FACTSHEET #3
RASOPATHIES

Noonan Syndrome Association

The genes associated with Noonan syndrome play a crucial role in the Ras-mitogen-activated protein kinase (Ras/MAPK) pathway.

Genes in this pathway are involved in the development and growth of cells in the body. Changes (mutations) in one or more of these genes means that, when the body is developing and growing – in the womb, after birth and during childhood – some of the processes may go awry.

For example, the protein produced by the PTP11 gene has an essential role in the development of heart valves in the womb. People with a change in this gene have a higher risk of congenital heart disease.

Several other syndromes are also associated with the Ras/MAPK pathway, including Costello syndrome, Cranio-facio-cutaneous (CFC) syndrome, Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome), and neurofibromatosis. Collectively, the group of syndromes are known as the RASopathies and they share many similar features.

Noonan syndrome

People with Noonan syndrome have characteristic facial features, particularly during childhood, which change with age and may be insignificant in adults. These include a broad forehead, widely spaced eyes, drooping of the upper eyelids, a high-arched palate, and low-set, posteriorly rotated ears. They may also have congenital heart defects, short stature, undescended testicles, eye problems, and bleeding disorders. Intellectual development may be normal or mildly impaired, but in rare cases may be more severe.

Noonan syndrome with multiple lentigines (NSML)

People with this condition have the same characteristics as Noonan syndrome with a higher incidence of cardiomyopathy but can also develop multiple skin lentigines or freckles. This syndrome was previously known as LEOPARD syndrome which represented the initial letters of the clinical features.

RASopathy disorders and their known disease genes

RASopathy	Disease genes	Cases accounted for by known disease genes (%)
Noonan syndrome	PTPN11, SOS1, RAF1, KRAS, MRAS, NRAS, RRAS, BRAF, RIT1, SOS2, LZTR1, RASA2, RRAS, RRAS2 MAP2K1	90
Noonan syndrome with multiple lentigines (NSML)	PTPN11, RAF1, BRAF	>90
Noonan syndrome-like with loose anagen hair	SHOC2, PPP1CB	100
Costello syndrome	HRAS	100
Cardiofaciocutaneous syndrome (CFC)	BRAF, MAP2K1, MAP2K2, KRAS	70
Noonan-like with juvenile myelomonocytic leukaemia	CBL	100
Neurofibromatosis 1	NF1	>90

Noonan Syndrome Association

Noonan syndrome-like with loose anagen hair

The characteristics of this condition are reminiscent of Noonan syndrome. However, it is associated with reduced growth, often associated with proven growth hormone deficiency, more significant cognitive deficits, distinctive behaviour, and easily pluckable, sparse, thin, slow-growing hair. Most people with this condition have heart problems.

Costello syndrome

The facial features associated with this condition are similar to those of Noonan syndrome but can be more coarse. People with this condition also suffer from congenital heart defects, failure to thrive, short stature, eye problems, skin problems including warts (papilloma), low muscle tone and a strong predisposition to cancer. Intellectual development may be normal or mildly impaired.

Cardiofaciocutaneous syndrome (CFC)

People with this condition tend to have facial features similar to those of Noonan syndrome. They are prone to congenital heart defects, failure to thrive, short stature; eye problems, low muscle tone, and multiple skin issues, including the progressive formation of moles (nevi). Intellectual development tends to be more impaired than in Noonan syndrome. Their predisposition to cancer is probably low.

Noonan-like with juvenile myelomonocytic leukaemia

This condition confers predisposition to juvenile myelomonocytic leukaemia during childhood. This blood cancer occurs when immature blood cells (called blasts) make too many myelocytes and monocytes (two types of white blood cells.) The myelocytes, monocytes, and blasts crowd the normal cells in the bone marrow and other organs in the body and cause problems. The response to treatment may be excellent. Relatively common issues include developmental delay and reduced growth, facial dysmorphism, and café-au-lait spots – pigmented skin patches or birthmarks that may vary in colour from light brown to dark brown.

Neurofibromatosis 1

This condition is characterised by soft, non-cancerous tumours on or under the skin that develop on the coverings of nerves (neurofibromas). If neurofibromas develop where multiple branches of nerves come together (plexiform neurofibromas), they can cause large swellings. It also causes café-au-lait spots and freckling in the armpit and groin, problems with the bones, eyes and nervous system, and predisposes to other cancers.

More details about Neurofibromatosis 1 are available from Nerve Tumours UK (https://nervetumours.org.uk).

REFERENCES/FURTHER READING

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Linglart L, Gelb BD. Congenital heart defects in Noonan syndrome: Diagnosis, management, and treatment. Am J Med Genet C Semin Med Genet. 2020;184(1):73-80.

NHS: Neurofibromatosis type 1 – Symptoms: https://www.nhs.uk/conditions/neurofibromatosis-type-1/symptoms/

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Factsheet created: Aug 2022