



# UPDATES ON THE CARE AND GENETICS OF CHILDREN WITH NOONAN SYNDROME

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# Outline

- Noonan syndrome clinical features
- Basics of genetics
- Genetic basis of Noonan syndrome
- Management of individuals with Noonan syndrome

# Noonan syndrome

- Dr. Jacqueline Noonan first described the condition in 1963.
- She recognized non-cardiac similarities in some of her patients, such as short stature, chest deformities, and similar facial features.
- Incidence is between ~1 in 1000 and 1 in 2500.
- Most are new cases, but ~30-75% will have a parent with NS.



Photo courtesy of A. Lin

## Noonan syndrome - Clinical Features

- Dysmorphic facial features
- Inverted triangular shaped head/face
- Broad or webbed neck
- Chest wall deformities (pectus carinatum and/or pectus excavatum)
- Undescended testes in males
- Cardiac involvement (80-90%)
  - *Pulmonic stenosis (PS) and atrial septal defect (ASD) (70-80%), other valve dysplasia*
  - *Hypertrophic cardiomyopathy (20-75%)*
  - *Arrhythmia (abnormal EKG in ~50%)*



## Noonan syndrome – Facial features

- Shows considerable change with age
- Most striking in the newborn period and middle childhood
- Most subtle in the adult
- Key features:
  - *hypertelorism, epicanthal folds, down-slanting palpebral fissures, ptosis*
  - *low-set, posteriorly rotated ears*
  - *vivid blue or blue-green irises*



<http://bestpractice.bmj.com/best-practice/monograph/1103/resources/image/tp/3.html>

# NS – Facial features over time



**FIGURE 1**  
A. Patient with NS at (from left to right) 10 days, 6 months, and 2 years of age. B. Patient with NS at (from left to right) 4 months and 1, 2, 5, 8, and 21 years of age.

Romano et al. 2010

## NS and lymphatics

- Lymphatic abnormalities have been described and may be localized or widespread, prenatal, and/or postnatal.
- Dorsal limb lymphedema is most common.
- Prenatal features suggestive of NS: transient or persistent cystic hygroma, polyhydramnios, and (rarely) hydrops fetalis.

## Noonan syndrome - Growth

### ■ Growth

- *Short stature is common*
- *Birth length is usually in normal range*
- *Height usually follows along the 3<sup>rd</sup> centile*
- *Average adult height in males is 161 cm (5'3") and females is 4' 11"*







## Growth hormone in Noonan syndrome

- Growth hormone (GH) deficiency has been documented in some individuals with Noonan syndrome.
- Several studies have evaluated GH therapy in those with NS.
- Growth rate in the first 6-12 months of therapy was highest.
  - *i.e. Height increase of ~8.4 cm per year in first year vs. 4.4 cm per yr in untreated patients.*
- Delayed puberty is common in males and females

## Hematologic abnormalities

- Myeloproliferative disorder can be seen in infants with NS (leukocytosis, thrombocytopenia, hepatosplenomegaly).
  
- Juvenile myelomonocytic leukemia (JMML) is often caused by somatic mutations in *PTPN11*.
  - *Individuals with NS and PTPN11+ have a predisposition JMML.*
    - Certain exons may be associated with greater risk.
  - *JMML in NS tends to run a more benign course than non-NS JMML.*
  
- Approximately 1/3 of individuals with NS have a coagulation (blood clotting) defect.

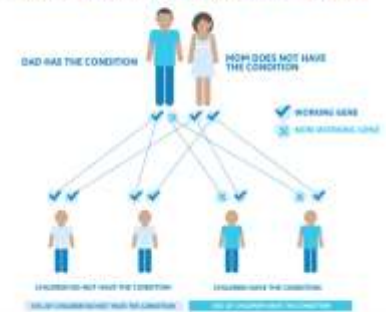
## Noonan syndrome - Development

- Development:
  - *Early developmental milestones may be delayed.*
  - *Approximately 25% will have learning disabilities, with 10-40% requiring special education.*
  - *Non-verbal performance is usually better than verbal performance.*

# Inheritance of Noonan syndrome

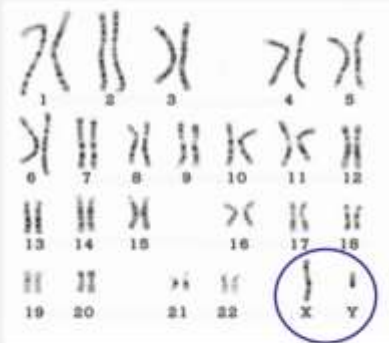
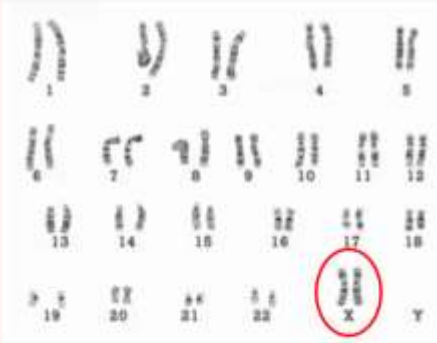
- Most individuals with NS are the first person in their family to have NS.
- However, about 30-70% of individuals with NS will have a family history of NS (a parent who also has NS).
- Noonan syndrome is inherited in an "Autosomal dominant" manner.
- If an individual has NS, there is a 50% chance that they will pass on the non-working gene to *each* child.
- If a parent *does not* have NS, the chances of having another child with NS will be very low (<1%).

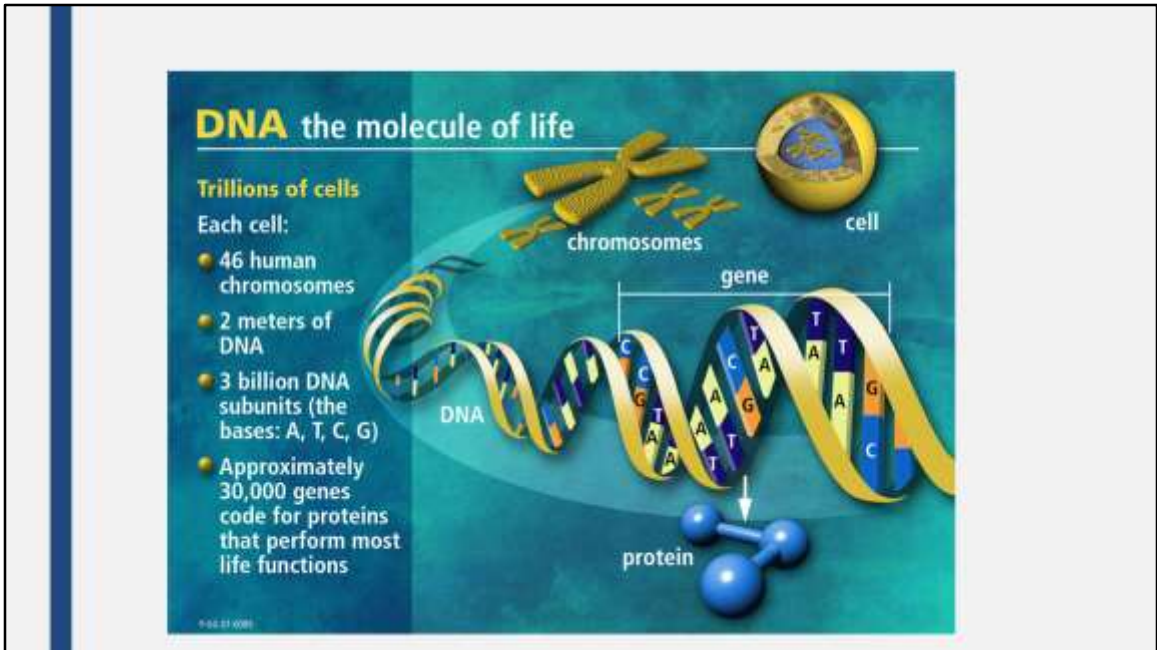
## Autosomal Dominant Inheritance Pattern



GENETICS!

# Chromosomes





- Our chromosomes are located in the nucleus (middle) of all of our cells.
- Chromosomes are composed of strands of DNA that are tightly coiled together
- DNA is composed of 4 letters (similar to letters of the alphabet) A, C, T, G that makes up a gene which codes for a protein.
- Since we have 2 copies of every chromosome, we have 2 copies of every gene.
- If there is a change in a gene (either a missing letter, changed letter, missing gene, missing part of the chromosome – missing lots of genes) – this can effect normal growth and development.
- The effect of the mutation often depends on if 1 gene mutated or both genes.



# Genetics

Genome



Chromosome



Gene

DNA – A, C, T, G

Encyclopedia



Volume



Sentence



Alphabet- A, B, C, D...

## Genetic variants

- We ALL have genetic variants in our genes – they are what make us unique!
- Some changes are “benign” and do not cause any problems.
- Some changes are more serious and can cause problems with what that particular gene is supposed to do.
  - *These are often called “Pathogenic” variants.*

## Pathogenic variants

### Original

THE CAT HAD RED FUR AND RAN FAR.

- Deletion

THE CAT HAR EDF URA NDR ANF AR.

- Missense

THE CAT HAD RED FER AND RAN FAR.

THE MAT HAD RED FUR AND RAN FAR.

- Nonsense

THE CAT HAD RED.



## Variants of unknown significance

- If a gene change is found but has NOT been seen before or reported in the medical literature, then it can make it very hard to interpret the results.
- These are called “variants of uncertain significance” (VUS)
- Testing other family members may help us interpret the results.
- If a parent or unaffected sibling has the same change, then it is probably benign.
- If neither parent has the same change, then it might be pathogenic.

## Noonan syndrome (NS) Genes

- To date, there are ~13 genes thought to be causative of NS or “Noonan-like” syndrome.
- The most common gene associated with NS is called *PTPN11*.
- Approximately 50% of individuals with a clinical diagnosis of NS will have changes in this gene.
- Some individuals may have features of NS, but test NEGATIVE (normal).
  - *If so, there may be other genes that cause NS that have not been identified yet.*
  - *Or there may be a change in another gene that is closely related to NS (such as CFC syndrome, NF1, or Costello syndrome).*

## Summary of genes

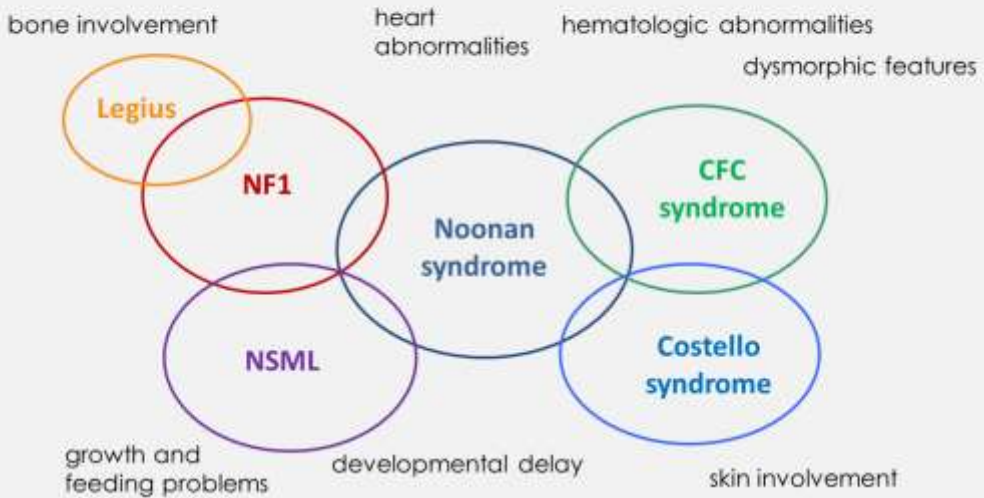
Gene	Phenotype(s)	Percentage
<i>PTPN11</i>	NS	50%
<i>SOS1</i>	NS	10-13%
<i>RIT1</i>	NS	9%
<i>RAF1</i>	NS	3-7%
<i>KRAS</i>	NS, CFC	<5%, <5%
<i>NRAS</i>	NS	Unknown (<1%)
<i>SOS2</i>	NS	Unknown
<i>SHOC2</i>	Noonan-like	Unknown
<i>CBL</i>	Noonan-like	Unknown (<1%)
<i>A2ML</i>	Noonan-like	Unknown (<1%)
<i>LZTR1</i>	Noonan-like	Unknown
<i>RASA2</i>	Noonan-like	Unknown (<1%)
<i>RRAS</i>	Noonan-like	Unknown

## Genotype-phenotype correlation in NS

- **PTPN11**
  - More likely to be found when *pulmonary stenosis* is present. Variants in certain parts of the gene seems to have a higher risk for *JMML*.
- **SOS1**
  - Increased *ectodermal (skin, hair, nails) abnormalities* and a greater likelihood of *normal development and stature* in these individuals compared to others with NS.
  - Pierpont et al (2009) studied intellectual abilities in Noonan syndrome and report that individuals with *SOS1* pathogenic variants generally have average or higher-level skills.
- **RAF1 and RIT1**
  - There is strong correlation with *hypertrophic cardiomyopathy*

in-frame three-[nucleotide](#) *PTPN11* [deletion](#) (p.Gly60del)

## RASopathies



Lentigines, EEG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, deafness



## Differential diagnosis - CFC syndrome

- ~200-300 individuals worldwide
  - *Prevalence in Japan: ~1 in 810,000*
- Moderate to severe ID
- Relative macrocephaly
- Dysmorphic facial features
  - *Bitemporal narrowing*
  - *Down-slanting eyes w/ epicanthic folds, ptosis*
  - *Flattened nasal bridge w/ upturned nose*
  - *Posteriorly rotated ears*
  - *Coarse facial features*
- Cardiac abnormality in ~75%
  - *PS +/- ASD, HCM: 40%*
- Hair
  - *Sparse and curly, wooly or brittle*
  - *Sparse or no eyebrows (67%)*



Photos courtesy of CFC International

## Differential diagnosis - Costello syndrome

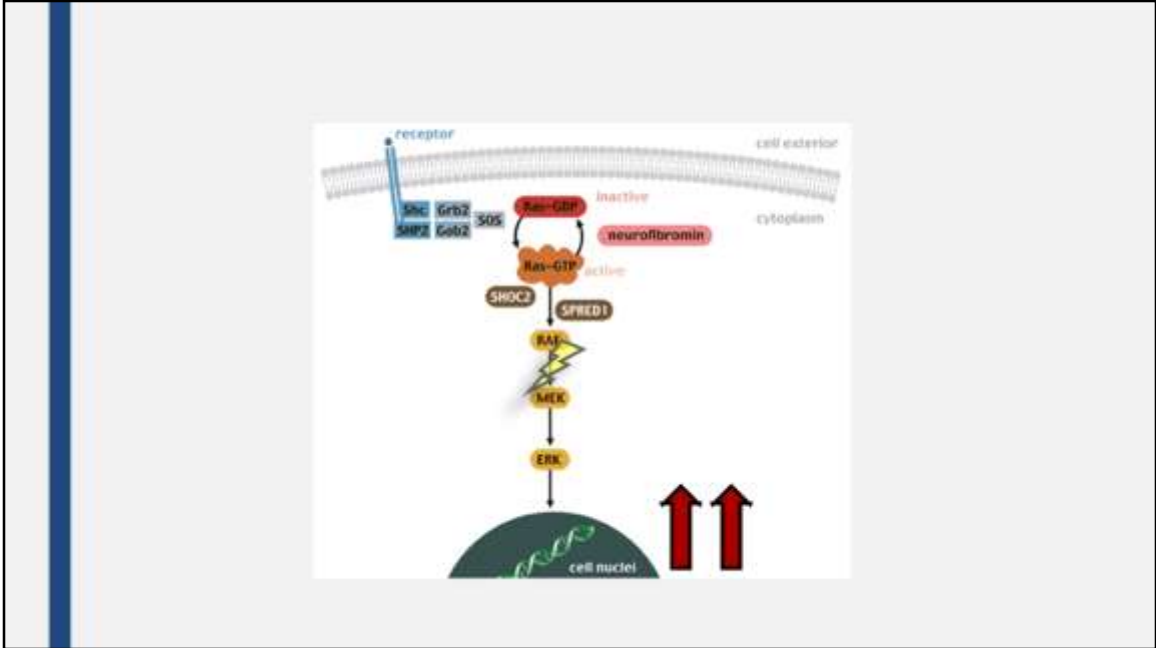
- Moderate to severe ID
- Craniofacial features
  - *Relative macrocephaly*
  - *Coarse features, full cheeks, full lips, large mouth*
  - *Curly or sparse, fine hair*
- Deep, hoarse or whispery voice
- Loose, soft skin with increased pigmentation
- Deep palm and foot creases
- Papillomata of face (72%) - typically absent in infancy but may appear in childhood
- Cardiac abnormalities in 80%
  - *Congenital heart defects: 20%, HCM: 60%, arrhythmias: 40%*
- Tumor risk – 15%



## RAS-MAPK Pathway

- All of these genes belong to the RAS-mitogen-activated protein kinase pathway.
- These genes code for proteins that serve as molecular on/off switches which activate or inhibit downstream molecules.
- This signaling pathway is important for cell proliferation, growth, and death.
- Most mutations are gain-of-function mutations that continually activate the pathway  
→ increased cell growth and proliferation.
- Well-known in cancer research because it is activated in most cancers.

→ Increased cellular proliferation – increase risk of tumors, ?hyperkeratosis, ?HCM.  
Proto-oncogenes.



The extra-cellular [mitogen](#) binds to the membrane ligand. This allows [Ras](#) (a GTPase) to swap its GDP for a GTP. It can now activate MAP3K (e.g., Raf), which activates MAP2K, which activates MAPK. MAPK can now activate a transcription factor, such as myc.

→ Increased cellular proliferation – increase risk of tumors, ?hyperkeratosis, ?HCM.  
Proto-oncogenes

# Noonan syndrome guidelines

## Noonan Syndrome: Clinical Features, Diagnosis, and Management Guidelines

### abstract

Noonan syndrome (NS) is a common, clinically and genetically heterogeneous condition characterized by distinctive facial features, short



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### ■ Multidisciplinary care:

- Cardiology
- Endocrine
- GI/feeding
- Developmental
- Neurology
- Speech/OT/PT
- Hematology
- Genetics

## Noonan syndrome - Management

System	Management
Cardiovascular issues	Cardiac evaluation at the time of diagnosis, including an electrocardiogram and echocardiogram. Regular follow-up if cardiac abnormalities detected
Growth and endocrine issues	Weigh and measure regularly by PCP on NS growth charts. If growth failure, refer to endocrine Therapeutic interventions as indicated (GH for growth failure, thyroid hormone replacement for hypothyroidism, estrogen or testosterone for pubertal delay)
Renal and genitourinary	All individuals should have a kidney ultrasound at the time of diagnosis. Orchiopexy should be performed by the age of 1 year if testicles remain undescended at that time
Gastrointestinal issues	Consultation for feeding difficulties/recurrent vomiting. Further testing as indicated (upper-gastrointestinal series, upper endoscopy, pH studies, etc) Therapeutic interventions as indicated/

System	Management
Hematology issues	<p>Screening CBC with diff and prothrombin time/activated partial thromboplastin time at diagnosis and after 6-12 mo of age</p> <p>May need hematology referral and factor deficiency evaluation.</p> <p>Surgery: preoperative evaluation of bleeding risk</p> <p>Avoidance of aspirin and aspirin-containing medications</p>
Neurological, cognitive, and behavioral issues	<p>Developmental screening annually</p> <p>Complete neuropsychological testing if screening result is abnormal</p> <p>Evaluations for speech pathology, PT, and OT if delays in speech, gross motor, and fine motor skills</p> <p>Early-intervention programs beginning in infancy if delays noted</p> <p>Regular, detailed developmental evaluations throughout childhood</p> <p>IEP for school-aged children</p> <p>EEG and/or Brain MRI and referral to neurology if seizures or other neurologic problems suspected</p>
Eye and ear issues	<p>Detailed eye examination in infancy and/or at diagnosis</p> <p>Hearing test in infancy and/or at diagnosis with annual hearing test throughout early childhood</p>

System	Management
Orthopedic and dental issues	Annual examination of chest and back, radiography if abnormal Careful oral exam at each visit Dental referral between the ages of 1 and 2 y and yearly visits thereafter
Lymphatic issues	Referral of those with peripheral lymphedema to specialty lymphedema clinics
Anesthesia risk	Individuals with NS should be considered at standard risk for malignant hyperthermia when receiving general anesthesia



## Comprehensive care for Noonan syndrome and the RASopathies

- Individually, they may be rare, but collectively, they are common (~1 in 1300).
- Need centers or clinics that specialize in the care of these patients given the vast array of complex medical and developmental problems that they can have.
- Multidisciplinary care is essential!
- GI, Feeding, Neurology, Endocrine, Orthopedics, Ophthalmology, ENT, Cardiology, Hematology/oncology, Renal, Developmental, Speech/OT/PT, ECI, Social work, Genetics, etc...

Home > Clinics > Medical Genetics > NF/Ras Pathway Clinic

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## NF/Ras Pathway Clinic

The **NF/Ras Pathway Clinic** provides prenatal, pediatric and adult care with comprehensive referral services to appropriate specialists in the UCSF NF/Ras Pathway Referral Network. This group consists of more than 50 UCSF specialists who have expertise in Ras pathway disorders, related to genetic mutations that cause certain cancers, skeletal muscle abnormalities and other disorders.

Our clinic provides health care support and management for patients who have or are at risk for having a Ras pathway disorder. These include:

- Neurofibromatosis type 1
- Neurofibromatosis type 2
- NF1-like
- Schwannomatosis
- Capillary malformation-AV malformation
- Noonan syndrome
- LEOPARD syndrome
- Costello syndrome

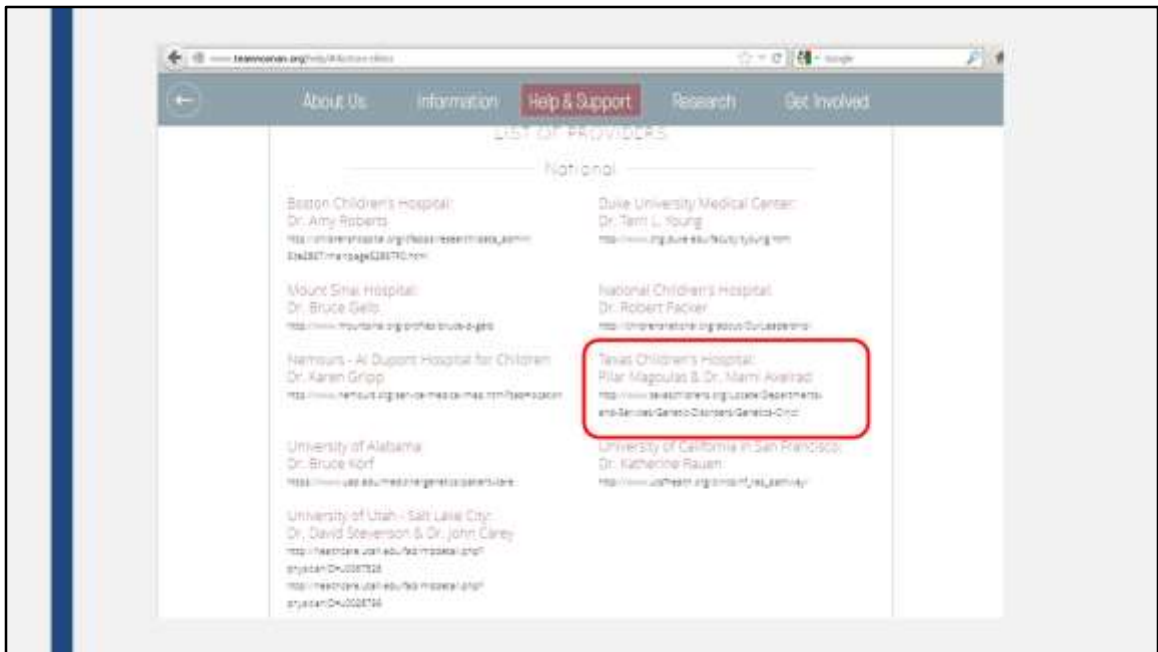
**Overview of Genetics Center****Genomic Medicine Clinic****Hereditary Disorders of Connective Tissue Clinic****Lysosomal Storage Diseases Clinic****Neurofibromatosis and RASopathy Center**[Clinic Appointments](#)[Our Specialists](#)**Phenylketonuria (PKU) Clinic****Preimplantation Genetic Diagnosis (PGD) Program**

## Neurofibromatosis and RASopathy Center

The Neurofibromatosis and RASopathy Center, a multidisciplinary clinic of the Genetics Center, is one of only a few designated centers nationwide that provides diagnosis, education, counseling, treatment and care coordination services to children and adult with neurofibromatosis and other disorders related to the RAS pathway.

Our specialists diagnose and treat the following conditions:

- Capillary malformation arteriovenous malformation syndrome
- Cardio-facio-cutaneous syndrome
- Costello syndrome
- Legius syndrome
- Multiple lentiginos syndrome (formerly known as LEOPARD syndrome)
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Noonan syndrome
- Schwannomatosis
- Tuberous sclerosis complex



# Pediatric Genetic Counseling

- Provide counseling regarding the diagnosis and genetic basis of the condition.
- Review the features, treatment, and management of the condition.
- Review family history and provide risk assessment
- Review testing and future reproductive options
- Offer testing for other relatives/spouses
- Provide information, support, and resources to the family.
- Address psychosocial implications of diagnosis on self and other family members



## Summary

- Noonan syndrome is one of nine conditions called "RASopathies"
- Common features of NS include:
  - *Musculoskeletal system, cardiac, GI, feeding, and growth, neurocognitive, distinct facial features, and lymphatic abnormalities*
- Noonan syndrome is caused by mutations in 1 of ~12 genes (and counting...)
- Individuals require multidisciplinary and comprehensive care.

## Questions?

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