

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

## Cardiofaciocutaneous syndrome

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

Cardiofaciocutaneous (CFC) syndrome causes heart issues (pulmonic stenosis and other valve dysplasias, septal defects, hypertrophic cardiomyopathy, rhythm disturbances), distinctive craniofacial appearance, and skin problems (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

Costello syndrome (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

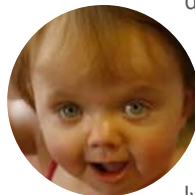
Neurofibromatosis 1 (NF1) includes multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules. At least 50% of individuals with NF1 have learning disabilities. Less common but potentially more serious issues include plexiform neurofibromas, 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

Noonan syndrome (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 disability.



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

Noonan syndrome with multiple lentigines (NSML) is also known as LEOPARD syndrome (LS) is an acronym for the key features **L**entigines, **E**CG conduction abnormalities, **O**cular hypertelorism (widely set eyes), **P**ulmonic stenosis, **A**bsnormal 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 LS do not develop lentigines. About 85% of people with NNSML/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.



# The RASopathies

## Fostering Research

The RASopathies network has been convening scientific meetings concurrently with the CFC, CS, Noonan and NF1 family forums since 2009. The next planned meeting is for Summer 2015.

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: Cardio-Facio-Cutaneous (CFC), Costello (CS), Legius, Neurofibromatosis type 1 (NF1), Noonan (NS), and Noonan with Multiple Lentigines (NSML) (formerly called LEOPARD (LS)).

These syndromes share many clinical features in common with one another, 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

### 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

<http://rasopathiesnetwork.org>

For More Information

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

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

# RASopathiesNet

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