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NHS Foundation Trust

Understanding Costello syndrome; a journey

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Costello syndrome

- Costello 1971, 1977
- Moderate MR
- Poor postnatal growth
- Distinctive facies
- Loose skin hands, feet
- Nasolabial warts

1991-1998 clinical features

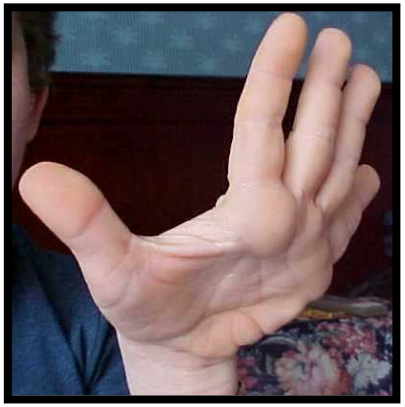
- Striking natural history
- Severe feeding difficulty invariable
- “Marasmic” phase
- Most NG feeding/ gastrostomy/ fundoplication

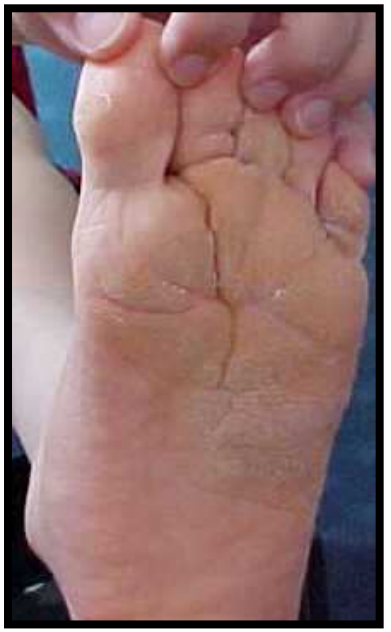
Key features

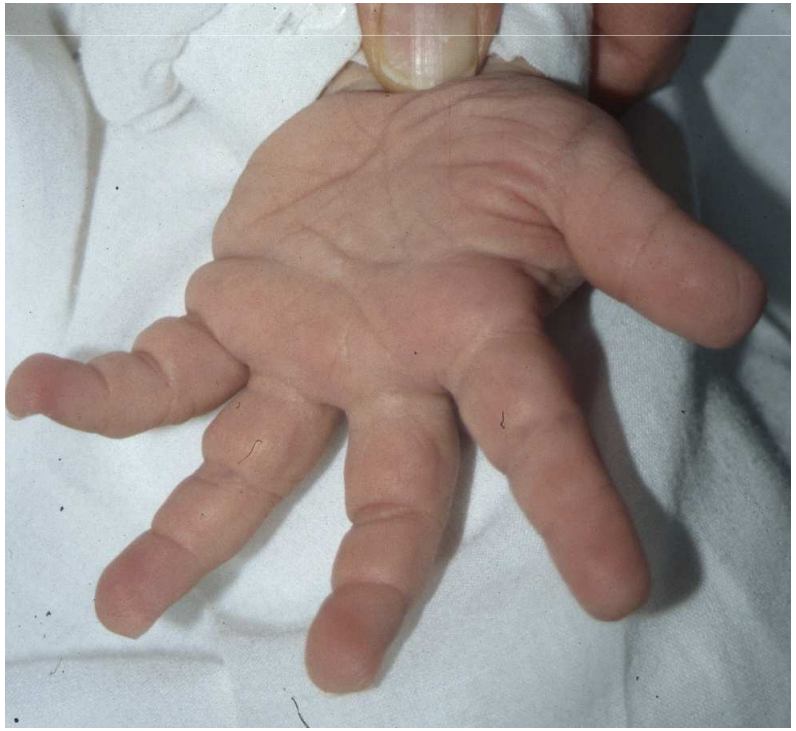
- Development; mild to moderate ID
- Pleasant sociable personality
- Distinctive face and hands
- Relative macrocephaly
- Short stature (Some GH)
- Warts at moist surfaces
- Cardiac abnormalities

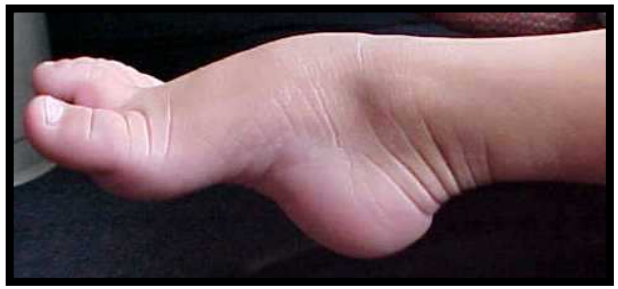
Hands and Feet

- Excess skin
- Hyperkeratosis
- Hyperextensible
- Square tips
- Ulnar deviation
- Flexion at wrists









1998

- Embryonal rhabdomyosarcoma in two children with CS from the north of England
- A cancer predisposing syndrome

Cancer risk 2002

- Published cancers; 21/127, 17%
- Embryonal rhabdomyosarcoma 11 of 21
- Mostly less than age 6
- Neuroblastoma/ ganglioneuroblastoma childhood
- Bladder carcinoma; adolescence and adult life
- Gastric polyps/leiomyoma/ breast fibroadenosis
- Benign bladder tumours

Families

- International Costello syndrome support groups 1996
- Web based
- Colin Stone
- Tammy Moore

Alabama 1999

International meetings

- 2001 Toronto
- 2003 Wilmington
- 2005 St Louis
- 2007 Portland
- 2009 San Francisco
- 2011 Chicago
- 2013 Orlando

French Costello Syndrome Association 2001

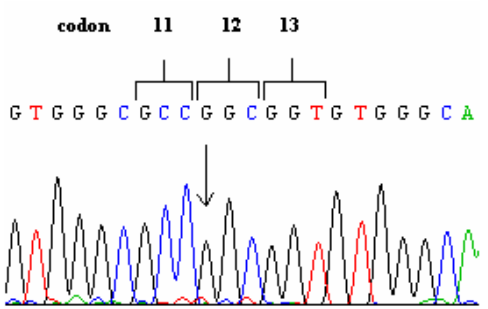
International Costello Family Forums

- Natural history growth, milestones, development, “ the phenotype”
- International collaboration, The adult phenotype, Sue White
- Powerful parent and professional partnership
- Strong research emphasis

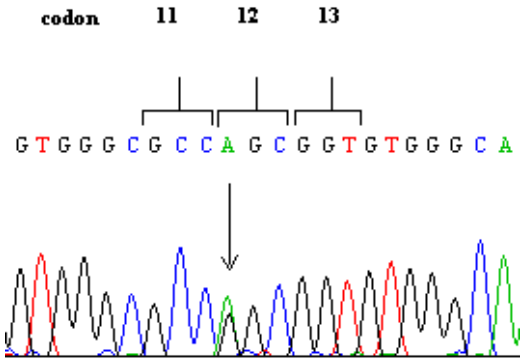
HRAS mutations cause CS
Aoki et al 2005

- HRAS mutations in >80% CS patients
- Mostly residues 12/13
- Activating
- Mostly paternal allele
- Somatic mosaicism reported

CONTROL



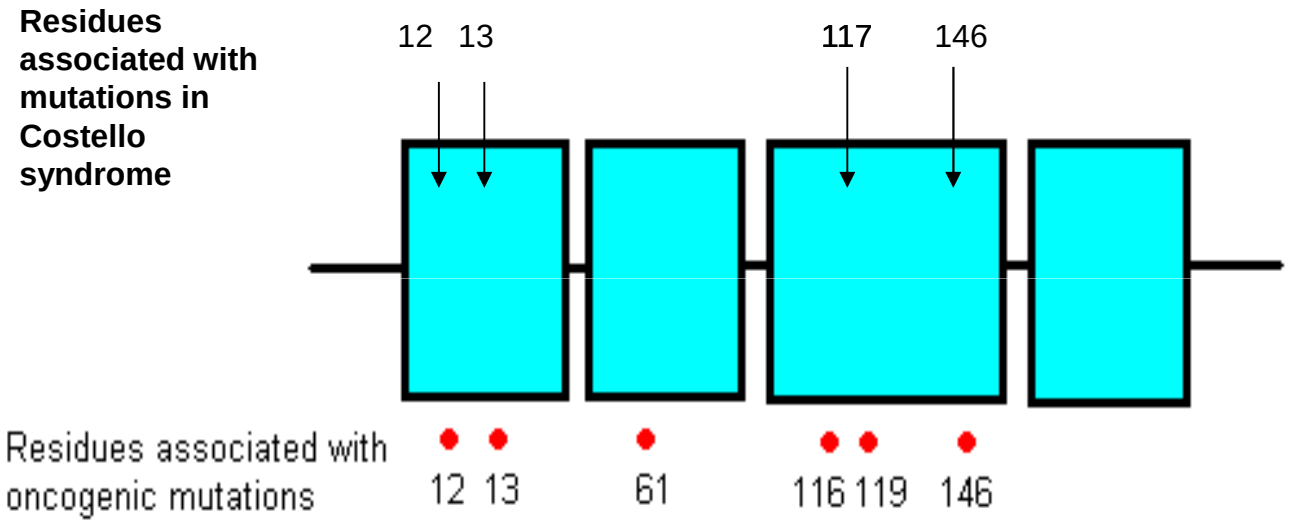
G12S



RAS-RAF-ERK-MAP kinase cascade

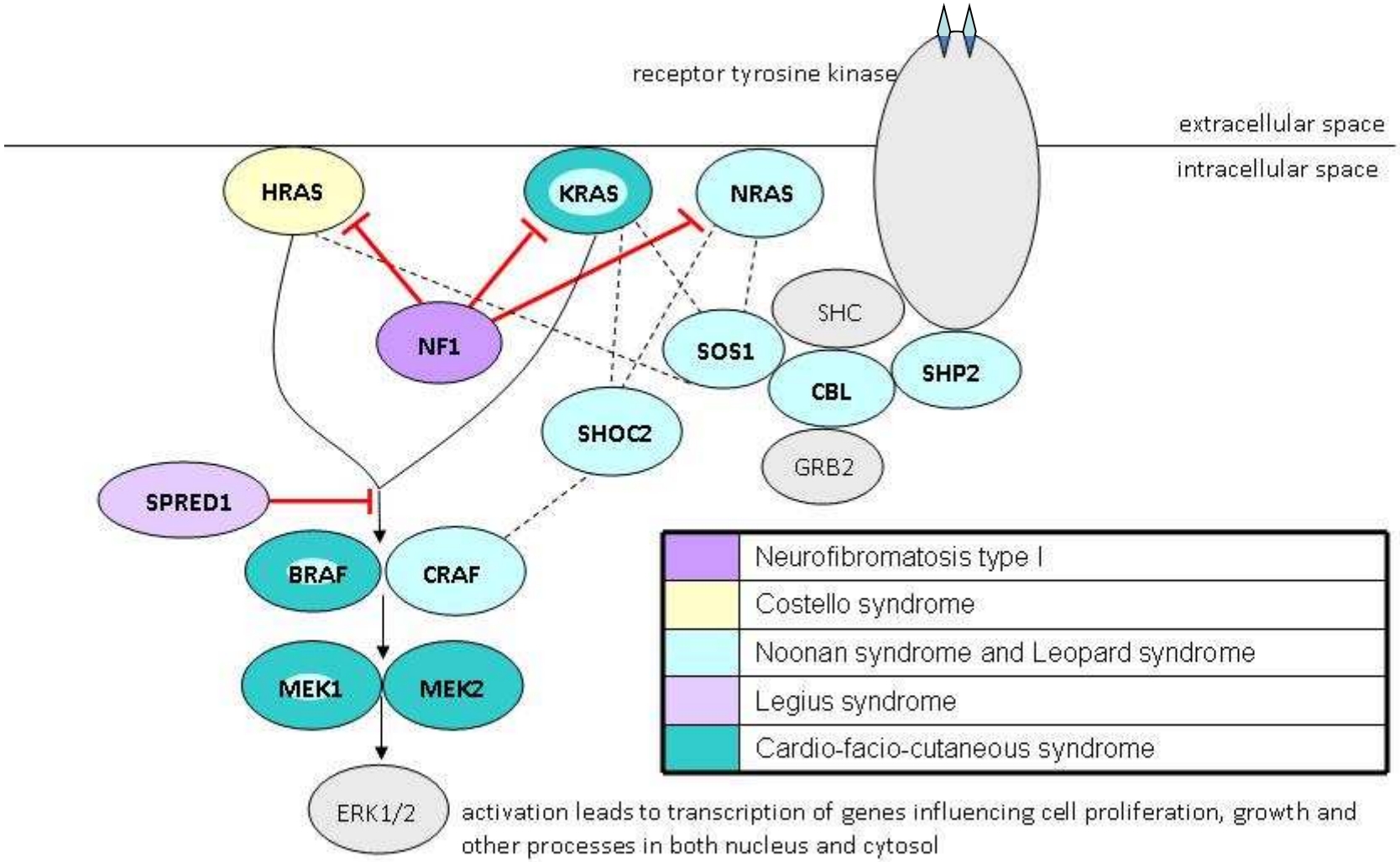
- Cancer pathogenesis
- Downstream of growth factor, cell adhesion and cytokine receptors
- Outcome: cell fate (proliferation, differentiation, cell death)
- Cognition; learning, memory, synaptic plasticity
- Immune modulation; vascular development

Genomic structure of *HRAS* with mutations



Aoki et al 2005
Kerr et al 2006, Zampino et al 2006

RAS-MAPK pathway genes/proteins in genetic disorders



“Rasopathies”

- Collectively common
- A single gene causes CS, multiple genes CFC, Noonan and NSML syndrome
- Collectively “ neuro-cardio-facio-cutaneous” syndromes (NCFCs)
- Overlapping clinical features
- Few genotype/phenotype correlations
- Precise clinical diagnosis often difficult

RAS/MAPK 1/1000

HRAS testing and the CS phenotype

Relatively homogenous. UK prevalence 2000-9;1/381,914 LB

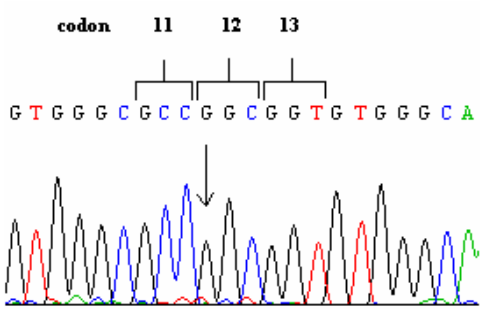
CS is due to HRAS mutations Aoki 2005

- Heterozygous *HRAS* mutations identified in 15 out of 16 UK patients

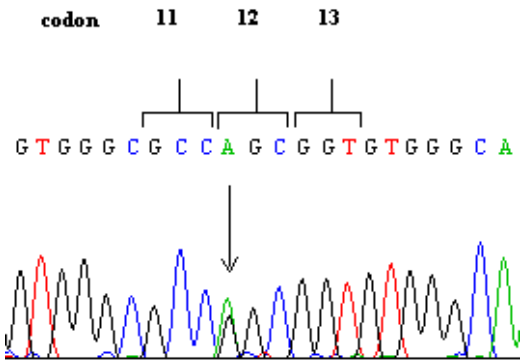
No. of patients	Heterozygous mutation	Amino acid change
11	**34 G > A**	**G12S**
2	**35 G >C**	**G12A**
1	**34 G >T**	**G12C**
1	**35 GC > AA**	**G12E**

Activating
Predominantly paternal
Somatic mosaicism reported
Germline mosaicism reported

CONTROL



G12S



CS versus CFC

BRAF

HRAS

Face evolves with time, 3-D studies;
overlap NS/CFC, CS/CFC, not CS/NS.
Peter Hammond

Diagnostic clues; prenatal

- Polyhydramnios 90%
- Macrocephaly
- Macrosomia
- Nuchal thickening
- Ascites
- Ventriculomegaly
- Hand posture
- Arrhythmia
- CS: G12D, G13C
- Prematurity 50%
- Advanced paternal age 50%

Smith, Padraza and Proud 2009,
Kuniba et al Am J Med Genet; 2009:
Lin et al, Prenat Diag; 2009
Lee et al; Clin Genet;2009

CS; malignancy risk

- Prospective study
  15% (Karen Gripp)
- Rhabdomyosarcoma
  60%
- Incomplete age
  dependence
- Neuroblastoma 15%
- Bladder carcinoma
  15%

Accurate clinical studies

- Cardiac manifestations
- Orthopaedic manifestations
- Eye
- Neurological manifestions
- Musculoskeletal manifestations
- Growth charts
- All underpinned by accurate molecular diagnosis
- Mutation specific

Neurodevelopmental evaluation

- Stable IQ
- Severe to average range
- Mean mild ID
- Adaptive behaviour scales show 70% in ID range
- Girls higher function
- Late childhood burst in non-verbal fluid reasoning
- Socialisation a strength
- Activities of daily living difficult
- Boys more behaviour difficulty

Longitudinal Course of Cognitive, Adaptive, and Behavioral Characteristics in Costello Syndrome
Axelrad et al 2009, Am J Med Genet

Milder phenotypes

- G13C
- Absent MAT,ulnar deviation, papillomata
- Less neurosurgical procedures
- Taller
- Loose anagen hair, very long eyelashes
- Gripp et al, 2011

- C.173C>T
- 3 patients, one father son
- No papillomata or malignancy
- One with significant cognitive impairment
- Gripp et al, 2012

Mutation specific counselling, when is Costello syndrome the right name?

Severe neonatal phenotypes

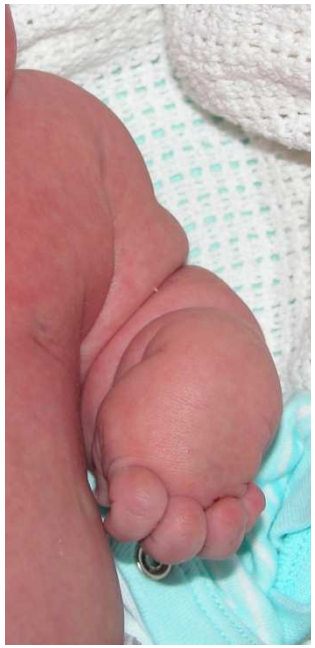
- Congenital myopathy with excess muscle spindles (CMEMS)
- Some Noonan like features
- Hypotonia, variable contractures, absence of spontaneous movement, areflexia, cardiomyopathy.
- G12S, G12V, E63K, Q22K

Van der Burght et al, J Med Genet; 2007

G12 D

Lo et al, J Med Genet; 2008

- Polyhydramnios, macrosomia
- Flexion contractures at wrist
- Septal/biventricular cardiac failure
- Severe jaundice
- Hypoglycaemia
- PAT; ASD, thickened septum
- Tracheomalacia/ bronchomalacia
- Chylothorax
- Pulmonary lymphangectasia PM



G12C

- Pleural and pericardial effusions
- W, HC 98th
- Small lungs
- CPAP dependent
- Atrial tachyarrythmia

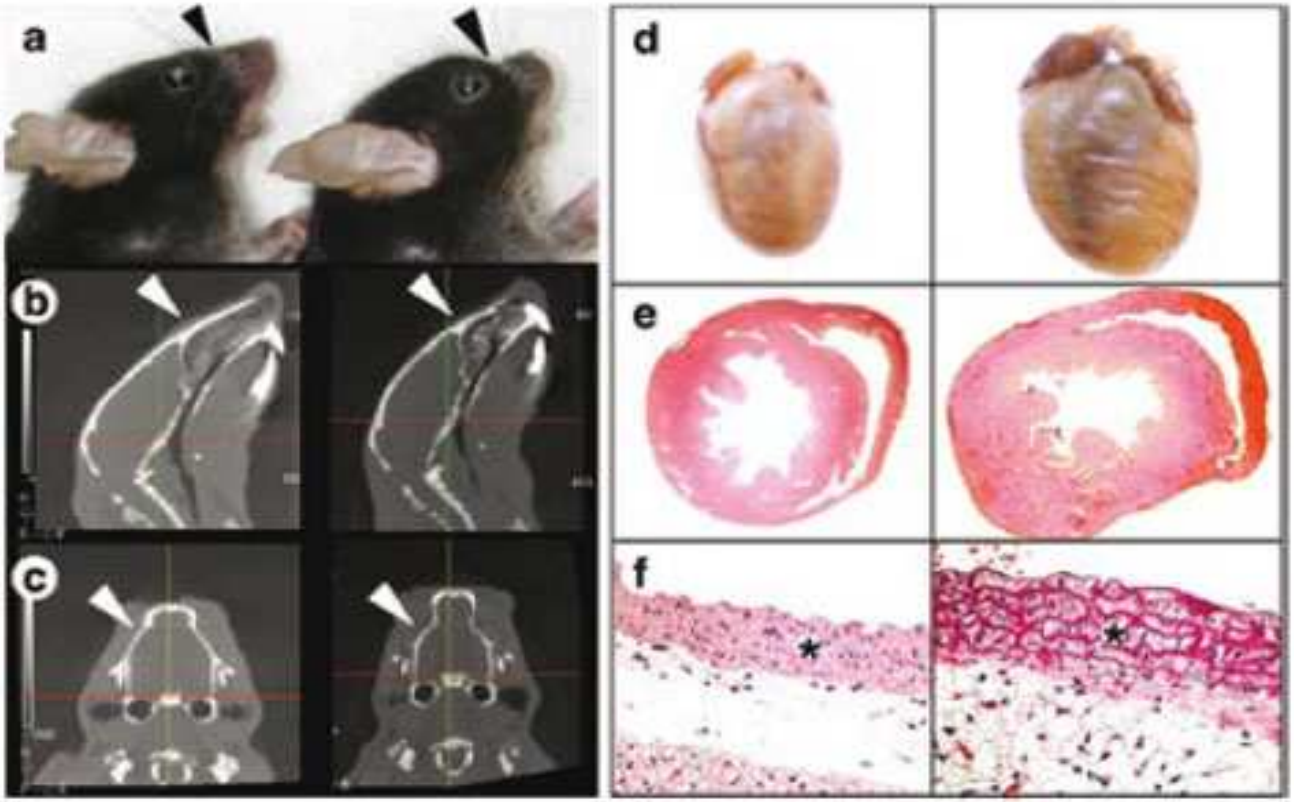
Severe neonatal phenotype

- Early lethality unrelated to tumour (UK 9/35, 6 multi-organ failure)
- Hypoglycaemia, Cardiomyopathy (G12V)
- Respiratory failure (aponea, airway, lung)
- Pleural and pericardial effusion
- Chylous ascites
- Severity scoring supports increased severity G12A and G12C (McCormack et al 2013)

Where are we now?

- Mutations in HRAS cause Costello syndrome
- Accurate description of phenotype
- A recognisable prenatal phenotype
- A core homogenous phenotype, milder and more severe variants (neonatal)
- Spectrum of mutation severity
- Differentiating from CFC may be difficult

H-ras G12V homozygotes vs wild type



Schuhmacher et al,
J Clin Invest. 2008;
118: 2169–2179

Mouse models: H-ras

- H-ras G12V mice generated at CNIO
- In homozygosity,
  - Noted to have unusual appearance
  - Some behavioural/cognitive differences
  - Hypertrophic cardiomyopathy and angiotensin-mediated hypertension

Schuhmacher et al, J Clin Invest. 2008; **118**: 2169–2179

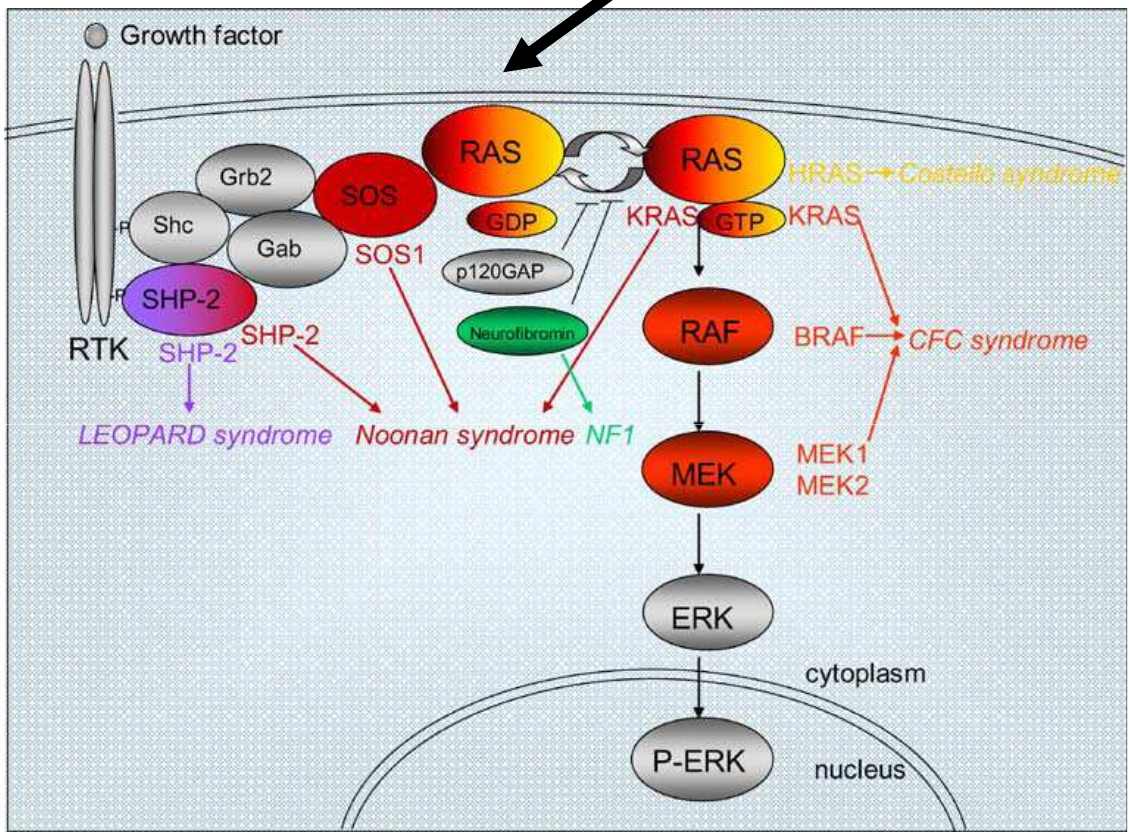
A Rasopathy

Altered clinical understanding

Increased research capability

Expanded international collaboration

Biannual research meeting



Denayer and Legius Eur J Paed;2007

A Rasopathy

- A clinical continuum
- Few truly specific or distinguishing features
- Research into one disorder may benefit all, cellular studies, animal models

- Treatment trials Novartis

Considering treatments

- Diagnostic test, major advances in natural history as a necessary baseline
- Treatment goals? Cardiomyopathy, adaptive behaviour or learning, muscular strength or endurance, skin manifestations, severe feeding difficulty and irritability of early life
- Improved understanding of mutation specific cellular biology

Acknowledgements

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