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Noonan Syndrome

- Ineke van der Burgt
- Human Genetics UMC Nijmegen
- The Netherlands

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What is Noonan syndrome?

Defining syndromes:

- Patients placed centrally
- Consequences for the patient main determinant:
  - The phenotype
  - Natural history and complications
  - Mode of inheritance or risk of recurrence

Hennekam, AmJMedGenet 2007

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NOONAN SYNDROME

- First described in 1963

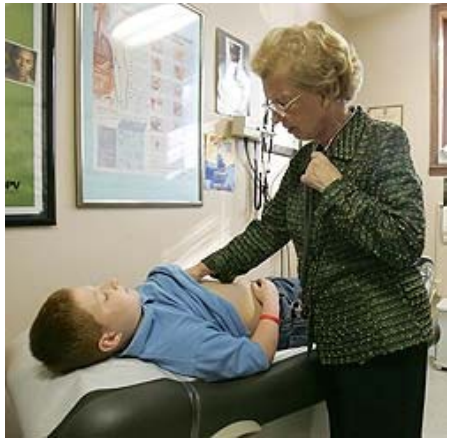
  by Jacqueline Noonan

Running Together:

*Characteristic Facies

*Pulmonary Valve Stenosis

*Short Stature



A Heart of Gold Honored 2006

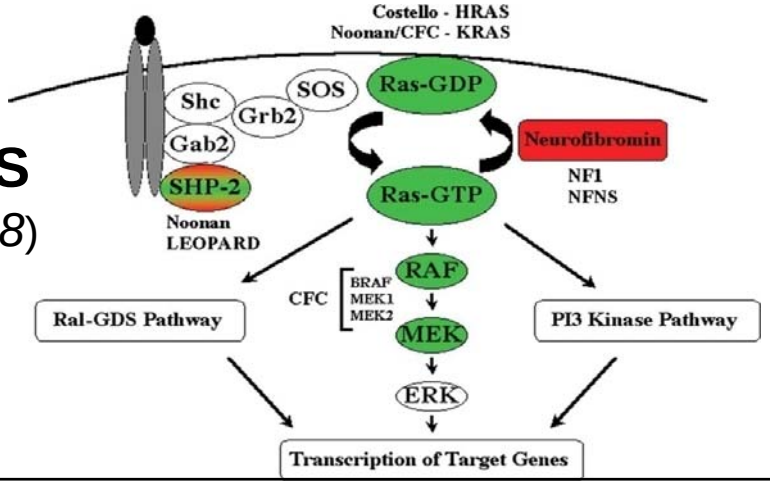
NS and the genes of the Ras- pathway

Gene	*Locus*	
PTPN11	**12q24.1**	**(50%)**
SOS1	**2p22-p21**	**(10-15%)**
KRAS	**12p12.1**	**(<5%)**
RAF1	**3p25**	**(3-17%)**

Duplication 12q24.11q24.23 --> NS

(*Oleg A. Shchelochkov,2008*)

BRAF, MEK1

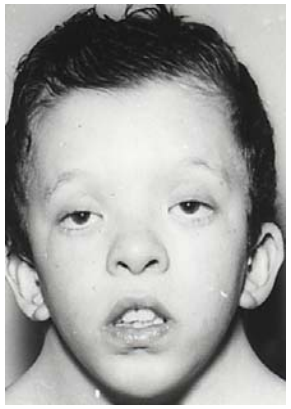


Who has Noonan syndrome?

NS Scoring systems

1981 Duncan (23 items)
1984 Preus
1992 Sharland
1994 van der Burgt

Suggestive face



Typical face

Lessons from molecular analysis; unexpected insights for phenotypes

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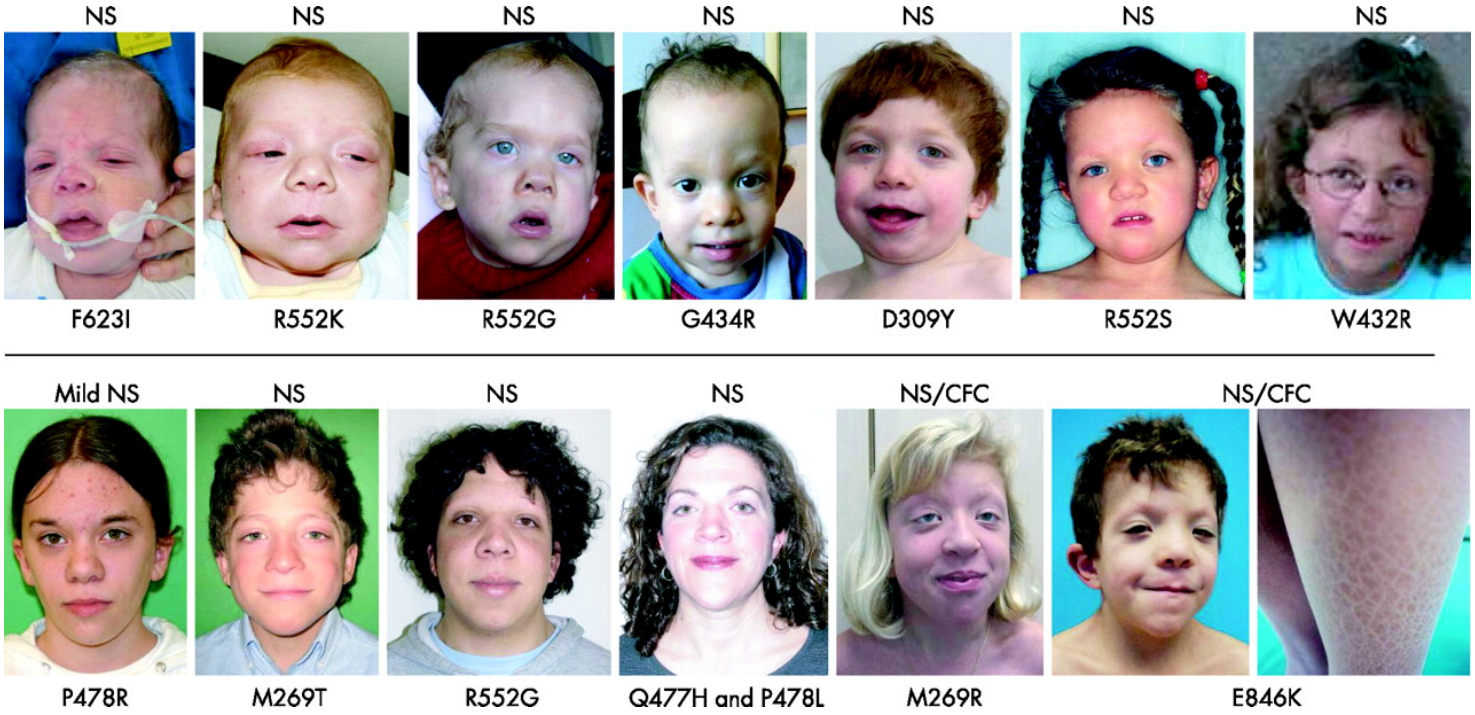
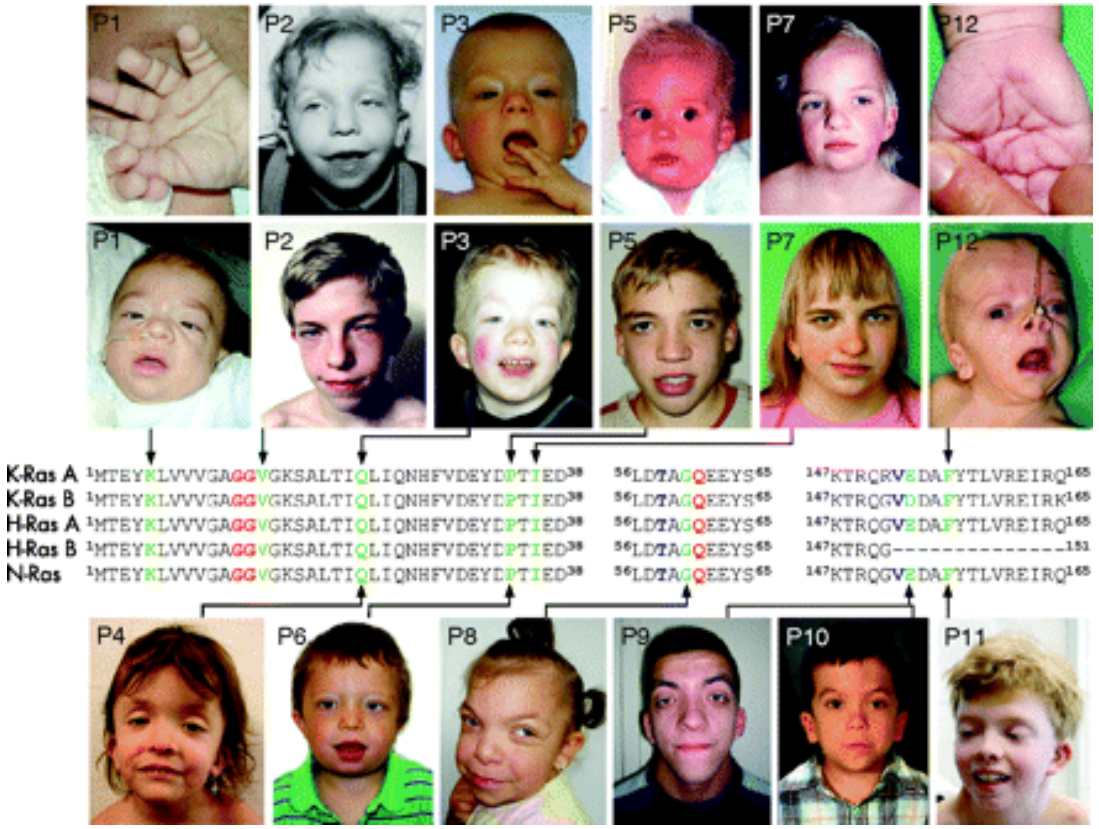
The face in *SOS1*+ NS



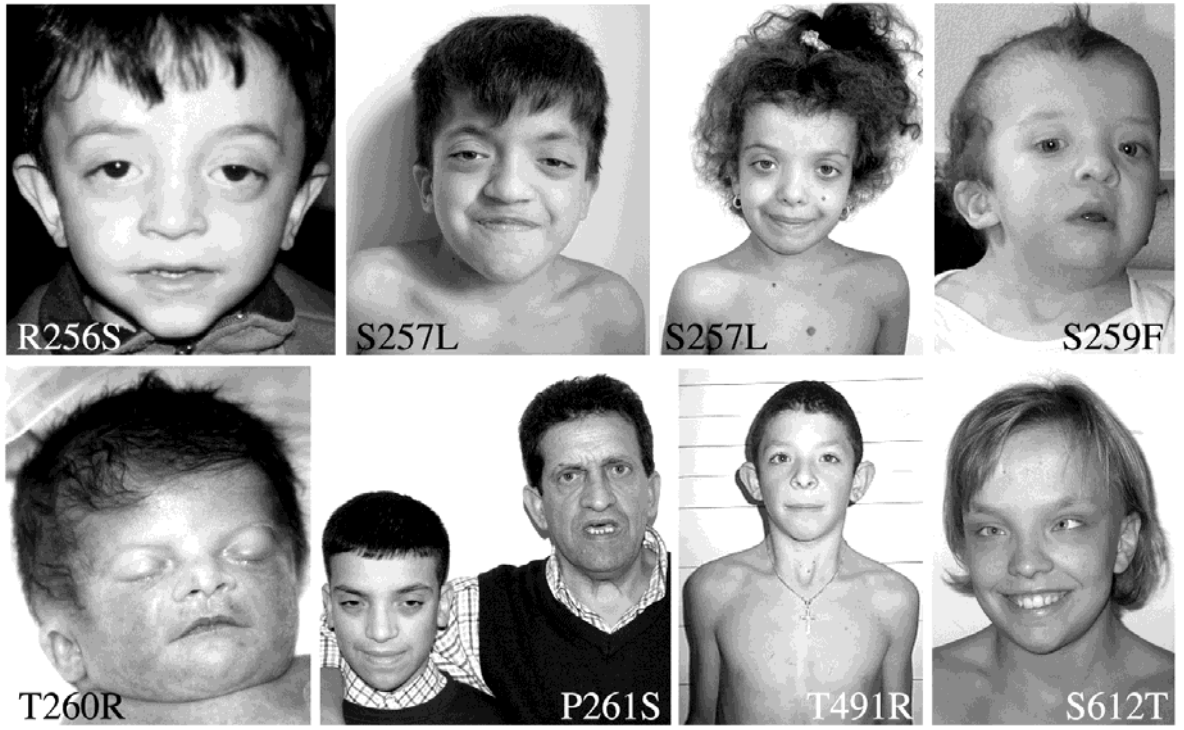
Zenker, JMedGenet 2007

The face in *KRAS*+ NS



Zenker JMedGenet 2007

The face in *RAF1*+ NS



Pandit, Nature Genetics 2007

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The Heart in Noonan Syndrome

- PS most common CHD (20 - 50%),
- HCM in ca 20 – 30% and ASD in ca 10%

- PS more common in *PTPN11*+ patients

- HCM more common in *RAF1*+ patients
- PS less prevalent in *RAF1*+ patients

(Pandit, 2007 Razzaque,2007)

- ASD less frequent in *SOS1*+ patients

(Roberts, 2007)

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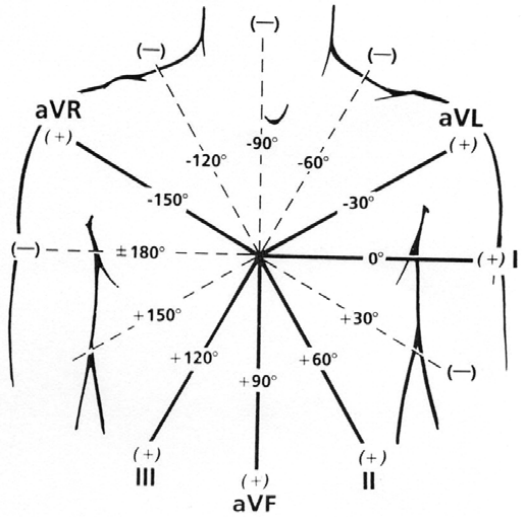
The electrocardiogram in Noonan syndrome

Wide QRS complex
Left-axis deviation
Pathologic Q
Little R development over the left precordium



Sanchez-Cascos 1983

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Study group	PTPN11 + (n=56)	PTPN11 – (n=29)	P-value*
Abberant ECG (%)	**30 (53,6%)**	**12 (41,4%)**	0,201
Number of ECG characteristics:			
1 ECG characteristic (%)	16 (28,6)	8 (27,6)	0,567
2 ECG characteristics (%)	12 (21,4)	3 (10,3)	0,166
3 ECG characteristics (%)	2 (3,6)	1 (3,4)	0,733
4 ECG characteristics (%)	**0 (0)**	**0 (0)**	------
Kind of ECG characteristic:			
Wide QRS complex	0 (0)	0 (0)	------
Left-axis deviation (%)	**27 (48,2%)**	**11 (37,9%)**	0,251
Pathologic Q (%)	3 (5,4)	2 (6,9)	0,559
Little R development over the left precordium (%)	**16 (28,6%)**	**4 (13,8%)**	0,103

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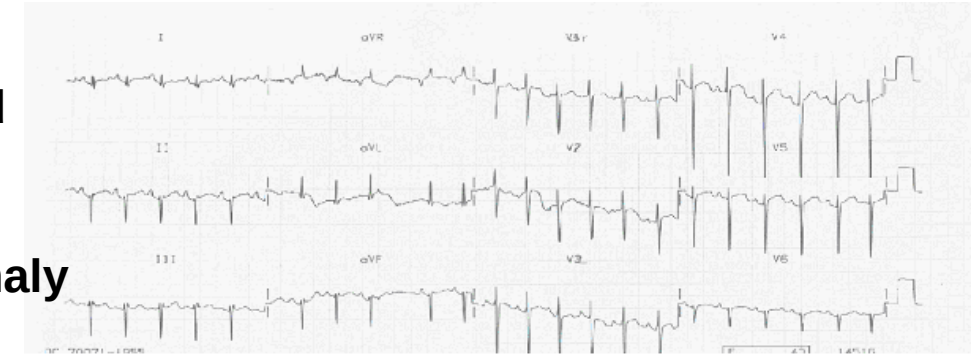
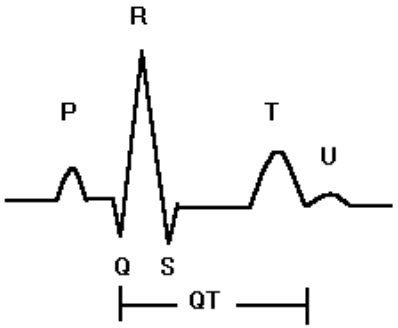
The electrocardiogram in Noonan syndrome

ECG findings not associated with a PTPN11 mutation or with a specific cardiac anomaly



Pre operative ECG in NS patient



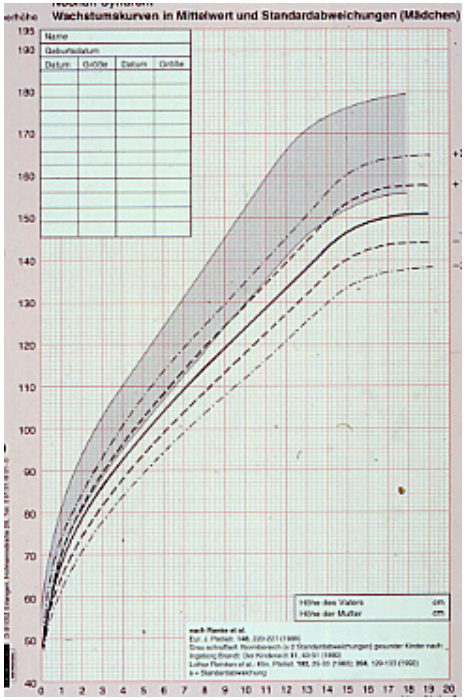
Normal ECG

45% **Left-axis deviation**

24% **Little R development over the left precordium**

Height in Noonan syndrome

- Normal length at birth
- Bone maturity and puberty delayed
- Final adult height; males 161 cm, females 152 cm (1986)



- Short stature more frequent in *PTPN11+*

(Zenker,2003)

- Mild GH resistance in *PTPN11+*

(Binder, 2005)

- Normal height more frequent in *SOS1+*

(Tartaglia, 2007)

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Evolution of Height-SDS during GH treatment (n=29) mean (SD) (range)

	At start	After 1 year	At final height
National standards	**–2.9**** (0.7)(–4.1 - –1.8)	-2.3** (0.7) (-3.8 - -1.2)	**–1.6**** (0.8) (-3.0 - -0.3)
Noonan standards	**–0.1**** (0.7) (–1.4 - +1.2)	+0.6 **/* (0.8) (-1.0 - +2.1)	**+1.2** * (0.9)(-1.1 - +2.9)

Mean age at start GH therapy 11 years

PTPN11 + n = 22

Boys n = 21

(Noordam, 2008)

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NOONAN SYNDROME
Other features

- “Webbed neck”
- Pectus car/excavatum
- Haematologic abnormalities
- Cryptorchidism
- Ophthalmologic and hearing abnormalities
- Ectodermal abnormalties
- Lymphatic vessel dysplasia
- Developmental delay / learning problems

Bleeding diathesis

- Up to 55% of all cases
- One-third have one or more coagulation defects
- Results do not correlate with bleeding risk

- Easy bruising more common in *PTPN11*+ patients

(Zenker,2003 Yoshida,2004)

- Roberts et al 2007: thrombocytopenia and/or easy bruising in *SOS1*+ patients
- Schubbert et al 2007: easy bruising in *KRAS*+ patient

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Myeloproliferative disorders (MPD)

- **Occasionally in NS patients**
- Specific mutations in *PTPN11* → (transient) JMML
  Kratz et al 2005; 8 out of 19: **218C>T (T73I)**
- JMML and ALL reported in *KRAS*+ patients
- No MPD in *SOS1*+ patients reported
- No MPD in *RAF1*+ patients reported

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Cryptorchidism in Noonan syndrome

- 60 – 80% of all boys with NS
  in *PTPN11*+, *SOS1*+, *KRAS*+ and *RAF1*+ patients
  * more frequent in *PTPN11*+ *(Zenker,2003)*

- Familial NS *PTPN11*+: maternal: paternal = 3:1
  (Tartaglia,2005)

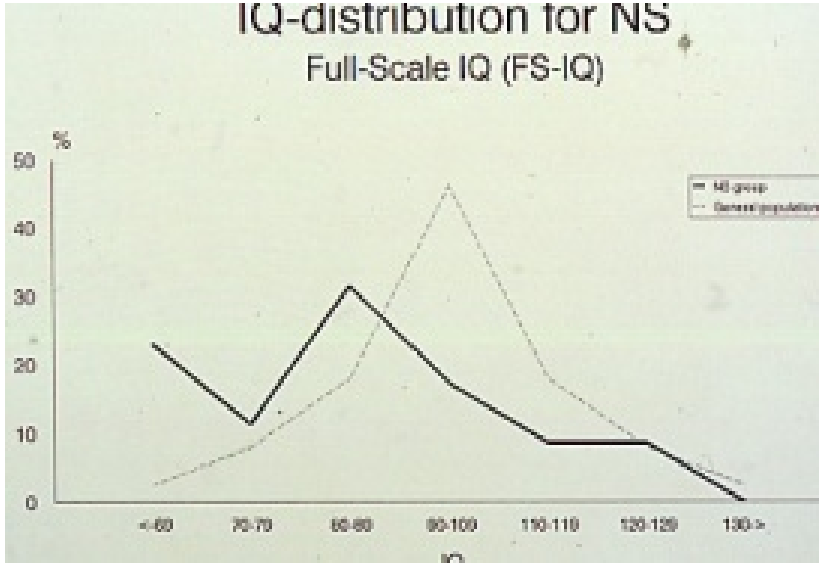
- Familial NS *SOS1*+: affected mothers and fathers

Developmental delay / learning problems

In general:

Mild motor delay (>70%)
Articulation problems (>70%)

Mild mental retardation 15-35%
Mean full scale IQ is 85



IQ scores in 35 children with NS, *1999*

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Developmental delay/ learning problems

PTPN11 hot spot mutation 922A>G (Asn308Asp)	More regular education *Jongmans,2005*
SOS1 mutations	Less MR/ special education *Tartaglia,2007 Zenker,2007*
KRAS mutations	Frequent developmental delay *Zenker,2007*
RAF1 mutations	8/21 (mild) Mental retardation *Pandit,2007*

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Social cognition and psychopathology in Noonan Syndrome

10 adult Patients (5 male, 5 female)

PTPN11 mutation in 6
KRAS mutation in 1
SOS1 mutation in 1

Heart:
PS in 6
Cleft MV in 1
No Heart Defect in 3

GH treatment in 5

No Mutation

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Results in first 10 persons with NS

Variability in IQ scores: 65 – 121

None met the criteria for ADHD/Pervasive Development Disorder

Social and emotional recognition and expression are moderately impaired

All patients were remarkably friendly, cooperative and willing to please

Tendency to desirable answering

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Online Abstract Submission ESHG 2008

14 with NS

- NS with multiple giant cell lesions > *PTPN11*+ and *SOS1*+

  Beneteau et al

- Low frequency of *PTPN11*+ in Mexican patients with NS

  Gonzalez-Huerta et al

- NS with marfanoid habitus in *SOS1*+ patient

  Morin et al

- NS phenotype in *BRAF*+ patient

  Nystrom et al

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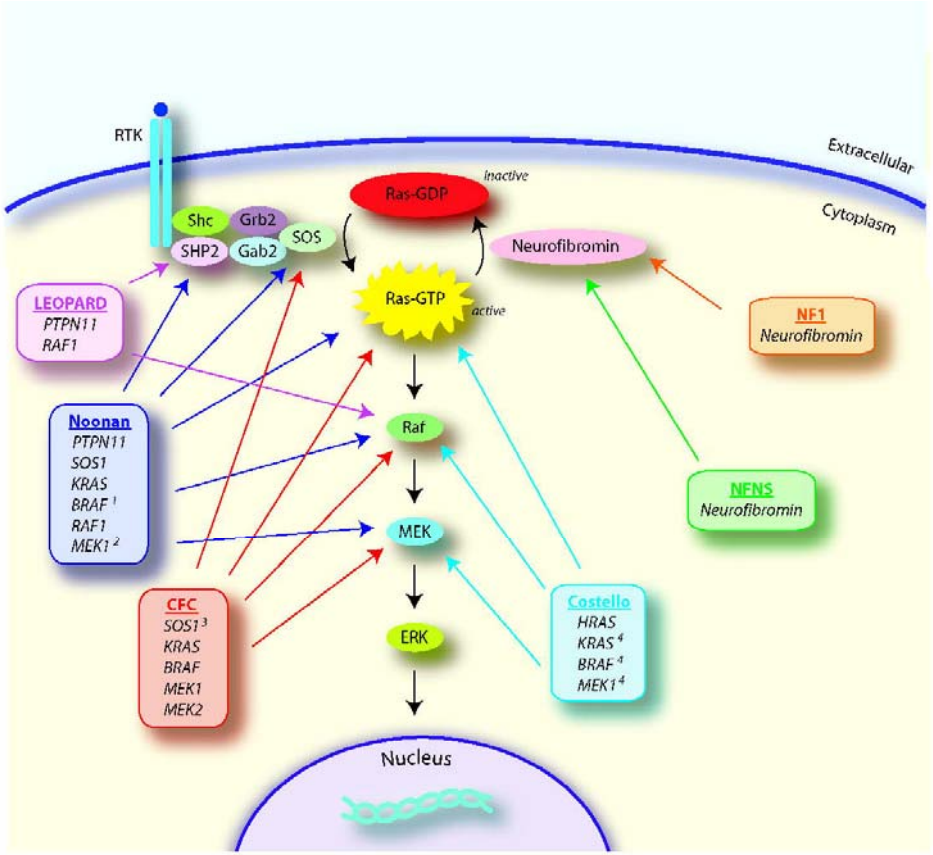
The Ras-MAPK pathway and the syndromes



Nystrom, J MedGenet, 2008