Genetic study of Noonan syndrome and other RASopathies

The rasopathies constitute a group of developmental disorders that course with mental retardation and / or learning problems, cardiac and skin alterations, and predisposition to cancer.

Among this group of pathologies, the best known is Noonan syndrome, which has an estimated incidence of between 1/1000 and 1/2500 live births.

This study analyzes the sequence of 14 genes, involved in the RAS / MAPK pathway, whose alteration is responsible for this group of syndromes.

- The majority of the pathogenic variants that cause rasopathies are de novo. However, familial cases have been reported.
- The pattern of inheritance is autosomal dominant, with complete penetrance and variable expressivity.

PHENOTYPE (OMIM #)	ASSOCIATED GENES
Noonan Syndrome (#163950, #609942, #610733, #611553, #613224, #613706, #615355, #151100)	*PTNP11, SOS1, RAF1, RIT1, NRAS, KRAS, BRAF, MAP2K1*
Noonan-like Syndrome (#613563, #607721)	*A2ML1, CBL, SHOC2*
Costello Syndrome (#218040)	*HRAS*
Cardiofaciocutaneous Syndrome (#115150, #615278, #615279, #615280)	*BRAF, MAP2K1, MAP2K2*
Legius Syndrome (#611431)	*SPRED1*

Frequency of pathogenic variants

Gene (OMIM#)	Noonan Syndrome	Noonan-like Syndrome	Cardiofaciocutaneous Syndrome	Costello Syndrome	Legius Syndrome
PTPN11 (*176876)	50%[1]	90%[5, 6]			
SOS1 (*182530)	10–13%[1]				
RAF1 (*164760)	5%[1]				
RIT1 (*609591)	5%[1]				
NRAS (*164790)	<1%[1]				
KRAS (*190070)	<5%[1]		75%[2]		
BRAF (*164757)			2–3%[2]		
MAP2K1 (*176872)	<2%[1]		25%[2]		
MAP2K2 (*601263)			25%[2]		
HRAS (*190020)				80–90%[3]	
SPRED (*609291)					>80%[4]
A2ML1 (*610627)	–[5]	–[6]			
CBL (*165360)		–[6]			>80%[4]
SHOC2 (*602775)		–[6]			

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