

# The RASopathies

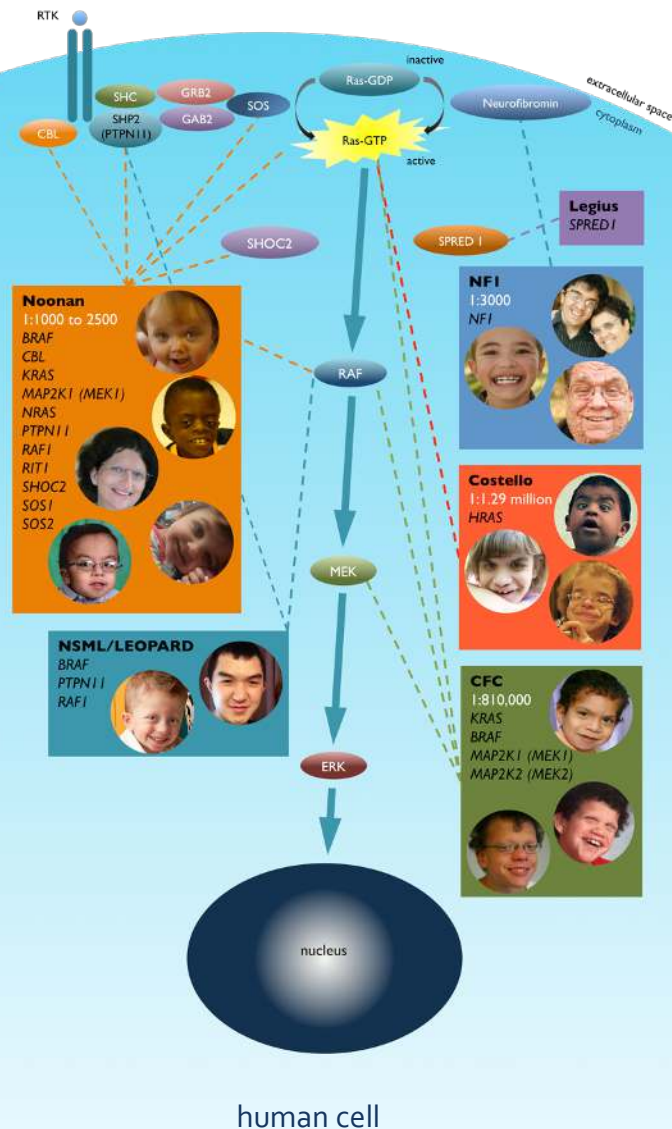
The RASopathies are a group of rare genetic conditions caused by mutations in genes of the Ras-MAPK pathway. Abnormalities of this pathway have profound effects on development and can cause one of several different syndromes, including:

- Cardiofaciocutaneous (CFC)
- Costello (CS)
- Legius
- Neurofibromatosis type 1 (NF1)
- Noonan (NS)
- Noonan with Multiple Lentigines (NSML) (formerly known as LEOPARD (LS))

These syndromes have many clinical features in common, such as distinct facial features, developmental delays, cardiac defects, growth delays, neurologic issues, and gastrointestinal difficulties. While these individual syndromes are rare, as a group, the RASopathies are among the most common genetic conditions in the world.

- Pilar Magoulas, Genetic Counselor, 2013

## The RAS/MAPK Pathway



Photos courtesy of Rick Guidotti/Positive Exposure, Anahita Avalos, families and individuals – with much appreciation and gratitude.

## Fostering Research

RASopathiesNet has been convening scientific meetings concurrently with the CFC, CS, Noonan and NF1 family forums since 2009.

### Notes:

- 1 CFC and CS prevalence numbers: high numbers published by Aoki et al; low numbers from the UK, unpublished.
- 2 CFC information from Rauen KA, GeneReviews for CFC syndrome, 2012
- 3 CS information from Gripp KW and Lin AE, GeneReviews, updated 2012
- 4 NF1 information from Friedman JM, GeneReviews for Noonan syndrome, 2012
- 5 NS information from Allanson JE, GeneReviews for Noonan syndrome, 2012
- 6 NSML/LS information from Gelb BD, Tartaglia M, for GeneReviews for LEOPARD syndrome, 2010

For More Information

<https://rasopathiesnet.org>

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A resource and repository for research on syndromes with mutations on the Ras/mitogen activated kinase signaling pathway

# RASopathiesNet

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# Genetic syndromes with mutations on the Ras/mitogen activated protein kinase pathway

## Cardiofaciocutaneous syndrome (CFC)

- 1:150,000 to 1:810,000

CFC syndrome causes heart issues (pulmonic stenosis and other valve dysplasias, septal



defects, hypertrophic cardiomyopathy, rhythm disturbances), distinctive craniofacial appearance, and skin conditions (including xerosis, hyperkeratosis, ichthyosis, keratosis pilaris, ulerythema ophryogenes,



eczema, pigmented moles, hemangiomas, and palmoplantar hyperkeratosis). The hair is typically sparse, curly, fine or thick, woolly or brittle; eyelashes and eyebrows may be absent or sparse. Nails may be dystrophic or fast growing. Some form of neurologic and/or cognitive delay

(ranging from mild to severe) is seen in all affected individuals. Tumors, mostly acute lymphoblastic leukemia (ALL), have been reported in some individuals.



## Costello syndrome (CS)

- 1:300,000 to :1.25 million

CS causes failure to thrive in infancy as a result of severe post-natal feeding difficulties; short stature; developmental delay or intellectual disability; coarse facial features (full lips, large mouth, full nasal tip); curly or sparse, fine hair; loose, soft skin with deep palmar and plantar creases; skin tags of the face and perianal region; diffuse hypotonia and joint

laxity with ulnar deviation of the wrists and fingers; tight Achilles tendons; and heart problems including cardiac hypertrophy



(usually typical hypertrophic cardiomyopathy [HCM], congenital heart defect (usually valvar pulmonic stenosis), and arrhythmia (usually supraventricular tachycardia), especially chaotic atrial rhythm/multifocal atrial tachycardia or ectopic atrial tachycardia).



Relative or absolute macrocephaly (unusually large head) is common, and postnatal cerebellar overgrowth can result in the development of a Chiari I malformation with associated anomalies including hydrocephalus or syringomyelia. Individuals with Costello syndrome have about a 15% lifetime risk for malignant tumors including rhabdomyosarcoma and neuroblastoma in young children, and transitional cell carcinoma of the bladder in adolescents and young adults.



## Neurofibromatosis type 1 (NF1)

- 1:3,000



NF1 includes multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules. At least 50% of individuals with NF1 have learning disabilities. Less common but potentially more serious issues include plexiform



neurofibromas, optic nerve and other central nervous system gliomas, malignant peripheral nerve sheath tumors, scoliosis, tibial dysplasia, and vasculopathy.

## Noonan syndrome (NS) - 1:1,000 to 1:2,500

NS causes short stature, congenital heart defect, and developmental delay of variable degree. Other effects can include broad or webbed neck, unusual chest shape



with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, characteristic facies, varied coagulation defects, lymphatic dysplasias, and eye abnormalities.

Although birth length is usually typical, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals.



Hypertrophic cardiomyopathy (HCM), found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural heart defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one third of affected individuals have mild intellectual disabilities.

## Noonan syndrome with multiple lentigines (NSML) formerly known as LEOPARD syndrome (LS)



NSML was formerly known as LEOPARD syndrome (LS), an acronym for the key features **L**entigines, **E**CG conduction abnormalities, **O**cular hypertelorism (widely set eyes), **P**ulmonic stenosis, **A**bnormal genitalia, **R**etardation of growth, and **D**eafness; however, all these traits may

not develop in an affected person. Multiple lentigines look like dispersed flat, black-brown spots, mostly on the face, neck and upper part of the trunk. In general, these spots do not appear until the person is four to five years old, but then increase to the thousands by puberty. Some individuals with NSML/LS do not develop lentigines. About 85% of people with NSML/LS have heart defects, including hypertrophic cardiomyopathy (HCM) (typically appearing during infancy and is sometimes progressive) and pulmonary valve stenosis. In fewer than half of individuals with NSML/LS, growth after birth is slow, which results in short stature. Sensorineural deafness, present in about 20%, is poorly defined. Intellectual disability, typically mild, affects about 30% of individuals with NSML/LS.



## Noonan syndrome with loose anagen hair (NSLAH)

NSLAH features include short stature, facial features typical of NS including macrocephaly, high forehead, hypertelorism, palpebral ptosis, and low set and posteriorly rotated ears, short and webbed neck, redundant skin, hypernasal voices and pectus abnormalities. Also enlarged cerebrospinal fluid spaces, severe growth hormone deficiency, mild



psychomotor delay with ADHD that improves with age, mild dilation of the pulmonary root, and a unique combination of ectodermal abnormalities (darkly pigmented skin with eczema or ichthyosis).

Generally the skin is darkly pigmented and hairless. The hair of the head has the characteristics of loose anagen hair syndrome, which is easily pluckable, sparse, thin, slow-growing and generally silver-blond. Common cardiac anomalies include mitral valve and septal defects. Mazzanti et al. (2003) suggested the disorder in these children is distinct from Noonan syndrome.