



R.C.P.U. NEWSLETTER

Editor: Heather J. Stalker, M.Sc.
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Vol. XX No. 2

R.C. Philips Research and Education Unit
A statewide commitment to the problems of mental retardation

January 2009

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Noonan Syndrome

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INTRODUCTION:

Noonan syndrome is a highly variable condition characterized by: short stature, congenital heart defects, developmental delay, and characteristic facial features. It occurs in about 1:1000 to 1:2,500 newborns. Four genes, PTPN11, SOS1, KRAS, RAF1, are known to be associated with this condition. These genes are components of the RAS-MAPK pathway which plays an important role in cell proliferation, growth, and death. Due to the involvement of several genes in this pathway, there is significant phenotypic overlap between Noonan syndrome and other genetic conditions such as: Cardiofaciocutaneous syndrome, LEOPARD syndrome, and Costello syndrome. A majority of individuals with Noonan syndrome have *denovo* mutations, however in some families, there is an affected parent. This forum will review the features, genetics, and management of Noonan syndrome.

HISTORY OF NOONAN SYNDROME:

Noonan syndrome was first recognized by Jacqueline A. Noonan, a pediatric cardiologist at the University of Iowa. She noticed that children with a rare heart defect, valvular pulmonary stenosis, also had characteristics such as short stature, webbed neck, wide spaced eyes, and low set ears. Dr. Optiz, a former student of Dr. Noonan characterized children with these characteristics as having Noonan syndrome. Noonan syndrome is now recognized as a genetic condition with distinctive facial features and physical malformations. Both boys and girls are equally affected by the syndrome.

NOONAN PHENOTYPE:

There are several features that are observed in children with Noonan syndrome. Some of the distinctive features of this syndrome include: high arched palate, low-set posteriorly rotated ears, malar hypoplasia, ptosis, hypertelorism, down-slanting paleobral fissures, and short webbed neck. These facial characteristics change over time in individuals with Noonan syndrome.

During infancy, the head is relatively large, eyes are prominent and round, and the nasal bridge is high and flat. At about three years of age, the body becomes stocky and the chest more prominent. Later in childhood, facial features become coarse and the head becomes triangular; eyes become less prominent and the ptosis becomes more apparent. As a teenager and young adult, the webbed neck is more prominent than at earlier

stages in life. The nose has a pinched root and a thin high bridge. As an adult the skin becomes transparent and wrinkled.

In addition to the characteristic facial features, we observe congenital heart defects, short stature, kyphoscoliosis and, ocular and kidney anomalies. Individuals with Noonan syndrome tend to bruise easily and may have a bleeding disorder.

Cardiovascular defects

Cardiac defects associated with Noonan syndrome are predominantly pulmonary valve stenosis and hypertrophic cardiomyopathy, occurring in 50-62% and 20% of individuals respectively. Other defects such as atrial septal defect and aortic coarctation have been also been noted.

Weight and length concerns

Birth weight and length is normal in individuals with Noonan syndrome. Weight loss begins to occur in the first week of life, which may be attributed to feeding difficulties and failure to thrive. As the child progresses into puberty, height and weight growth parallels the third percentile. Onset of puberty is usually delayed by two years in these individuals. Noonan specific growth charts have been designed and can be used to plot the growth of an individual. Long term and short term growth hormone therapy has been studied in patients with Noonan syndrome, and growth hormone may be used in pharmacologic doses to overcome short stature.

Orthopedic findings

Chest deformities such as thoracic scoliosis, pectus excavatum and pectus carinatum have been observed, and occur in approximately 70-95% of individuals. Other orthopedic features include cubitus valgus, joint hyperextensibility, clinodactyly and brachydactyly.

Ophthalmologic and hearing abnormalities

Commonly seen ophthalmic abnormalities include: strabismus, refractive errors, and amblyopia, occurring in approximately 60% of the individuals. Nystagmus is seen in 10% of patients with Noonan syndrome. Hearing loss due to otitis media is a frequent complication occurring in 15-40% of cases. However, sensorineural hearing loss is less commonly observed.

Bleeding diathesis

Fifty-five percent of cases have mild to moderate bleeding tendencies. Coagulation studies have revealed prolonged bleeding times. Factor VIII, XI, and XII deficiencies, thrombocytopenia, and platelet function defects have been found in patients with Noonan syndrome. Since many individuals with Noonan syndrome undergo one or more operations, special care is required to prevent intraoperative or postoperative hemorrhage. Suitable blood products should be available if complications arise, and hematologic evaluation is always recommended prior to surgery in individuals with this condition.

NOONAN SYNDROME MANAGEMENT:

Due to the varied problems in patients diagnosed with Noonan syndrome, a series of medical management evaluations are recommended. A complete physical and neurologic examination must be performed annually. Height, weight, and head circumference should be plotted on a Noonan syndrome growth chart. Cardiac, hearing, and ophthalmologic evaluations are recommended. Coagulation screening to determine the presence of any bleeding disorders must be conducted. Renal ultrasounds and clinical and radiographic assessment of spine and rib cage must be carried out on the patient. Brain and cervical spine MRI must also be performed in patients that present neurologic symptoms.

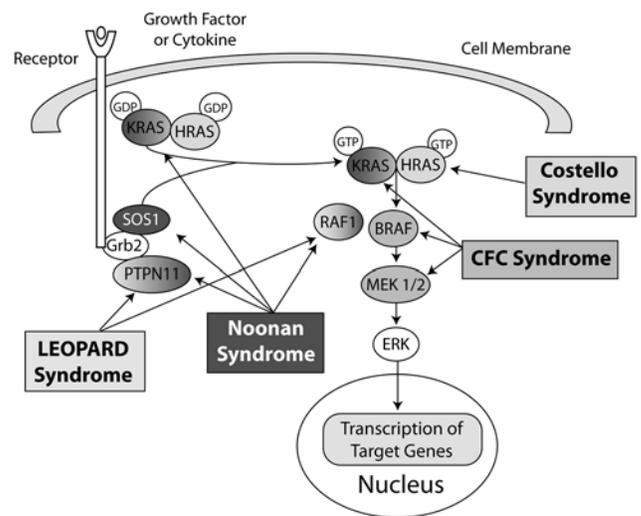
GENETIC ETIOLOGY

Currently four genes, PTPN11, SOS1, KRAS, and RAF1, are associated with Noonan syndrome. These genes account for 60-80% of the cases.

PTPN11 located on 12q24.1, accounts for approximately 40-50% of cases. SOS1 is the second most common gene found in children with Noonan syndrome. It is located on 2p21-p22 and accounts for 20% of the cases. PTPN11 and SOS1 were discovered by Tartaglia and colleagues in 2001 and 2007 respectively. KRAS and RAF1 account for approximately 6% of the cases. KRAS is located on 12p12.1 and RAF1 on 3p25.2.

PTPN11, SOS1, KRAS, and RAF1 are major components of the RAS-MAPK pathway. Mutations in the genes lead to a gain in function of respective proteins which results in a disruption of downstream signaling, permanent activation of the MAPKinase pathway and over expression of proteins. This over expression during embryonic development disrupts growth and maturation of normal tissue leading to the characteristics of Noonan syndrome.

PTPN11, SOS1 and RAF1 show some genotype/phenotype correlation. Atrial septal defects are more prevalent in individuals with PTPN11 mutations. Additionally, short stature, pectus deformities, easy bruising, characteristic facial features and cryptorchidism are also linked to PTPN11 mutations. Individuals with SOS1 mutations tend to have normal development and stature. However, pulmonary stenosis is more frequently found in individuals with SOS1 mutations. Additionally, these patients have frequent ectodermal anomalies such as keratosis pilaris (skin abnormality) and curly hair. Ninety-five percent of Noonan individuals showing hypertrophic cardiomyopathy have a RAF1 mutation.



DIAGNOSIS:

Although four genes have been discovered to be associated with Noonan syndrome, diagnosis is generally made on a clinical basis. The presence of classical facial features in addition to any one of the following features: pulmonary valve stenosis, stature plotting less than the third percentile, pectus carinatum/excavatum, a first degree relative with Noonan syndrome, mental retardation, cryptorchidism or lymphatic dysplasia results in the clinical diagnosis of Noonan syndrome. Characteristic facial features include: hypertelorism, down-slanting anti-mongoloid palpebral fissures, ptosis, and low-set posteriorly rotated ears. When the cardinal features of Noonan syndrome are not present, diagnosis can be difficult. A patient may be diagnosed as having a Noonan phenotype but not having the classical Noonan syndrome.

Noonan syndrome should be considered in all fetuses with polyhydramnios, pleural effusions, edema, and increased nuchal fluid. If it is suspected in the fetus or a first degree relative, an obstetric ultrasound is recommended at 12-14 weeks, 20 weeks and in the third trimester. Additionally physical examination of the parents for features of the syndrome is warranted.

Genetic Testing in Noonan Syndrome:

Genetic testing is available for the four genes involved in Noonan syndrome. Sequence analysis of exons is available for PTPN11, SOS1, KRAS, and RAF1 genes. Fifty percent of individuals with Noonan syndrome have PTPN11 mutations detected via sequence analysis. An additional one percent have mutations in PTPN11 that are detected via FISH analysis. Five percent of individuals have mutations in KRAS which are detected via sequence analysis. Ten to thirteen percent have SOS1 mutations and three to seventeen percent have RAF1 mutations are detected by sequence analysis.

The typical testing strategy for patients with Noonan syndrome is to begin with PTPN11 sequence analysis for exons 3, 8, 9, and 13. These are the known mutational hot spots. If no mutation is identified, SOS1 sequence analysis follows. If still no mutations are found, the remaining exons of PTPN11 and RAF1 exons 7, 14, and 17 are tested. Lastly, if no mutation is identified within these genes, the remaining exons of RAF1 and exons of KRAS are sequenced.

Genetic Counseling in Noonan Syndrome:

Noonan syndrome is an autosomal dominant condition. This means that just one mutation in a gene can cause an individual to have Noonan syndrome. Although many cases are sporadic, studies have reported that between 30-75% of families do have an affected parent making it crucial to explain the management and recurrence risks of this condition to families. Genetic counseling is recommended.

A careful physical examination of both parents is necessary to look for features of Noonan syndrome. If the family has an affected parent, the risk to have an offspring with Noonan syndrome is 50%. If the parents are clinically unaffected and do not have the same disease causing-mutation as their affected offspring, the risk to have an offspring with Noonan syndrome is less than 1%.

The affected child has a 50% risk of passing this condition to its offspring. Prenatal testing is possible if the specific mutation is known. Ultrasound evaluations, although not definitive, can be used to look for anomalies related to Noonan syndrome.

DIFFERENTIAL DIAGNOSIS:

Cardiofaciocutaneous syndrome, Costello syndrome, Watson syndrome, and LEOPARD syndrome share phenotypic features with Noonan syndrome. This overlap is attributed to their respective genes all being involved in the RAS-MAPKinase pathway.

Cardiofaciocutaneous syndrome (CFC) and Noonan syndrome have the greatest overlap. Patients with CFC, like Noonan, have downward slanted palpebral fissures, posteriorly rotated ears, and delayed motor and mental skills, gastrointestinal and cardiovascular abnormalities. Patients with CFC also have short stature. However, mental deficiency is more severe, and there is a higher likelihood of structural central nervous system anomalies in individuals with CFC. Additionally, skin pathology such as keratosis pilaris with patchy hyperkeratosis is more severe and long lasting; bleeding disorders are rare in CFC.

People affected with Costello syndrome (CS) and Noonan syndrome share many facial characteristics. These individuals have a large head, short wide nose, and short neck. Cardiovascular abnormalities such as pulmonary stenosis, atrial septal defects, and hypertrophic cardiomyopathy found in CS are similar to those found in Noonan syndrome. However, unlike in patients with Noonan syndrome, individuals with Costello syndrome have thick and prominent lips and tongue, and loose skin on the hands and feet.

LEOPARD syndrome and Noonan syndrome share similar facial dysmorphisms and cardiac defects. Hypertrophic cardiomyopathy is more commonly seen in patients with LEOPARD syndrome. Findings of cutaneous lentiginos and unilateral or bilateral hearing loss are the distinguishing features of LEOPARD syndrome.

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Support Groups:

The Noonan syndrome support group inc.

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Human Growth Foundation

For more information please contact:

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The MAGIC Foundation

For more information please contact:

6645 West North Avenue
Oak Park, IL 60302
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About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on

the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

Acknowledgments:

The RCPU Newsletter is funded by the Raymond C. Philips Research and Education contract with the Department of Health, Children's Medical Services.

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