

# **CARDIOMIOPATIE RARE, CARDIOPATIE NEUROMUSCOLARI E MALATTIA DI ANDERSON-FABRY**

## **RASopatie e malattie cardiovascolari**

**Delogu Angelica Bibiana**



# The RAS-MAPK Pathway and RASopathies

RAS proteins are small GTP/GDP-binding GTPases, acting as molecular switches.

GTP binding, and the consequent RAS/MAPK pathway activation, stimulate a major intracellular network guiding diverse biological functions such as:



cell proliferation



migration



survival



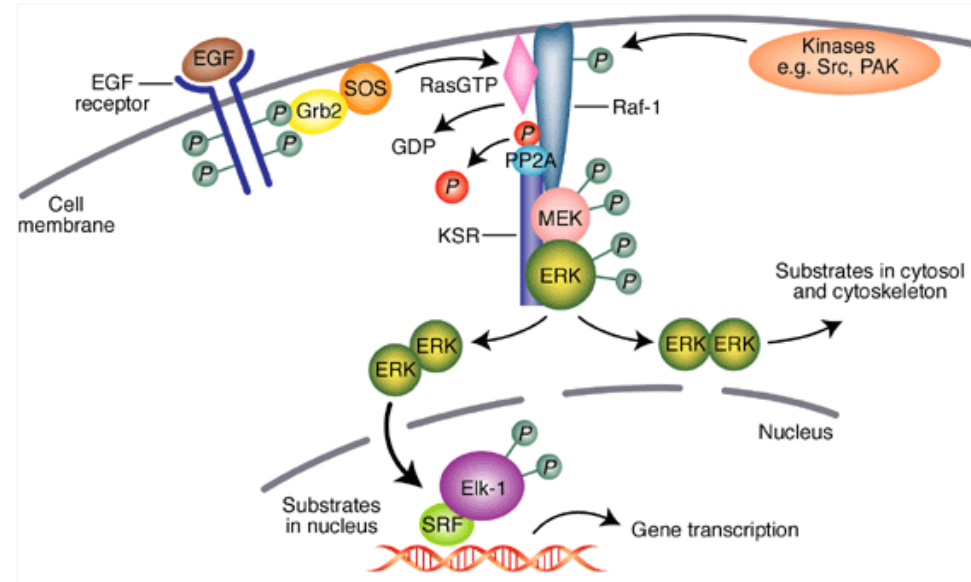
cell fate determination



differentiation



senescence

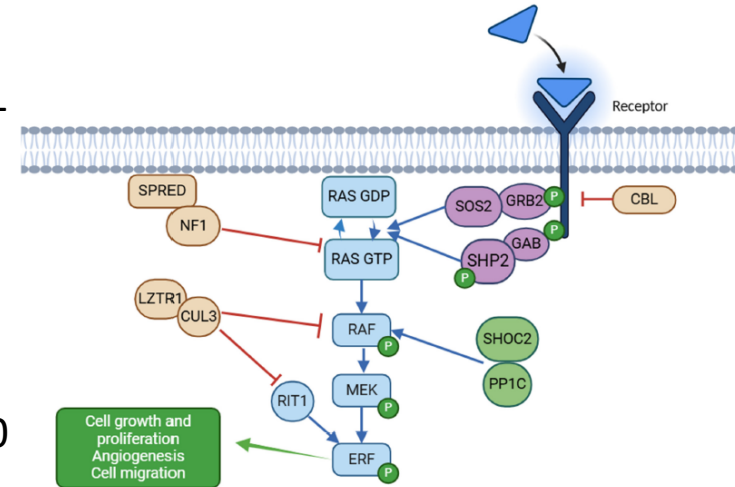


*Kamoub et al, 2008; Bader et al, 2000; Malubres et al, 2003*





- Germline alterations in genes coding for components of the RAS/MAPK cascade
  - germline variants in KRAS, HRAS
  - positive regulators of the cascade: PTPN11, SOS1, SHOC2
  - negative regulators: NF1, SPRED1
  - pathway effectors: BRAF, RAF1, MEK1-2
  - regulators of tyrosine kinase receptor activity: CBL
- Sporadic mutations in heterozygosity
- Autosomal dominant transmission
- Collectively, estimated prevalence of 1 in 1000 to 1 in 2500 among live births

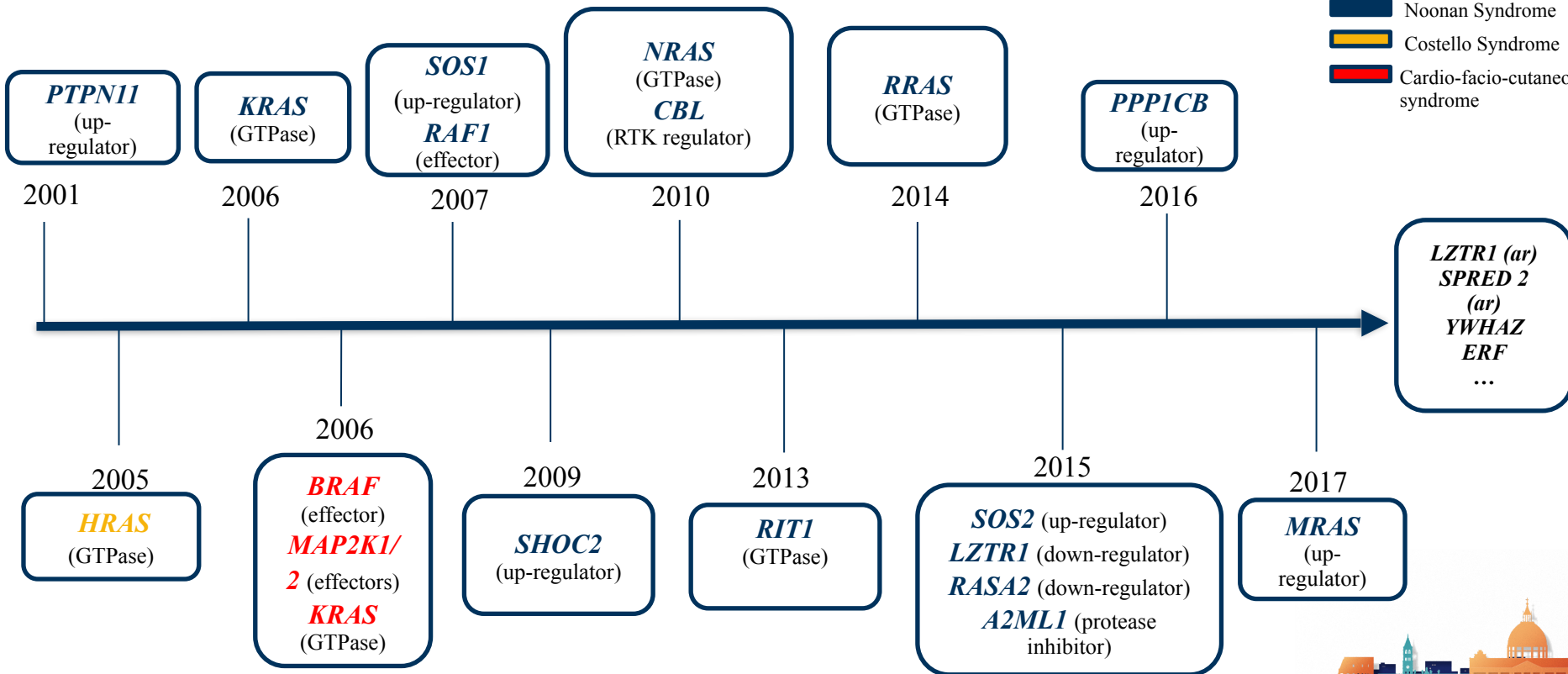


*Kamoub et al, 2008; Bader et al, 2000; Malubres et al, 2003; Aoki et al, 2016; Reynolds et al, 2025*





- Noonan Syndrome
- Costello Syndrome
- Cardio-facio-cutaneous syndrome



## Genes Involved and Inheritance Patterns

| Gene            | Protein / Function      | Syndrome(s)          | Inh.  | Freq. in NS | Notable variant effects                   |
|-----------------|-------------------------|----------------------|-------|-------------|-------------------------------------------|
| <b>PTPN11</b>   | SHP-2 phosphatase       | NS, NS-MLS (LEOPARD) | AD    | ~50%        | Loss of auto-inhibition; gain of function |
| <b>SOS1</b>     | GEF for RAS             | NS                   | AD    | ~10–13%     | Milder phenotype; rare HCM; tall stature  |
| <b>RAF1</b>     | RAF1/CRAF kinase        | NS, NS-MLS           | AD    | ~3–5%       | High HCM risk (>70%); skin anomalies      |
| <b>RIT1</b>     | RAS-related GTPase      | NS                   | AD    | ~5%         | HCM >50%; distinct facial features        |
| <b>KRAS</b>     | RAS GTPase              | NS, CFC, NS-like     | AD    | ~5%         | Usually severe; atypical phenotypes       |
| <b>BRAF</b>     | Ser/Thr kinase (RAF)    | CFC, NS-like         | AD    | <1% in NS   | CFC most common gene (75%); severe ID     |
| <b>MAP2K1/2</b> | MEK1/2 kinase           | CFC                  | AD    | <1%         | CFC (~25%); erythrokeratoderma            |
| <b>HRAS</b>     | RAS GTPase              | Costello Syndrome    | AD    | —           | p.Gly12Ser in ~80% CS; tumor risk         |
| <b>NF1</b>      | Neurofibromin (RAS-GAP) | NF1, Legius-like     | AD    | —           | Loss of function; dominant negative       |
| <b>SPRED1</b>   | RAS-GAP regulator       | Legius Syndrome      | AD    | —           | Café-au-lait, NO neurofibromas            |
| <b>SHOC2</b>    | Scaffold protein        | NS-LAH               | AD    | —           | p.Ser2Gly: constitutive membrane assoc.   |
| <b>CBL</b>      | E3 ubiquitin ligase     | NS-like/JMML         | AR/AD | —           | Somatic+germline; JMML risk ~50%          |
| <b>LZTR1</b>    | BTB/kelch protein       | NS                   | AD/AR | ~2%         | AR form: severe NS; AD: milder            |
| <b>RRAS</b>     | RAS-related protein     | NS-like              | AD    | Rare        | Rare cause; dilated cardiomyopathy        |

## Diagnostic Workflow and NGS Genetic Testing



### Stepwise Diagnostic Algorithm

1

#### Clinical recognition

Score-based clinical criteria (van der Burgt score for NS  $\geq 3$  major /  $\geq 4$  minor features; Rauhen criteria for CS/CFC). Dysmorphology review + cardiac workup (Echo, ECG).

2

#### Family history & pedigree

AD inheritance: examine parents for mild features. De novo in ~60% NS. AR suspected if consanguinity or two affected sibs. Document 3-generation pedigree.

3

#### Targeted gene panel (NGS)

First-line: multi-gene RASopathy panel. Avoids sequential single-gene testing delays.

4

#### Exome / Genome Sequencing (WES/WGS)

If panel negative but clinical diagnosis maintained. Detects deep intronic, structural and non-coding variants; identifies novel genes.

5

#### Functional studies / RNA analysis

For VUS (variants of uncertain significance): mRNA splicing analysis, RAS-ERK phosphorylation assays, biochemical characterisation.



## RASopathies: Main Conditions

### Noonan Syndrome (NS)

OMIM 163950 | prev. 1:1,000–2,500

Most common RASopathy. Short stature, **pulmonary stenosis (50–80%)**, **HCM (20–30%)**, pterygium colli, cryptorchidism, intellectual disability (mild).



### Costello Syndrome (CS)

OMIM 218040 | prev. 1:300,000

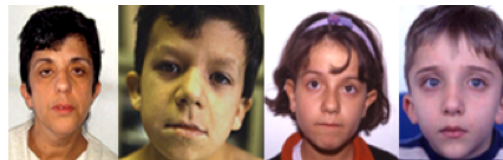
HRAS mutations. Severe intellectual disability, papillomata, **HCM**, extreme short stature, high risk of solid tumors (rhabdomyosarcoma, neuroblastoma).



### Neurofibromatosis type 1 (NF1)

OMIM 162200 | prev. 1:2,700–3,000

NF1/neurofibromin. Café-au-lait, neurofibromas, Lisch nodules, optic gliomas, plexiform neurofibromas, MPNST risk.



### NS with Loose Anagen Hair (NSLAH)

OMIM 607721 | prev. Rare

SHOC2 mutations. NS features + sparse, slow-growing 'loose anagen' hair, mild intellectual disability.



## RASopathies: Main Conditions

### NS with Multiple Lentigines

OMIM 151100 | prev. Rare (<1:1M)

Lentigines, Ocular hypertelorism, **ECG abnormalities**, **Pulmonary stenosis**, Abnormal genitalia, Retarded growth, Deafness. Now called NS-MLS.



### Cardio-Facio-Cutaneous (CFC)

OMIM 115150 | prev. 1:800,000

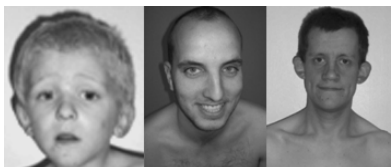
BRAF, MEK1/2, KRAS. Severe intellectual disability, characteristic hair/skin abnormalities, **HCM**, failure to thrive.



### Noonan Syndrome–Like (CBL)

OMIM 613563 | prev. Rare

CBL mutations. NS-like features, high risk of JMML (juvenile myelomonocytic leukaemia).



### Legius Syndrome

OMIM 611431 | prev. Rare

SPRED1 mutations. Café-au-lait spots + freckling, but no neurofibromas or Lisch nodules. NF1 phenocopy.





# RSopathies: Distinctive phenotype

**NS**



**CS**



**CFCS**





# RASopathies: Growth Failure

**NS**



**CS**



**CFCS**



# RASopathies: Musculoskeletal Anomalies

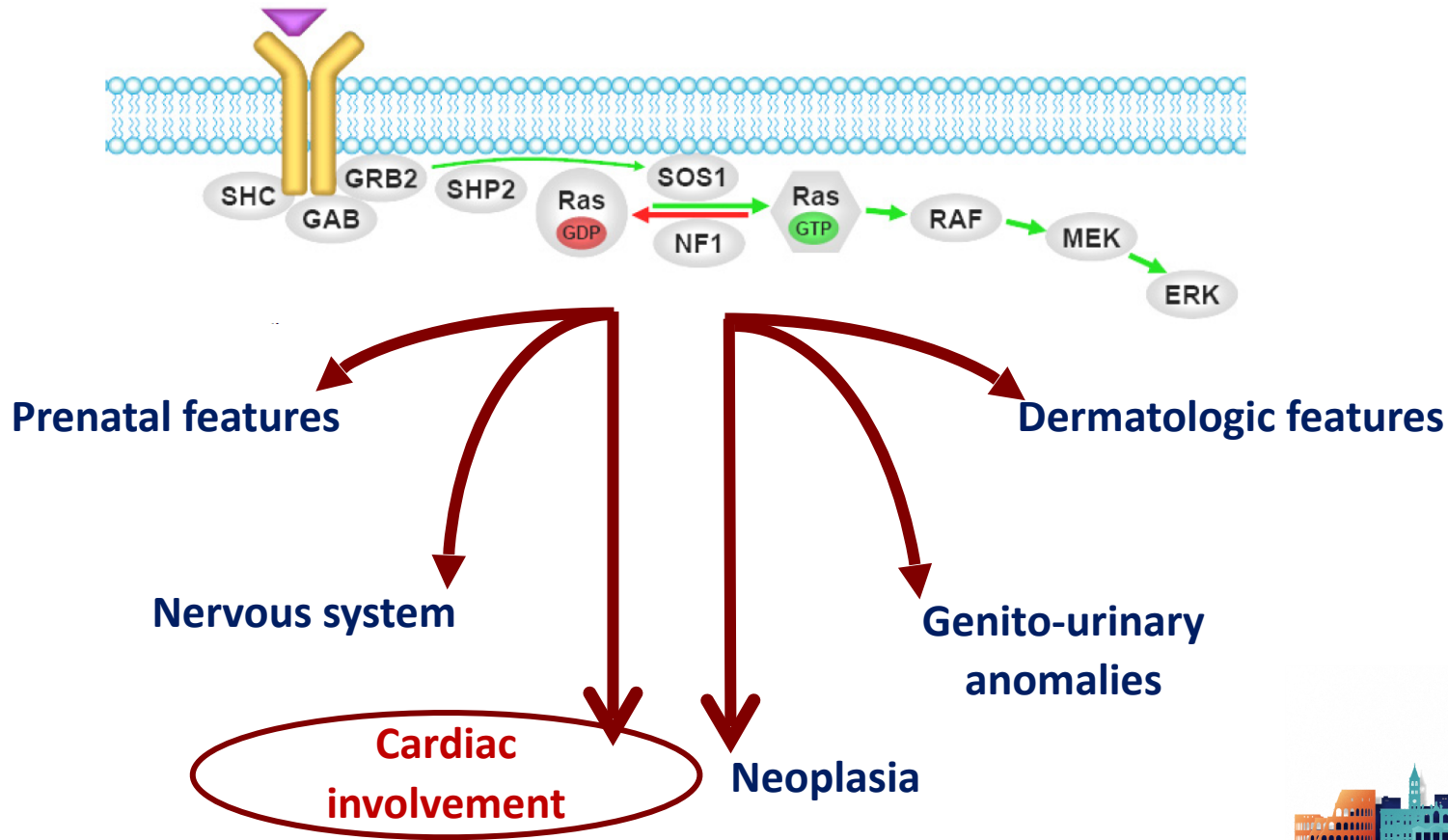
**NS**

**CS**

**CFCS**



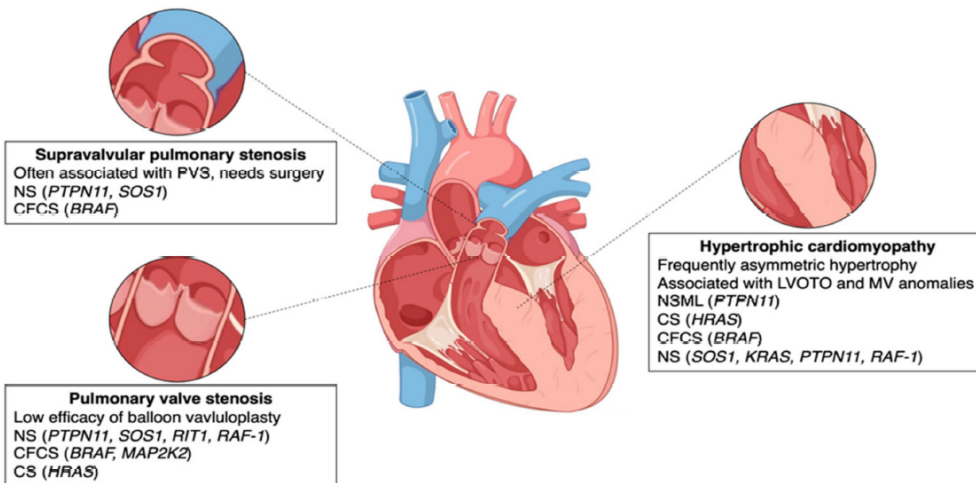
# RASopathies: Other Systems



## Shared Cardiovascular Manifestations across RASopathies



- Pulmonary valve stenosis (50–80% of NS)
- Hypertrophic cardiomyopathy (20–30% NS; >60% CFC/CS)
- ASD, VSD, AVSD (especially PTPN11 mutations)
- Dysrhythmias (LEOPARD/NS-MLS)
- Thoracic aorta dilation (HRAS, RAF1 variants)





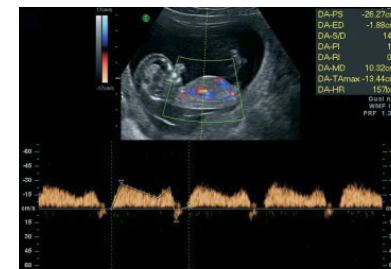
- Genes causing NS: *PTPN11*, *SOS1*, *BRAF*, *RAF1*, *RIT1*, *LZTR1*
- Estimated prevalence: 1/1500-2500 live births
- Nuchal translucency  $\geq 2.5$  mm (41%) at prenatal US
- Polyhydramnios (38%), hydrothorax (10.6%), chylothorax, ascites and/or hydrops, **cardiomyopathy**
- Cystic hygroma



- Normal birth weight and height
- Feeding difficulties, sometimes requiring nasogastric tube
- Failure to thrive (75%)
- GERD



- **Pulmonary valve stenosis 50% – *PTPN11***
- **Hypertrophic cardiomyopathy 20-25% – *RAF1***
- Septal defects
- Patent ductus arteriosus
- Aortic stenosis



Sharland et al, 1992; Shaw et al, 2007; Baldassarre et al, 2011; Allanson 2011; Tartaglia, Zampino, Gelb 2010

Noonan et al, 1968; Romano et al, 2010; Calcagni et al, 2016; Tartaglia et al, 2018; Stuurman et al, 2018

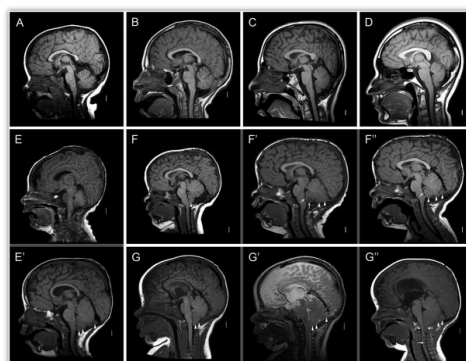






- **Gene causing CS: *HRAS***
- **About 300 reported individuals in literature**
- Polyhydramnios (>90%), macrosomia
- Feeding difficulties
- Failure to thrive
- CNS abnormalities (non-hypertensive ventriculomegaly at birth, type I Chiari malformation, syringomyelia)
- Moderate to severe intellectual disability
- Cancer predisposition
- Irritable behaviour during infancy followed by friendly personality later on

- Delayed puberty
- Short stature
- Musculo-skeletal abnormalities
- Distinctive facies
- Ectodermal abnormalities



- **Pulmonary valve stenosis 15-20%**
- **Hypertrophic cardiomyopathy 65% (LVOT 60%)**

*Costello, 1977; Zampino et al, 1993; Zampino et al, 2007; Gripp et al, 2010; Calandrelli et al, 2015; Gripp and Rauen 2020*





- Genes causing *CFCs*: *BRAF*, *MAP2K1/MAP2K2* and, less frequently, *KRAS*
- Less than 200 individuals reported worldwide
- Polyhydramnios
- Feeding difficulties and failure to thrive (75%)
- Distinctive gestalt
- Definitive short stature
- Delayed puberty
- Florid skin and ectodermal manifestations
- Mild-to-moderate-to-severe intellectual disability
- Variable signs of musculoskeletal involvement
- Severe epileptic encephalopathy
- Systematic studies about cancer predisposition are lacking



- Pulmonary valve stenosis 30-45%
- Hypertrophic cardiomyopathy 40%



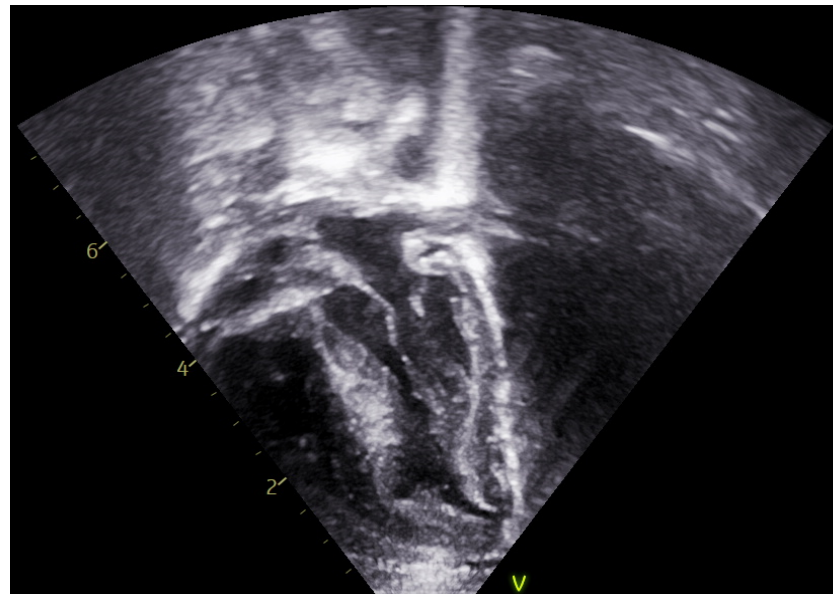
Pierpont et al, 2014



- **Genes causing NSML: *PTPN11* (85%), *BRAF*, *MAP2K1*, e *RAF1***
- **Rare condition**
- Facial dysmorphisms
- Multiple lentigines
- Ocular hypertelorism
- Abnormal genitalia
- Retardation of growth
- Sensorineural Deafness



- **Hypertrophic cardiomyopathy 80%**
- **Pulmonary valve stenosis 25%**
- **EKG abnormalities: conduction defects 23%**



*Limongelli et al, 2007*



RASopathies are the most common cause of syndromic HCM, representing up to **18% of HCM cases presenting in childhood** and up to **≈ 42% of infantile HCM**

The occurrence is heterogeneous among the different RASopathies

- **NSML** in up to **80%**
- **Costello Syndrome** about **65%**
- **CFCS** **40%**
- **Noonan Syndrome** **20-25%**

Prevalence varies depending on the underlying gene

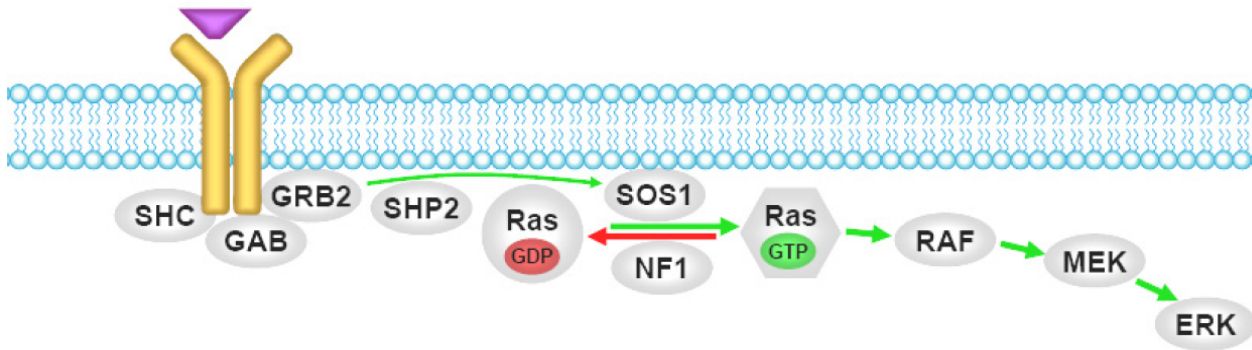
- **RAF1/RIT1**: 80-100%
- **HRAS**: 60-70%
- **BRAF**: 37.5-75%
- **SHOC2**: 30%
- **PTPN11**: 20%
- **SOS1**: 16%

*Limongelli et al, 2007; Monda, Rubino, Lioncino et al, 2021*

*Alexander et al, 2018; Norrish et al, 2019; Lioncino et al, 2022*



# RASopathy-related HCM: Disease Mechanisms



It has been suggested that the pathophysiology of HCM is related to a hyperactivation of the RAS-MAPK cascade, responsible for cardiomyocyte hypertrophy and myocardial disarray

However, this pathophysiological mechanism cannot be generalized to all RASopathies

Different signaling pathways seem to be involved in the molecular pathogenesis of HCM in RASopathies.

*Gelb & Tartaglia, 2011*



# RASopathy-related HCM: Disease Mechanisms

Variants in PTPN11 associated  
with **Noonan Syndrome**

Missense gain-of-function alleles with  
increased basal phosphatase activity



mechanism of HCM development is the  
upregulation of MAPK signaling

Variants in PTPN11 associated  
with **NSML**

Variants responsible for  
catalytic impairment



mechanism of HCM development is  
enhanced signal flow through the PI3K-  
AKT-mTOR pathway

**The elucidation of the pathophysiology of RASopathy-related HCM has significant clinical  
relevance for the possible development of targeted therapies**

*Gelb & Tartaglia, 2011; Keilhack et al, 2005; Lauriol & Kontaridis, 2011*



## Differentiating primary-HCM from RAS-HCM

|                           | Sarcomeric/Non-syndromic HCM                                     | RASopathy-associated HCM                                                                                                        |
|---------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| <b>Genetic cause</b>      | Sarcomere Genes                                                  | RAS-MAPK signaling genes                                                                                                        |
| <b>Disease mechanisms</b> | Defect in sarcomeric function<br>Impaired actomyosin interaction | Activating mutations<br>in RAS-MAPK signaling                                                                                   |
| <b>Disease onset</b>      | Adolescence/early adulthood                                      | Infantile/early childhood                                                                                                       |
| <b>Morbidity</b>          | Sudden death risk stratification<br>LVOTO                        | > Severe phenotype (LVOTO, RVOTO)<br>> Congestive Heart Failure<br>> CHF hospitalizations<br>> Septal myectomy during childhood |
| <b>Mortality</b>          | Sudden death > Heart Failure                                     | Heart Failure > Sudden death                                                                                                    |
| <b>Novel Therapies</b>    | Myosin inhibitors                                                | MEK and mTOR inhibitors                                                                                                         |

*Ackerman and Garman, JACC 2023*





## Risk of Sudden Death in Patients With RASopathy Hypertrophic Cardiomyopathy

J Am Coll Cardiol. 2023 Mar 21;81(11):1035-1045. doi: 10.1016/j.jacc.2023.01.012

This study showed **similar incidence of SCD** in children with RAS-HCM compared to nonsyndromic-HCM patients (4.7% vs 4.2%), with an average age of 10.6 years in RAS-HCM

RAS-HCM patients were **diagnosed at a younger age** than P-HCM patients (1 year vs 10 years;  $P < 0.001$ ) and had **twice the incidence of nonarrhythmic deaths or transplantation** (11% vs 5.4%)

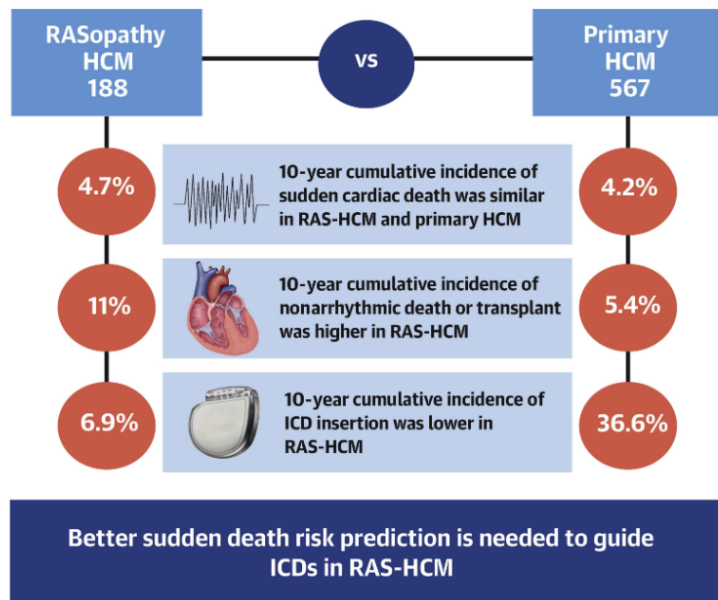
There were **2 high risk periods in RAS-HCM patients**. The first high risk period was during the first year of life with primarily nonarrhythmic events, whereas the second peak in early adolescents (11 to 16 years) was mostly SCD

Although the similar SCD profile, RAS-HCM patients had a 5-fold **lower incidence of ICD placement** (6.9% vs 36.6%)

**Critical alarm in the management of RAS-HCM patients and the avoidable deaths that occur.**

### CENTRAL ILLUSTRATION: Transplant-Free Survival, Sudden Death, and ICD Use in RASopathy HCM

**Objective:** To compare sudden cardiac death, nonarrhythmic death or transplant and ICD use in pediatric RASopathy and primary hypertrophic cardiomyopathy



Lynch A et al, 2023

**Risk stratification for SCD** in patients with RASopathies is challenging and is extrapolated from sarcomeric HCM:

- family history of SCD
- unexplained syncope
- repetitive nonsustained ventricular tachycardia
- massive left ventricular hypertrophy
- left ventricular apical aneurysm
- extensive late gadolinium enhancement
- reduced ejection fraction

HCM Risk-Kids SCD risk prediction model does not have a good discriminatory power for this population

**Unexplained syncope and NSVT appear to be predictors of SCD risk**

Int J Cardiol. 2023 Dec 15:393:131405. doi: 10.1016/j.ijcard.2023.131405. Epub 2023 Sep 28.

## Sudden cardiac death in childhood RASopathy-associated hypertrophic cardiomyopathy: Validation of the HCM risk-kids model and predictors of events

Olga D Boleti<sup>1</sup>, Sotirios Roussos<sup>2</sup>, Gabrielle Norrish<sup>1</sup>, Ella Field<sup>1</sup>, Stephanie Oates<sup>3</sup>, Jennifer Tollit<sup>1</sup>, Gauri Nepali<sup>4</sup>, Vinay Bhole<sup>4</sup>, Orhan Uzun<sup>5</sup>, Piers E F Daubeney<sup>6</sup>, Graham A Stuart<sup>7</sup>, Precylia Fernandes<sup>8</sup>, Karen McLeod<sup>8</sup>, Maria Ilina<sup>8</sup>, Muhammad Najih Ali Liaqath<sup>9</sup>, Tara Bharucha<sup>9</sup>, Grazia Delle Donne<sup>10</sup>, Elspeth Brown<sup>10</sup>, Katie Linter<sup>11</sup>, Bernadette Khodaghalian<sup>12</sup>, Caroline Jones<sup>13</sup>, Jonathan Searle<sup>14</sup>, Sujeev Mathur<sup>15</sup>, Nicola Boyd<sup>16</sup>, Zdenka Reindhardt<sup>16</sup>, Sophie Duignan<sup>17</sup>, Terence Prendiville<sup>17</sup>, Satish Adwani<sup>18</sup>, Martin Zenker<sup>19</sup>, Cordula Maria Wolf<sup>20</sup>, Juan Pablo Kaski<sup>21</sup>

ESC HEART FAILURE

ESC Heart Failure 2024; 11: 923–936

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ORIGINAL ARTICLE

## Natural history and outcomes in paediatric RASopathy-associated hypertrophic cardiomyopathy

Olga Boleti<sup>1,2</sup> , Gabrielle Norrish<sup>1,2</sup>, Ella Field<sup>1,2</sup>, Kathleen Dady<sup>1</sup>, Kim Summers<sup>2</sup>, Gauri Nepali<sup>3</sup>, Vinay Bhole<sup>3</sup>, Orhan Uzun<sup>4</sup>, Amos Wong<sup>4</sup>, Piers E. F. Daubeney<sup>5</sup>, Graham Stuart<sup>6</sup>, Precylia Fernandes<sup>7</sup>, Karen McLeod<sup>7</sup>, Maria Ilina<sup>7</sup>, Muhammad Najih Liaqath Ali<sup>8</sup>, Tara Bharucha<sup>8</sup>, Grazia Delle Donne<sup>9</sup>, Elspeth Brown<sup>9</sup>, Katie Linter<sup>10</sup>, Caroline B. Jones<sup>11</sup>, Jonathan Searle<sup>12,15</sup>, William Regan<sup>12</sup>, Sujeev Mathur<sup>12</sup>, Nicola Boyd<sup>13</sup>, Zdenka Reinhardt<sup>13</sup>, Sophie Duignan<sup>14</sup>, Terence Prendiville<sup>14</sup>, Satish Adwani<sup>15</sup> and Juan Pablo Kaski<sup>1,2\*</sup>

Boleti OD et al, 2023





ESC

European Society  
of Cardiology

European Heart Journal (2026) 47, 2388–2390  
<https://doi.org/10.1093/eurheartj/ehaf1012>

**RAPID COMMUNICATIONS**

*Heart failure and cardiomyopathies*

## Childhood-onset RASopathy-associated hypertrophic cardiomyopathy, diastolic dysfunction, and arrhythmias

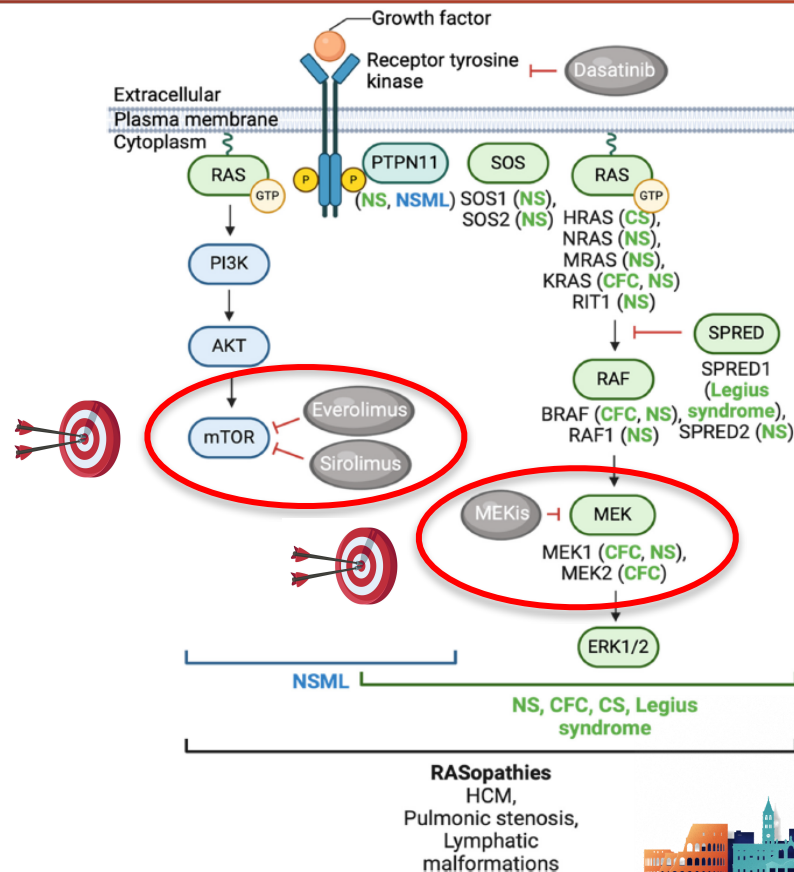
- Long-term phenotype changes in a large multicentre cohort of **201 children with childhood-onset RAS-HCM**
- Patients presenting with RAS-HCM in childhood develop progressive diastolic dysfunction and LA dilatation, stable left ventricular hypertrophy and left ventricular outflow tract gradient, resulting in complex atrial arrhythmias in early adulthood
- NYHA/Ross functional Class >I was a time-independent predictor of major adverse cardiac events

*Boleti OD et al, Eur Heart J 2026*

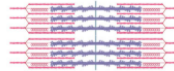


**Targeting RAS-MAPK signaling:**  
a novel therapeutic option for RAS-HCM?

MEK inhibition?  
Akt/mTOR inhibition?



# RAS-HCM: Targeting RAS-MAPK signaling

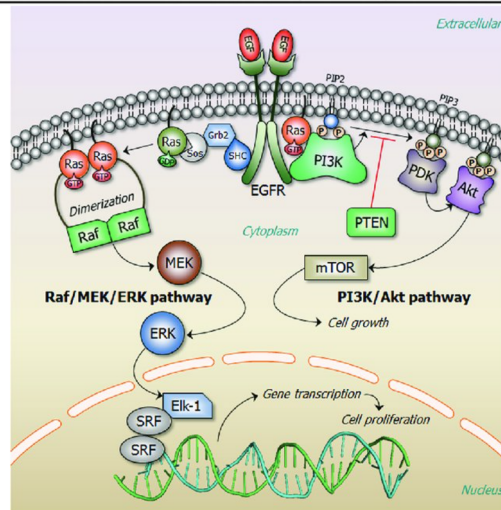
|                | Etiology                                                                      |                                                      | Novel Therapies          |                                                                                     |
|----------------|-------------------------------------------------------------------------------|------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|
| Sarcomeric HCM | Mutations in Sarcomeric Genes Responsible for an Hypercontractility Phenotype | Myosin Inhibitors<br>Gene Therapy                    | Mavacamten<br>Aficamten  |  |
| RASopathy      | LVH Caused by Upregulation of RAS-MAPK or PI3K-AKT-mTor Pathway               | MEK1 Inhibitors (in NS)<br>mTor Inhibitors (in NSML) | Trametinib<br>Everolimus |  |

## Trametinib (GSK1120212)

FDA/EMA approved (melanoma, NSCLC, LGSOC, paediatric NF1 plexiform)

Mech: Allosteric MEK1/2 inhibitor; non-ATP competitive.

*Evidence: SPRINT phase II (NF1): ORR 68% for plexiform neurofibromas (Gross et al., NEJM 2020).*



*Monda et al, Circulation: Heart Failure 2023*

## Everolimus / Rapamycin

FDA approved (KRAS G12C NSCLC, CRC — oncology)

Mech: mTOR inhibitor downstream of RAS pathway; anti-proliferative.

*Evidence: Preclinical models promising; no RASopathy-specific RCT data yet. Molecular target overlap with some CFC/NS variants.*



## Treatment of RAF1-Related Obstructive Hypertrophic Cardiomyopathy by MEK Inhibition Using Trametinib

Omid Kiamanesh <sup>1 2</sup>, Steven C Greenway <sup>3</sup>, Franciscus Dicke <sup>3</sup>, Brennan Ballantyne <sup>1 2</sup>,  
Sasha Mitrovic <sup>2</sup>, Kaitlin McGrath <sup>1</sup>, James A White <sup>1 4</sup>, William D T Kent <sup>5</sup>, Gregor Andelfinger <sup>6</sup>

Affiliations + expand

PMID: 38827265 PMCID: [PMC11137563](#) DOI: [10.1016/j.jaccas.2024.102379](#)

## Successful MEK-inhibition of severe hypertrophic cardiomyopathy in RIT1-related Noonan Syndrome

Anne Leegaard <sup>1</sup>, Pernille A Gregersen <sup>2</sup>, Trine Ø Nielsen <sup>3</sup>, Jesper V Bjerre <sup>4</sup>, Mette M Handrup <sup>5</sup>

Affiliations + expand

PMID: 36184070 DOI: [10.1016/j.ejmg.2022.104630](#)

## MEK Inhibition in a Newborn with *RAF1*-Associated Noonan Syndrome Ameliorates Hypertrophic Cardiomyopathy but Is Insufficient to Revert Pulmonary Vascular Disease

Alessandro Mussa <sup>1 2</sup>, Diana Carli <sup>1 3</sup>, Elisa Giorgio <sup>4 5</sup>, Anna Maria Villar <sup>6</sup>, Simona Cardaropoli <sup>1</sup>,  
Caterina Carbonara <sup>7</sup>, Maria Francesca Campagnoli <sup>7</sup>, Paolo Galletto <sup>7</sup>, Martina Palumbo <sup>8</sup>,  
Simone Olivieri <sup>1</sup>, Claudio Isella <sup>8 9</sup>, Gregor Andelfinger <sup>10</sup>, Marco Tartaglia <sup>11</sup>, Giovanni Botta <sup>12</sup>,  
Alfredo Brusco <sup>13 14</sup>, Enzo Medico <sup>8 9</sup>, Giovanni Battista Ferrero <sup>15</sup>

Affiliations + expand

PMID: 35052347 PMCID: [PMC8774485](#) DOI: [10.3390/genes13010006](#)

## MEK Inhibition for RASopathy-Associated Hypertrophic Cardiomyopathy: Clinical Application of a Basic Concept

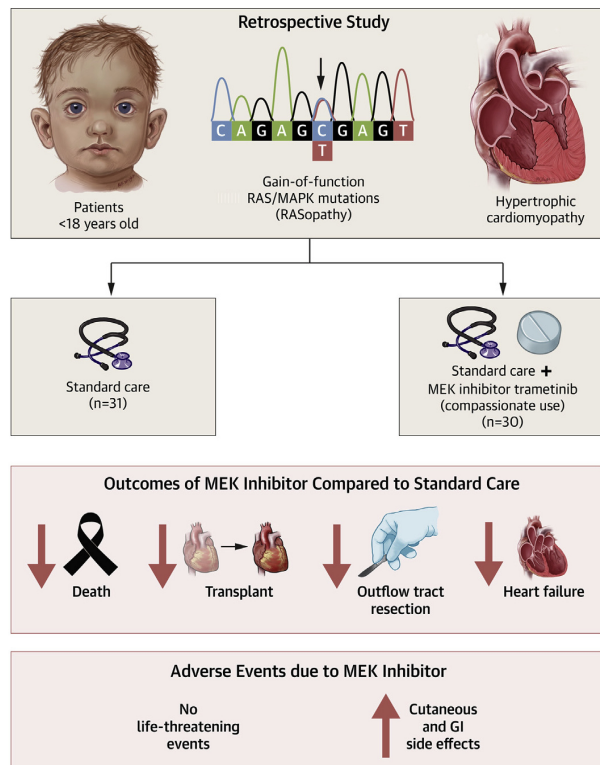
Dominic Chaput <sup>1</sup>, Gregor Andelfinger <sup>2</sup>

Affiliations + expand

PMID: 38432396 DOI: [10.1016/j.cjca.2024.02.020](#)







Wolf CM, et al. JACC Basic Transl Sci. 2025;10(2):152-66.

## HIGHLIGHTS

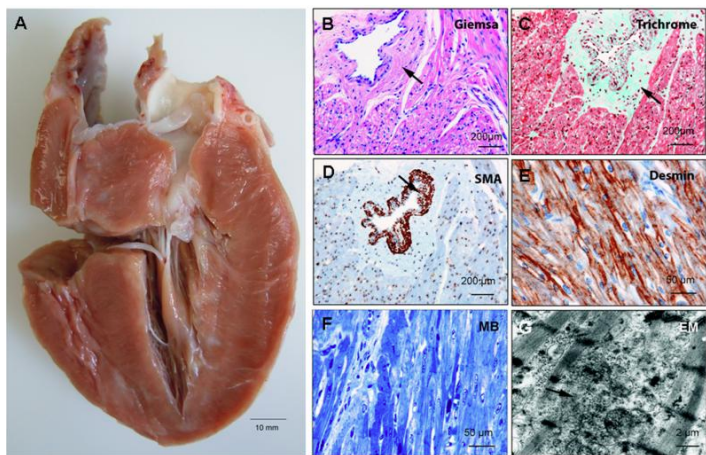
- RAS/MAPK variants cause infant hypertrophic cardiomyopathy, increasing morbidity.
- Hyperactivated pathway inhibition improves cardiomyopathy in RASopathy mouse models.
- Retrospective study: 30 children on trametinib vs 31 on standard care for cardiomyopathy.
- Trametinib significantly reduced death, transplant, and cardiac surgery risk.
- Trametinib showed no severe adverse events; frequent skin and mucous side effects noted.



## Rapidly progressive hypertrophic cardiomyopathy in an infant with Noonan syndrome with multiple lentigines: palliative treatment with a rapamycin analog

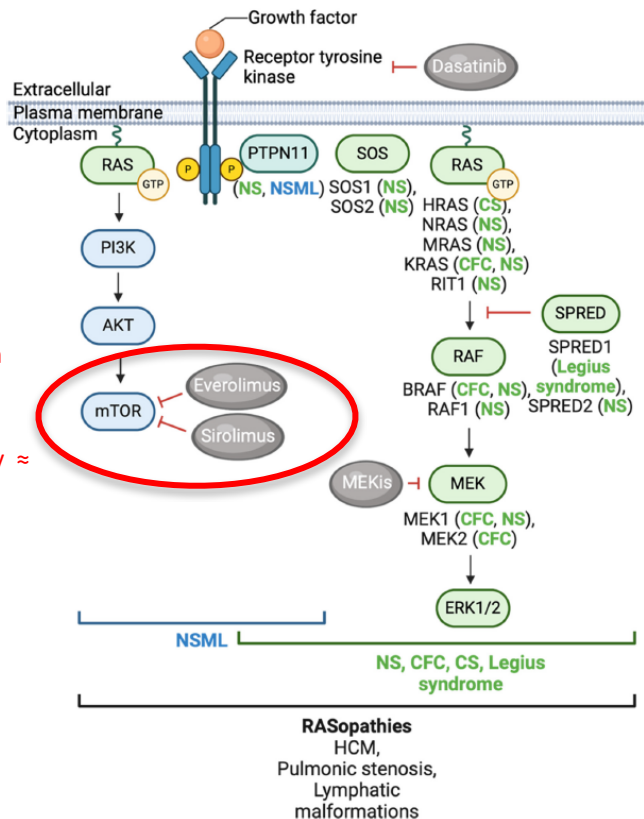
Andreas Hahn <sup>1</sup>, Jessica Lauriol, Josef Thul, Kachina Behnke-Hall, Tushia Logeswaran, Anne Schänzer, Nuray Boğürçü, Boyan K Garvalov, Martin Zenker, Bruce D Gelb, Susanne von Gerlach, Reinhard Kandolf, Maria I Kontaridis, Dietmar Schranz

Am J Med Genet A. 2015 Apr;167A(4):744-51. doi: 10.1002/ajmg.a.36982.



**Akt/mTOR inhibition**

Heart failure ↓  
Myocardial hypertrophy ≈



Examination of the explanted heart revealed severe hypertrophy and myofiber disarray with extensive perivascular fibrosis. These findings provide evidence that Akt/mTOR activity is enhanced in NSML with HCM and suggest that rapamycin treatment could principally be feasible for infantile NSML. The preliminary experiences made in this single patient indicate that therapy should start early to prevent irreversible cardiac remodelling.



# Key Takeaways for Clinical Practice

- 01 RASopathies share a common molecular basis (RAS-MAPK dysregulation) but differ markedly in gene, phenotype severity, and cancer risk — molecular diagnosis is mandatory.
- 02 Multi-gene NGS panel (Tier 1:  $\geq 18$  genes) is the diagnostic gold standard; detection rate  $\sim 70\text{--}75\%$ . WES/WGS for panel-negative cases with typical clinical phenotype.
- 03 AD inheritance is the rule; de novo mutations account for  $\sim 60\%$  of NS. AR forms exist (LZTR1, CBL) and carry higher severity and recurrence risk.
- 04 Cardiac and oncological surveillance must be lifelong, syndrome-dependent, and genotype-informed; one protocol does not fit all RASopathies.
- 05 MEK inhibitors (selumetinib, trametinib) have transformed care of NF1 plexiform neurofibromas and are under investigation for HCM, JMML and neurodevelopment.
- 06 The precision medicine pipeline (SHP2i, SOS1i, base editing, combinatorial MEKi) is advancing rapidly; specialist physicians must follow evolving evidence and enrol eligible patients in clinical trials.

*"Understanding the molecular switch that drives RASopathies is the key to turning it off"*



# Future Perspectives



Studies to identify RAS-HCM patients with specific risk factors for SCD and specific guidelines for ICD placement in order to prevent avoidable deaths



Studies to elucidate whether genetics contributes to risk prediction



Clinical trials to establish indications, long-term efficacy, long-term side effects, surveillance strategies, optimal dosing, and optimal treatment windows for targeted therapy of trametinib or other MEK-i on larger cohorts of patients with RAS-HCM



*Grazie per  
l'attenzione!*

