based on the different gene mutations, NS can be divided into categories with associated clinical features; for instance, In NS type 1 (OMIM 163950), *PTPN11* mutations can lead to extended

**Table I.** Clinical features in Noonan syndrome (from [1, 5, 18, 27])

| |
|---|
| Cardiovascular: |
| PVS, aortic valvular stenosis (pulmonary hypertension = rarely) |
| Secundum ASD, supravalvular pulmonary stenosis (aortic root dilation = rarely) |
| HCM, bicuspid aortic valve (aortic dissection = rarely) |
| Partial atrioventricular canal defect |
| Mitral insufficiency |
| VSD |
| Dental/oral: |
| Articulation difficulty, high arched palate, malocclusion, micrognathia |
| Facial features: |
| (Change with ages, see the text) |
| Ears: |
| Hearing difficulties |
| Eyes: |
| Ptosis, hypertelorism, nystagmus, strabismus, epicanthal folds |
| Gastrointestinal: |
| Feeding difficulties (prolonged feeding time, recurrent vomiting, and reflux) |
| Genitourinary: |
| Cryptorchidism, normal female fertility, males can have fertility problems, renal and kidney malformation |
| Growth: |
| Failure to thrive and short stature in most patients, developmental delay, birth weight and length are normal |
| Hematological: |
| Bleeding diathesis, thrombocytopenia, leukemia |
| Lymphatic: |
| Lymphedema, lymphangiectasia |
| Neurological: |
| Attention deficit/hyperactivity disorder, learning difficulties, central nervous system malformation, mild intellectual disability (in 33% of NS patients), speech difficulties |
| Skeletal: |
| Spinal abnormality, pectus excavatum and/or carinatum, scoliosis |
| Skin and hairs: |
| Hyperelastic skin, multiple lentigines, nevi, thick curly hair or thin sparse hair, low posterior hairline with webbed neck |

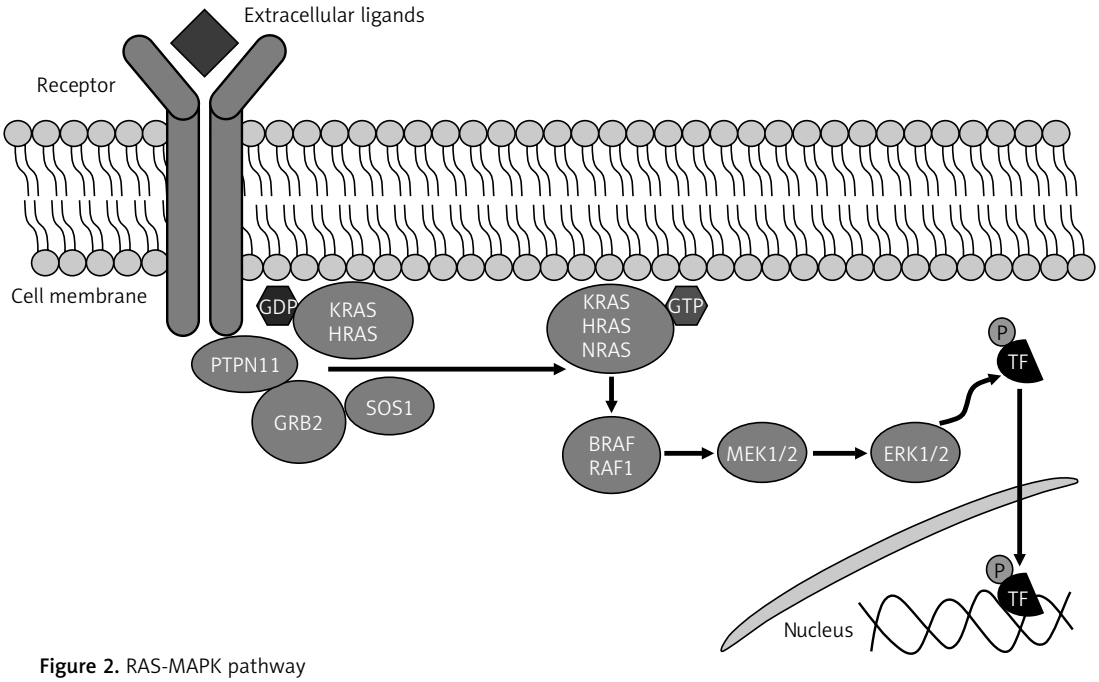


**Figure 2.** RAS-MAPK pathway

pulmonary stenosis, lower hypertrophic cardiomyopathy, and atrial septal abnormality (ostium secundum type), shorter stature, lower insulin growth factor-1 (IGF1) levels, more bleeding diathesis and juvenile myelomonocytic leukemia. On the other hand, in NS type 3 (OMIM 609942), *KRAS* mutations have been detected due to more hypertrophic cardiomyopathy and naevi, lentigines, and café au lait spots. In this regard based on the location of the mutations responsible for NS occurrence, different types of NS presentations might be detected in patients. These divisions can be useful to determine genotype-phenotype correlations [2, 5, 32, 36, 51].

## Diagnosis (clinical and molecular)

Conducting obstetric ultrasound and fetal echocardiography during the prenatal screening as the main diagnosis methods is strongly recommended for patients with possible clinical signs of NS in their fetus or those with first-degree family with NS. Based on the literature obstetric ultrasound is suggested to be performed at 12–14 and 20 weeks of gestation and again in the third trimester and fetal echocardiography at 18–20 weeks of gestation. DNA from blood, chorionic villi, or amniotic fluid can be analyzed for mutations [18]. Facial and musculoskeletal abnormalities mostly result in the primary diagnosis of NS. Although the facial features associated with NS change with age [14, 52], the clinical manifestations are sufficient to be the first step to diagnosis.

With many similarities in clinical manifestations displayed between NS and other RASopathies, differential diagnosis is still based on differences in clinical features and symptoms. Also, other disorders such as Aarskog syndrome/faciogenital dysplasia, Baraitser-Winter syndrome, fetal alcohol syndrome, neurofibromatosis type 1, and Turner syndrome share many features with NS. These cases can be diagnosed by molecular testing in addition to different clinical symptoms and signs [5]. Van der Burgt diagnostic criteria (Table II) are commonly used to distinguish patients with NS [53]. All cases should be confirmed by molecular testing for appropriate specific treatments and follow-up procedures in addition to making correct genotype-phenotype correlations. Despite various recognized gene mutations involved in NS in 15–30% of cases the responsible genes are not clear [3, 8]. Karyotype and copy number analysis are suggested only in cases with intense neurocognitive involvement and are not performed routinely for patients with typical phenotypes of NS. However, subtle chromosomal abnormalities may be detected using array comparative genomic hybridization (aCGH) [5, 50, 51, 54–56].

DNA sequencing is the gold standard for the detection of genetic variants; however, due to the high number of genes associated with NS and other RASopathy disorders, standard diagnostic testing using Sanger sequencing is expensive and time-consuming [8]. Currently, next-generation sequencing (NGS) is faster and more accurate and cost-effective for the diagnosis of RASopathies than Sanger sequencing [3, 8]. Next-generation sequencing is a useful approach for finding genetic variants in locus heterogeneity conditions such retinitis pigmentosa, hypertrophic cardiomyopathy, and NS [57]. Next-generation sequencing

**Table II.** Diagnostic criteria for Noonan syndrome

| Feature | A = Major | B = Minor |
|---|---|---|
| Facial | Typical facial dysmorphology (also change with age) | Suggestive facial dysmorphology |
| Cardiac | Pulmonary valve stenosis, HOCM and/or ECG Typical of Noonan syndrome | Other defect |
| Height | < P3* | < P10* |
| Chest wall | Pectus carinatum/excavatum | Broad thorax |
| Family history | First-degree relative with definite Noonan syndrome | First-degree relative with suggestive Noonan syndrome |
| Other features | Mental retardation, cryptorchidism, and lymphatic vessel dysplasia | One of mental retardation, cryptorchidism, or lymphatic vessel dysplasia |

*HOCM – hypertrophic obstructive cardiomyopathy; *P3 and P10 refer to percentile lines for height according to age, with the normal range of variation defined as P3-P97 inclusive: definitive Noonan syndrome: 1 "A" plus one other major sign or two minor signs; 1 "B" plus two major signs or three minor signs. Adapted with permission from van der Burgt I, Berends E, Lommen E, van Beersum S, Hamel B, Mariman E. Clinical and molecular studies in a large Dutch family with Noonan syndrome. Am J Med Genet 1994; 53: 187-91.*

RASopathy panels for specific genes and targeted resequencing (Centogene, Germany) result in more efficient and rapid mutation detection than previous methods. Subsequent protein modeling to analyze the mutations and characterize the effects of protein structure changes on patient phenotypic signs and symptoms in many areas of research is becoming routine [58, 59].

## Genetic counseling

Noonan syndrome in patients with *PTPN11* mutations is more likely to be familial than NS without *PTPN11* mutations [6, 60]. Because facial phenotype tend to normalization as the patient grows up, it is helpful for diagnosis to review childhood photographs of both parents [18]. There is almost 50% likelihood for a mutation to be inherited by a child who has parents with NS. The risk of occurrence of NS in the first degree relatives of an affected person is 50%, but if the parents are unaffected the risk is less than 1% in siblings. Because of the wide variety of NS representations, the responsible patient of a child with NS might be undiagnosed. In most cases heterogeneous NS might be the consequence of sporadic mutations with symptoms similar to other syndromes. Pre-implantation genetic diagnosis (PGD) is a diagnostic technique used for screening embryos of cases with known mutations [4, 27, 61].

## Management

Due to the wide spectrum of symptoms and presentations in Noonan cases, accurate clinical and genetically diagnosis and comprehensive management of the disorder is strongly recommended. Despite the ordinary intellectual and physical capacities in Noonan cases, multidisciplinary assessments and follow-up screenings are suggested for patients [5, 18].

Age-specific guidelines for management that emphasize screening and testing for common health issues are available [27].

The NS Support Group (NSSG) is a supportive organization involved in designing guidelines regarding the diagnosis and management of NS through recent genetic findings [5] http://healthfinder.gov/FindServices/Organizations/Organization.aspx?code=HR2560. Moreover there are some other websites which have a parents' guide that provides useful information and guidelines for people affected by NS. Table III lists the management guidelines for patients with Noonan syndrome.

## Cancer risk in patients with Noonan syndrome

Because *PTPN11* and other genes such as *KRAS*, *HRAS*, *NRAS,* and *BRAF* have essential roles in the RAS-MAPK signal transduction pathway, which controls several developmental processes, it is not surprising that patients with NS are predisposed to benign or malignant cell proliferative disease [13]. According to previous estimates, the occurrence rate of hematological malignancies was highest among patient with NS when compared with other cancers [13]. Mild myeloproliferative disorder occurs in almost 10% of children with NS, and a lower portion of cases reveals juvenile myelomonocytic leukemia (JMML) [62–64] and/or other hematological malignancies [65–71].

Some missense mutations in *PTPN11* are detected in patients with myeloid and lymphoid malignancies which are also identified as principal mutations in NS cases [72]. The prevalence of solid tumors including neuroblastoma and embryonal rhabdomyosarcoma has been reported to be elevated in some cases with NS patients [73–80]. Low rates of somatic mutations in *PTPN11* have also been identified in solid tumors of the lung and liver, and colorectal malignancies [80, 81].

**Table III.** Management guidelines for patients with Noonan syndrome (from [2, 27])

| |
|---|
| Cardiovascular: |
| Cardiac examination, electrocardiogram, echocardiogram at diagnosis |
| Regular follow-up with cardiologist after diagnosis |
| Dental/oral: |
| Dental assessment between ages 1–2 years at diagnosis |
| Follow-up dental assessment each year after diagnosis |
| Developmental: |
| Development assessment between 6 months – first year at diagnosis |
| Developmental surveys annually for patients aged 5–18 years after diagnosis |
| Growth: |
| To be assessed three times a year for the first three years, then yearly, and then evaluation according to age-based Noonan syndrome growth charts |
| Gastrointestinal: |
| Refer to gastroenterologist for feeding problems or recurrent vomiting and other issues |
| Audiological: |
| Hearing assessment at diagnosis, repeat if there are otitis issues or speech delay |
| Ophthalmological: |
| Eye examination in early years and/or at diagnosis, repeat every 2 years, after indication |
| Hematological: |
| CBC, PT, and PTT test at diagnosis, Repeat all the mentioned tests if aged 6–12 months was for initial screen; factor IX, XI, and XII concentrations, von Willebrand factor, platelet aggregation evaluation if needed |
| Renal: |
| Kidney ultrasound, follow-up and refer to nephrologist |
| Reproductive: |
| Orchiopexy if testes are undescended at 1 year, fertility assessment in males |
| Skeletal: |
| Examination of chest and spine, consider radiography of the spine yearly |
| Pregnancy: |
| Refer to obstetrician, chorionic villus sampling or amniocentesis for diagnosis if indicated |

Most findings support a *PTPN11* mutation in Noonan patients with malignancies, but mutations in other genes in RAS-MAPK pathways have also been associated with cancers in NS and other related disorders. For instance, mutation in *HRAS* was also seen in Costello syndrome, with an increasing incidence of tumors [82].

## Conclusions

Because of the heterogeneity in both clinical and genetic characteristics of NS, every physician should be aware of the complexity of this disorder. Many interesting aspects of NS are remained unsolved; these include the near absence of large families with NS, all cohorts in studies of NS having included more male than female patients [18], and the fact that the genes and/or mutations responsible for 15–30% of cases have not yet been identified [3]. Continuous follow-up of patients is essential to control the medical and developmental implications of NS. Many questions regarding the molecular and genetic causes of NS have yet to be answered [2].

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## Conflict of interest

The authors declare no conflict of interest.

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