ERN ITHACA

Webinar 2025

ENDOCRINE ASPECTS OF RASOPATHIES

Tuesday, 18 nov 2025 - 17h00 - 18h30 CEST

Chair by

Laura Mazzanti, Italy

European Commission

EUROPEAN REFERENCE NETWORKS

Helping patients with rare or low-prevalence complex diseases

European Reference Networks ITHACA

Welcome – Technical points

- **We are please to be numerous 97 registrations**
- **Webinar being recorded**

- **Thank you to**
  - Turn off your microphone and disconnect your camera
  - Use the Chat for your questions or Raise your hand at the time of the discussions (end)
  - A satisfaction survey will be sent to you :

- **Webinars # will be available on ITHACA's Website**
- **https://ern-ithaca.eu/documentation/educational-resources/**

- **Anne Hugon Project Manager ERN ITHACA - anne.hugon@aphp.fr**

Welcome and Introduction

Webinar: "Endocrine aspects of RASopathies"

"**RASopathies**" represent one of the most common non-chromosomal diseases affecting development and growth.

A brief introduction will outline their genetic heterogeneity and clinical variability.

We'll then explore the endocrinological aspects of **RASopathies,** focusing on key areas such as - growth, growth therapy, puberty and metabolic profiling – to better understand their impact on patient care and long-term outcomes .

The webinar is designed for all specialists involved in the care of individuals with **RASopathies**, particularly pediatricians, endocrinologists, geneticists and, of course, *patients* and *Families*, whose engagement and collaboration remain at the heart of effective management.

Introduction

Webinar: "Endocrine aspects of RASopathies"

Chaired by

- ***Laura Mazzanti***, - Alma Mater Honorary Professor, University of Bologna, Bologna, Italy

A few words on our speakers

- ***Marco Tartaglia*** *- Head of Molecular Genetics and Functional Genomics, Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy*
- ***Thomas Edouard*** *- Endocrine, Bone Diseases, and Genetics Unit, Children's Hospital, Toulouse University Hospital, Toulouse, France*
- ***Federica Tamburrino -*** *Rare Disease Unit, Department of Pediatrics, IRCCS Policlinico di Sant'Orsola, Bologna, Italy*
- ***Alexander A L Jorge*** *- University of São Paulo (USP), Head and Principal Investigator of the Genetic Endocrinology Unit at Hospital das Clínicas, University of São Paulo, São Paulo, Brazil*

Agenda

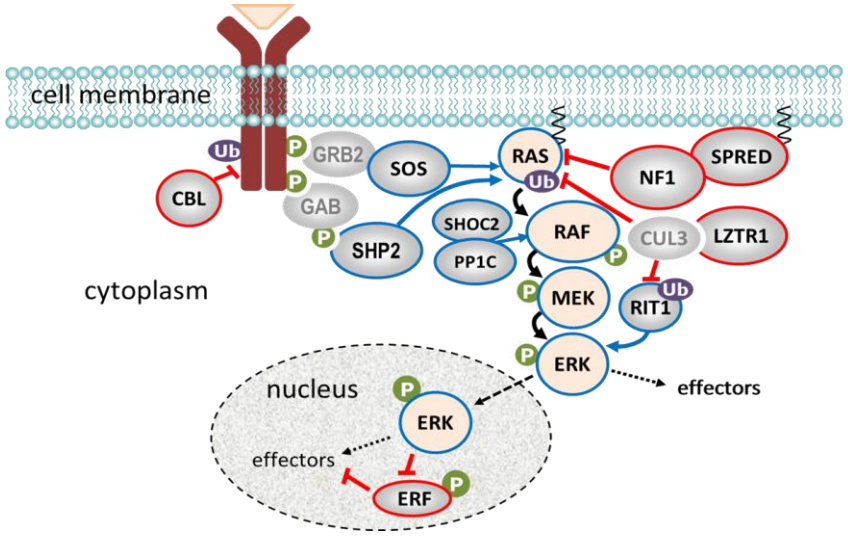
1. ‘The molecular genetics of RASopathies’, Marco Tartaglia
2. ‘Growth and growth therapies in RASopathies’, Thomas Edouard
3. ‘Puberty in RASopathies’, Federica Tamburrino
4. ‘Metabolic Profile in Patients with Noonan Syndrome’, Alexander A L Jorge

- Conclusion with speakers and moderator

Topic 1- The molecular genetics of RASopathies

Marco Tartaglia
Head Molecular Genetics and Functional Genomics, Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy

ERN-ITHACA
Webinar 2025



Molecular Genetics of RASopathies

Marco Tartaglia

Molecular Genetics and Functional Genomics

marco.tartaglia@opbg.net

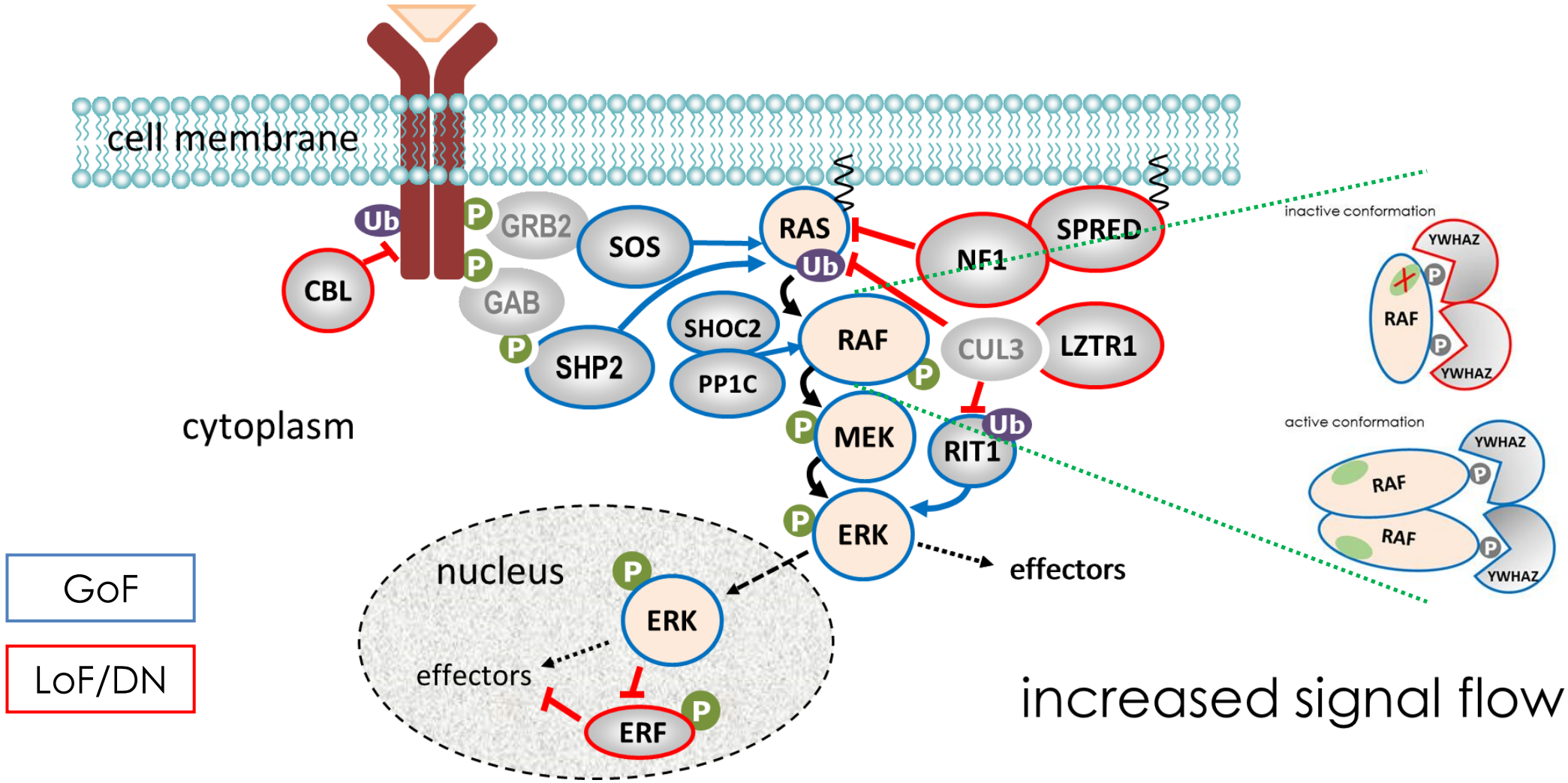
Bambino Gesù
OSPEDALE PEDIATRICO

Marco Tartaglia
Disclosure Information (last three years)

Speakers Bureau/Honoraria: Novo Nordisk, Sandoz

Consultant/Advisory Board: Novo Nordisk, BioMarin

Molecular basis



Tartaglia, Aoki & Gelb (2022) *Am J Med Genet C 190:425-39*

major clinical features

Distinctive facies
CHD/HCM
Short stature
Variable DD/ID
Variable cancer predisposition
Hair and skin abnormalities
Lymphatic abnormalities
Skeletal abnormalities
Bleeding diathesis
Feeding difficulties
Immunological abnormalities
Delayed puberty
Visual and hearing defects

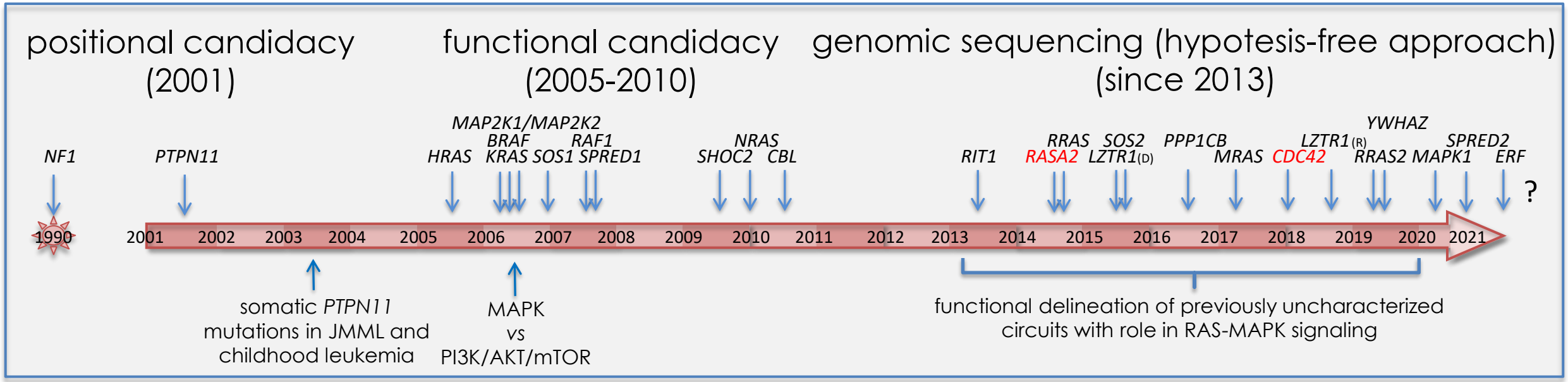
systemic RASopathies

Noonan syndrome
NS with multiple lentigines
cardiofaciocutaneous syndrome
Costello syndrome
Mazzanti syndrome
CBL-associated syndrome,
MAPK1-associated syndrome
ERF-associated syndrome
neurofibromatosis, type 1
Legius syndrome

M. Zenker

Tartaglia & Gelb (2010) *Ann N Y Acad Sci 1214:99-121*
Zenker (2022) *Am J Med Genet C 190:414-24*

Timeline - Milestones



25 genes implicated in RASopathies

Insights on the mechanism(s) of disease

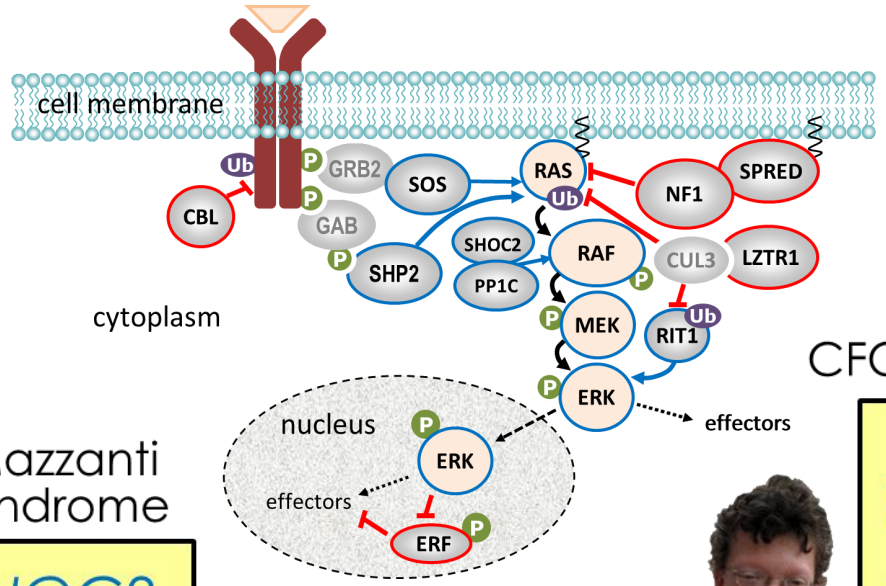
Molecular diagnosis in >90% of patients with clinical diagnosis

Improved care and more accurate counseling

Development of targeted therapies

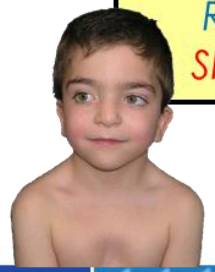
Tartaglia, Aoki & Gelb (2022) *Am J Med Genet C 190:425-39*

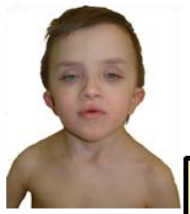
systemic RASopathies - genetic landscape



Noonan syndrome

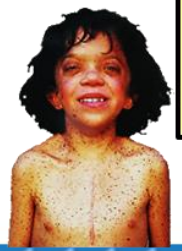
PTPN11
SOS1
KRAS
NRAS
RAF1
BRAF
MAP2K1
RIT1
SOS2
LZTR1
MRAS
RRAS2
SPRED2





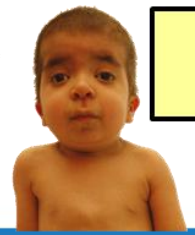
Mazzanti syndrome

SHOC2
PPP1CB



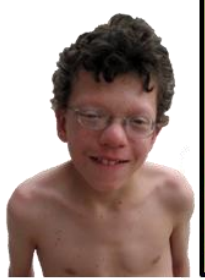
LEOPARD syndrome

PTPN11
RAF1
BRAF



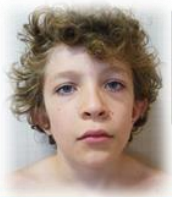
Costello syndrome

HRAS



CFC syndrome

KRAS
YWHAZ
BRAF
MAP2K1
MAP2K2

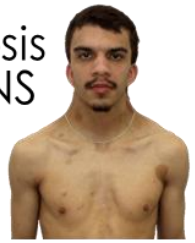


MAPK1-associated Syndrome

MAPK1

CBL-associated syndrome

CBL

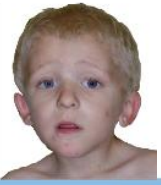


neurofibromatosis type 1, incl. NFNS

NF1

ERF-associated syndrome

ERF



Legius syndrome

SPRED1

Tartaglia & Gelb (2010) *Ann N Y Acad Sci 1214:99-121*
Tartaglia, Aoki, Gelb (2022) *Am J Med Genet C Semin Med Genet 190:425-39*

What have we learned?

"They don't give us time to learn anything in school; we have to listen to the teacher all day."

NS incidence has been estimated as between 1:1000 to 1:2500

Mendez HMM & Opitz JM (1985) *Am J Med Genet* 21:493-506.

Nora JJ et al. (1974) *Am J Dis Child 127:48-55*.

Noonan Syndrome

An Update and Review for the Primary Pediatrician

Jacqueline A. Noonan, M.D.

Introduction

Noonan syndrome[1] is a relatively common multiple congenital anomaly syndrome, with an estimated incidence of between one per 1,000 and one per 2,500 live births.[2] Affected individuals have characteristic facial features, are usually short in stature with a chest deformity, and about half have a congenital cardiac abnormality. Autosomal dominant inheritance, with variable expression, has been documented in a number of families. Many cases, however, appear to be sporadic. The diagnosis rests solely on clinical criteria, and so far, the underlying cause or genetic defect is unknown.

The natural history of this syndrome is still being defined. Children with Noonan syndrome have a large number of potential health problems, making it essential for the primary-care pediatrician to be aware of this syndrome, so that the special needs of such children may be met.

History

In 1883, Kobylinski[3] reported a 20-year-old male with clinical features compatible with what is now called Noonan syndrome. Many early publications reported both males and females with a webbed neck, small stature with low-set ears, micrognathia, and other anomalies which probably represented a number of different syndromes including Noonan syndrome. In 1930, Ullrich[4] described a number of patients with webbed neck and short stature, some of whom represented Turner syndrome and, no doubt, some Noonan syndrome. While Ullrich was intrigued primarily by the webbed neck, in 1938, Turner[5] described a number of patients with sexual infantilism who also had a webbed neck and short stature. Turner syndrome was later recognized as a sex chromosome abnormality with either the absence or an abnormality of one of the X chromosomes. Ullrich was intrigued by the work of a mouse geneticist, Bonnevie, who had bred a mutant strain of mice with a webbed neck and swelling of the limbs. In 1949, Ullrich[6] speculated on the possible similarity between his patients and the mice bred by Bonnevie. The term Bonnevie-Ullrich syndrome became popular, particularly in Europe, and was used to describe children, some of whom would now be recognized as having Noonan syndrome. In 1943, Flavell[7] reported a male who had a phenotype similar to that reported by Turner, and he used the term "male Turner" syndrome. In 1963, Noonan and Ehmke[8] reported nine patients — six males and three females, with short stature and characteristic facies including hypertelorism, ptosis, and low-set ears — whom we felt represented a distinct syndrome. Several of the males had undescended testes. Chest deformities were frequent, and all had valvular pulmonary stenosis. Chromosome studies were normal. Dr. John Opitz[9] suggested the eponym Noonan syndrome be used to describe such patients. He felt my observation that this syndrome occurred in both males and females was not associated with chromosomal abnormalities and could be inherited justified the eponym. For a number of years, the term Turner phenotype persisted, but in 1968, the eponym Noonan syndrome appeared in print for the first time. Thereafter, Dr. Victor McKusick listed Noonan syndrome as a hereditary congenital disorder of the cardiovascular system. Since the eponym Noonan syndrome is relatively recent, many pediatricians have only a limited knowledge of this condition. This review is intended to be an update and review for the primary pediatrician.

Genetics

Because of the superficial resemblance between patients with Noonan syndrome and those with Turner syndrome, an abnormality of the X chromosome has been

Department of Pediatric Cardiology, University of Kentucky, Lexington, Kentucky

Address correspondence to: Jacqueline A. Noonan, M.D., University of Kentucky, Department of Pediatric Cardiology, 800 Rose Street, Room MN 472, Lexington, KY 40536-0084

Syndrome of the month

Journal of Medical Genetics 1987, **24**, 9–13

Noonan syndrome

JUDITH E ALLANSON

From The Genetics Centre, Southwest Biomedical Research Institute, PO Box 8845, Scottsdale, Arizona 85252, USA.

Noonan syndrome was first described over 20 years ago by Noonan and Ehmke[1]; they defined a specific group of nine patients with valvular pulmonary stenosis who, in addition, had short stature, mild mental retardation, hypertelorism, and unusual facies. In retrospect, the first case was probably described by Kobylinski in 1883.[2] Since that time, over 300 cases have been reported in medical publications. The incidence of Noonan syndrome has been estimated to be between 1 in 1000 and 1 in 2500 live births.[3] The cardinal features of Noonan syndrome are short stature, congenital heart defect, broad or webbed neck, a peculiar chest deformity with pectus carinatum superiorly and pectus excavatum inferiorly, and characteristic facies, which alter predictably with age to produce a discrete but changing phenotype which is described and illustrated below. Good reviews of Noonan syndrome are to be found by Mendez and Opitz,[4] Nora *et al*,[5] Char *et al*,[6] and Pearl.[7]

Received for publication 22 April 1986.
Accepted for publication 2 May 1986.

Clinical features*

GROWTH

At birth the average length is 47 cm. Birth weight is generally normal (40%) but can be high, secondary to subcutaneous oedema. Prepubertal growth tends to parallel the 3rd centile (60%) with a relatively normal growth velocity. The pubertal growth spurt is often reduced or absent.[9] Delayed bone age has been reported in up to 20% of cases. Normal growth hormone levels with slightly raised somatomedin levels have been found in some patients.[10] Detailed growth curves for males and females with Noonan syndrome are now available.[11]

CRANIOFACIAL

In the newborn period the main features are hypertelorism with downward slanting palpebral fissures (95%), low set, posteriorly rotated ears with a thick helix (90%), deeply grooved philtrum with

*Incidence figures are derived from reviews by Mendez and Opitz,[4] Pearl,[7] and Allanson[8] unless specifically referenced.

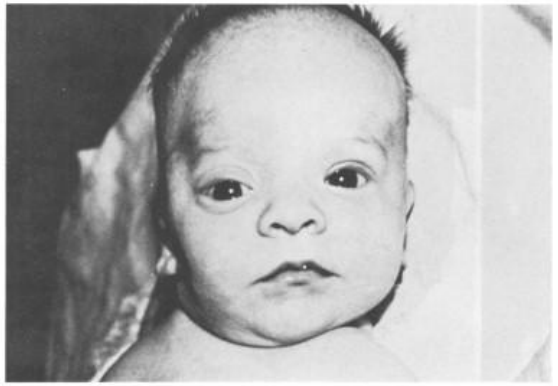
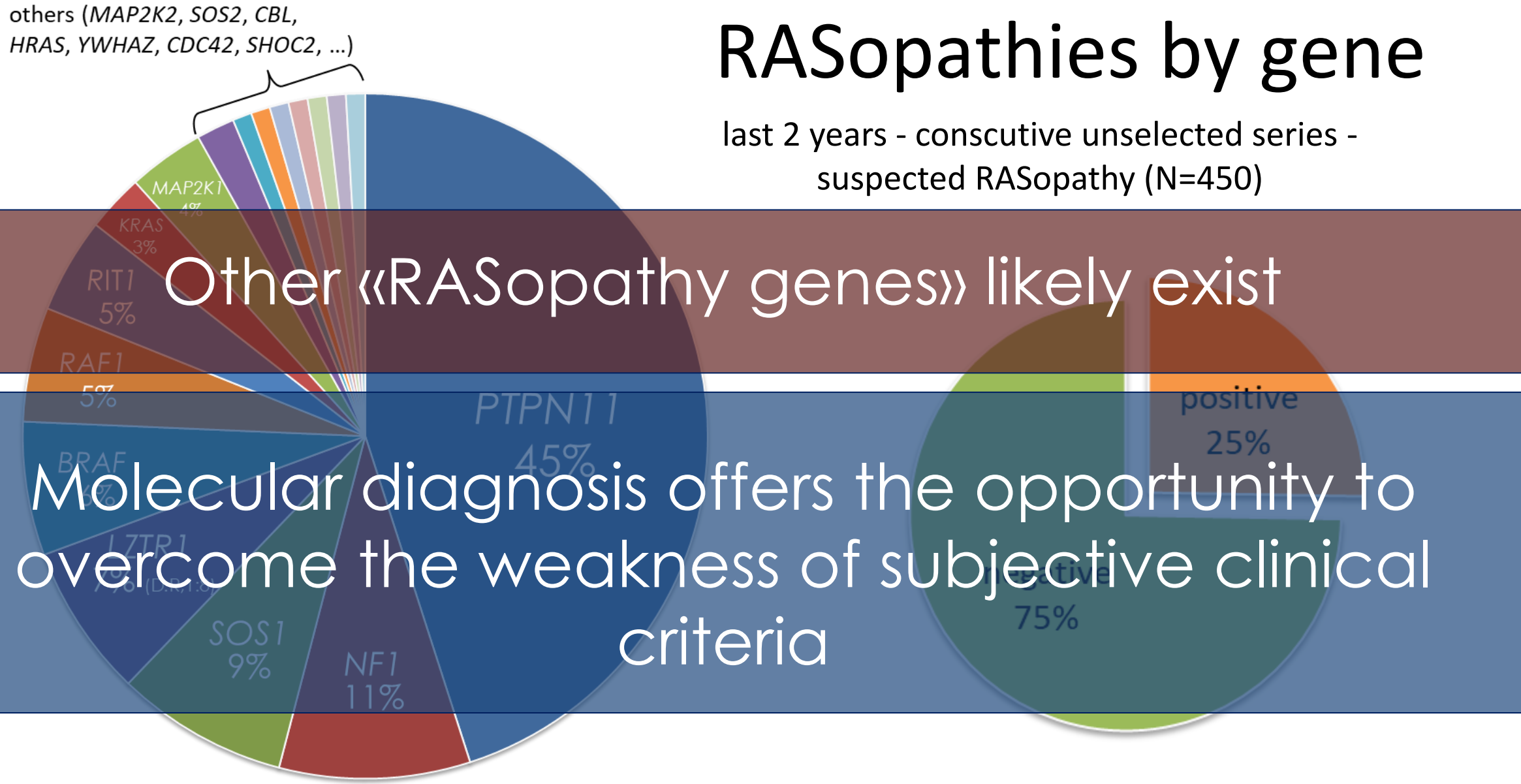


FIG 1 *Facial appearance in newborn period.*

RASopathies by gene

last 2 years - conscutive unselected series - suspected RASopathy (N=450)



Other «RASopathy genes» likely exist

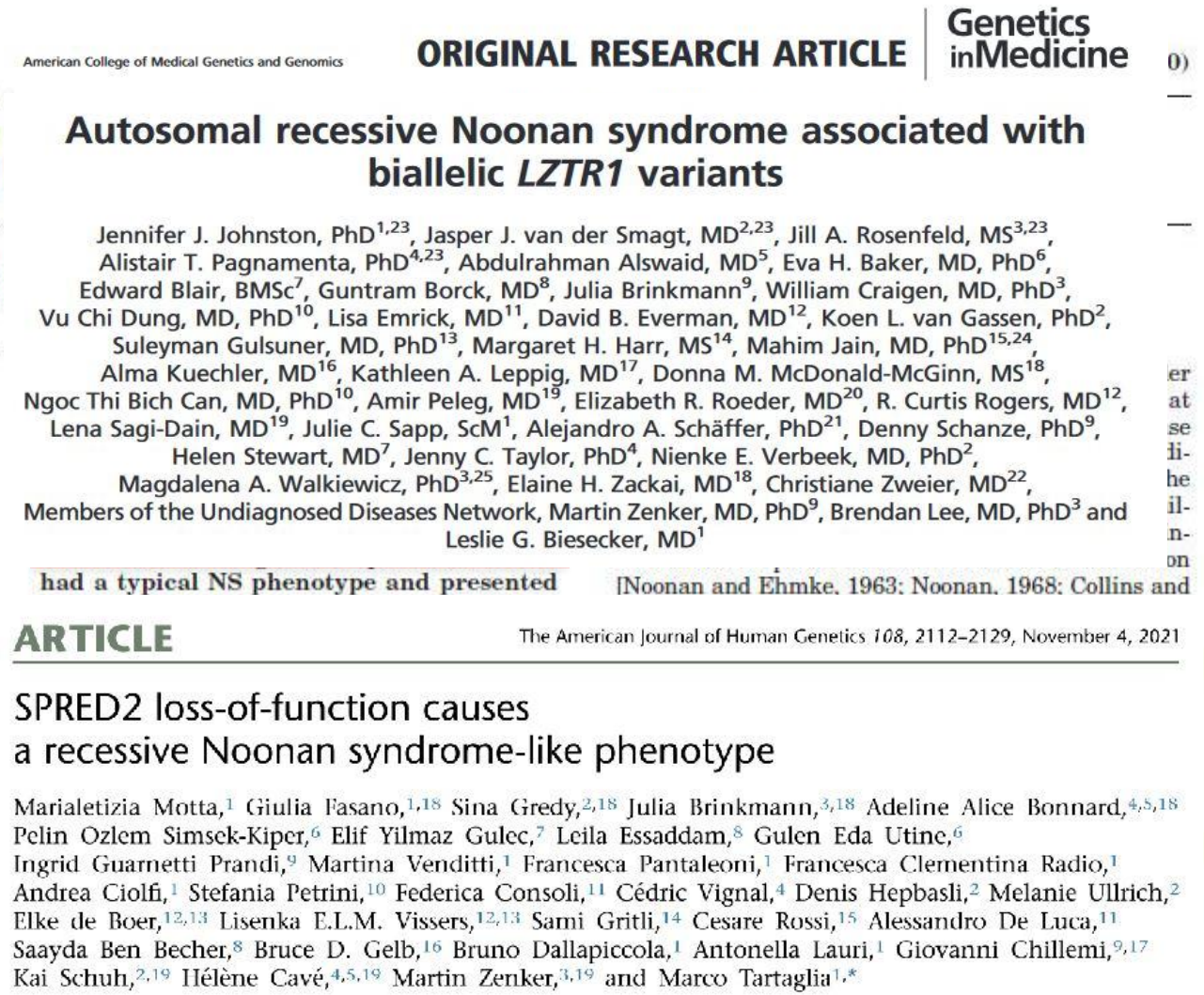
Molecular diagnosis offers the opportunity to overcome the weakness of subjective clinical criteria

Alessandro De Luca, unpublished (Istituto CSS-Mendel, *Rome, Italy*)

Inheritance

RASopathies are largely autosomal dominant disorders …

… but recessive forms do exist



American College of Medical Genetics and Genomics

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Autosomal recessive Noonan syndrome associated with biallelic *LZTR1* variants

Jennifer J. Johnston, PhD[1,23], Jasper J. van der Smagt, MD[2,23], Jill A. Rosenfeld, MS[3,23], Alistair T. Pagnamenta, PhD[4,23], Abdulrahman Alswaid, MD[5], Eva H. Baker, MD, PhD[6], Edward Blair, BMSc[7], Guntram Borck, MD[8], Julia Brinkmann[9], William Craigen, MD, PhD[3], Vu Chi Dung, MD, PhD[10], Lisa Emrick, MD[11], David B. Everman, MD[12], Koen L. van Gassen, PhD[2], Suleyman Gulsuner, MD, PhD[13], Margaret H. Harr, MS[14], Mahim Jain, MD, PhD[15,24], Alma Kuechler, MD[16], Kathleen A. Leppig, MD[17], Donna M. McDonald-McGinn, MS[18], Ngoc Thi Bich Can, MD, PhD[10], Amir Peleg, MD[19], Elizabeth R. Roeder, MD[20], R. Curtis Rogers, MD[12], Lena Sagi-Dain, MD[19], Julie C. Sapp, ScM[1], Alejandro A. Schäffer, PhD[21], Denny Schanze, PhD[9], Helen Stewart, MD[7], Jenny C. Taylor, PhD[4], Nienke E. Verbeek, MD, PhD[2], Magdalena A. Walkiewicz, PhD[3,25], Elaine H. Zackai, MD[18], Christiane Zweier, MD[22], Members of the Undiagnosed Diseases Network, Martin Zenker, MD, PhD[9], Brendan Lee, MD, PhD[3] and Leslie G. Biesecker, MD[1]

had a typical NS phenotype and presented

[Noonan and Ehmke. 1963; Noonan. 1968; Collins and

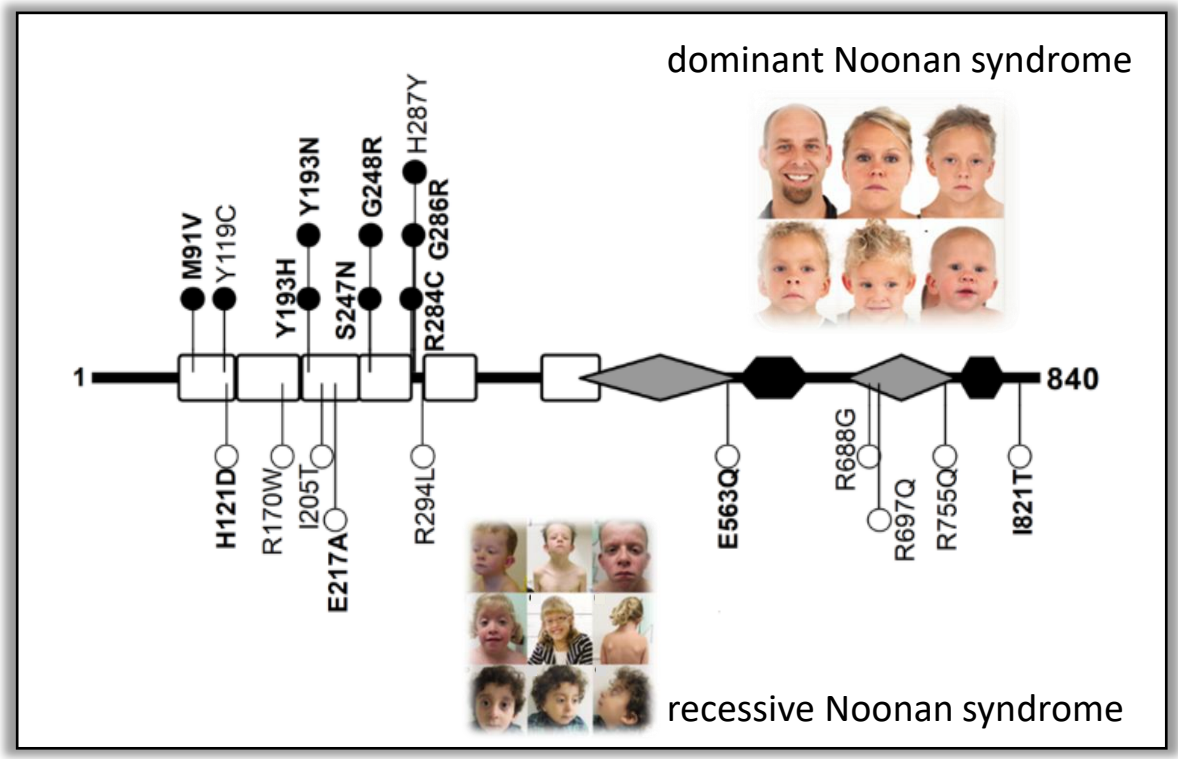
ARTICLE

The American Journal of Human Genetics *108*, 2112–2129, November 4, 2021

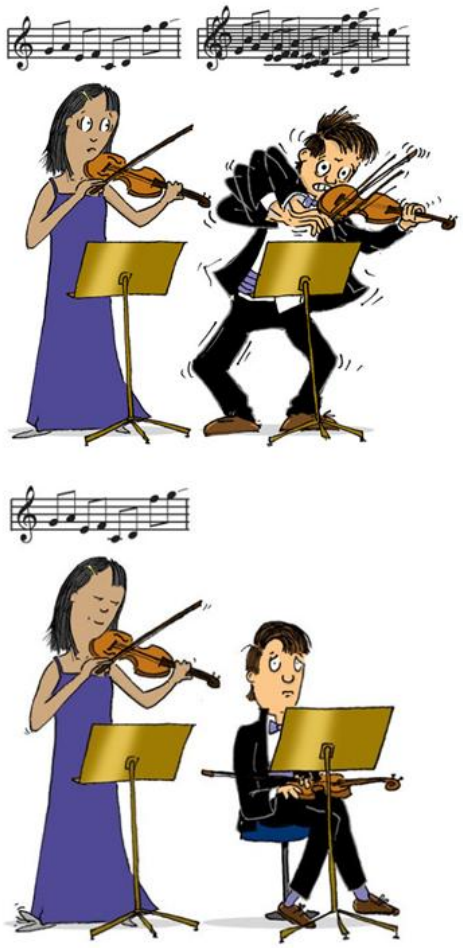
SPRED2 loss-of-function causes a recessive Noonan syndrome-like phenotype

Marialetizia Motta,[1] Giulia Fasano,[1,18] Sina Gredy,[2,18] Julia Brinkmann,[3,18] Adeline Alice Bonnard,[4,5,18] Pelin Ozlem Simsek-Kiper,[6] Elif Yilmaz Gulec,[7] Leila Essaddam,[8] Gulen Eda Utine,[6] Ingrid Guarnetti Prandi,[9] Martina Venditti,[1] Francesca Pantaleoni,[1] Francesca Clementina Radio,[1] Andrea Ciolfi,[1] Stefania Petrini,[10] Federica Consoli,[11] Cédric Vignal,[4] Denis Hepbasli,[2] Melanie Ullrich,[2] Elke de Boer,[12,13] Lisenka E.L.M. Vissers,[12,13] Sami Gritli,[14] Cesare Rossi,[15] Alessandro De Luca,[11] Saayda Ben Becher,[8] Bruce D. Gelb,[16] Bruno Dallapiccola,[1] Antonella Lauri,[1] Giovanni Chillemi,[9,17] Kai Schuh,[2,19] Hélène Cavé,[4,5,19] Martin Zenker,[3,19] and Marco Tartaglia[1,*]

Two different classes of *LZTR1* mutations underlie dominant and recessive forms of Noonan syndrome



Yamamoto *et al.* (2015) *J Med Genet 52:413-21*
Johnston *et al.* (2018) *Genet Med 20:1175-85*



Negative Dominance

VS

Loss of Function

Motta *et al.* (2019) *Hum Mol Genet 28:1007-1022*

Noonan syndrome (12 genes)


PTPN11

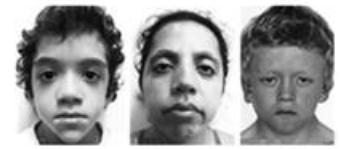

SOS1


KRAS


BRAF

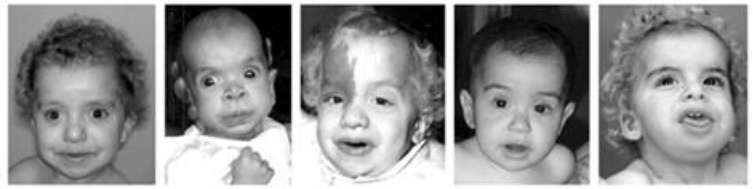

RAF1

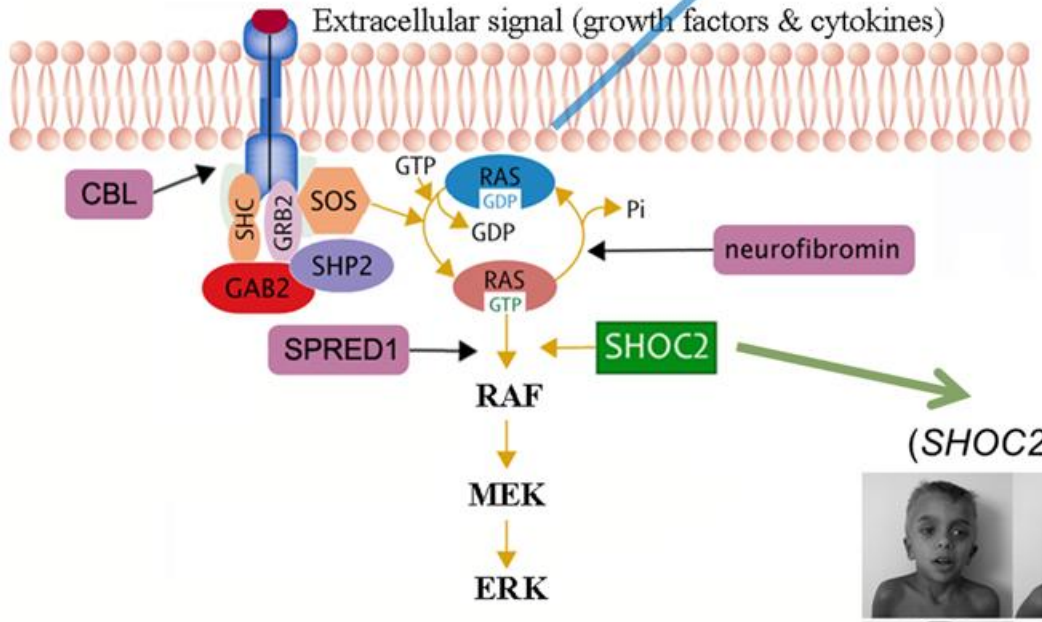

NRAS


LZTR1

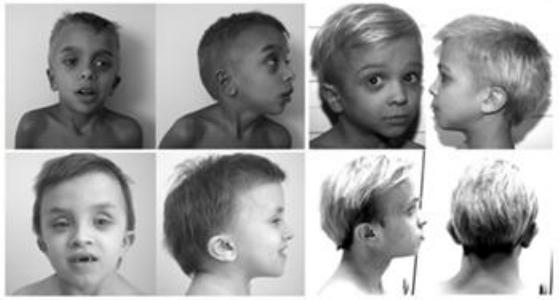
Genetic heterogeneity and extent of phenotypic variation

Costello syndrome (*HRAS*, c.34G>A, >85% cases)

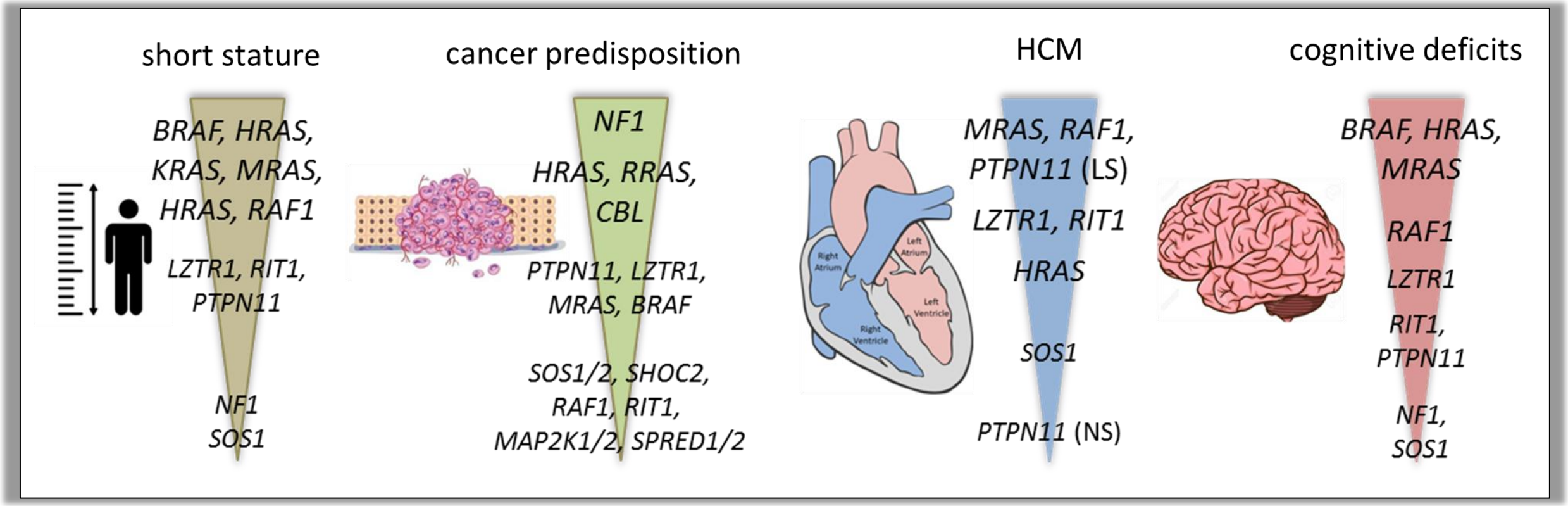




Mazzanti syndrome
(*SHOC2*, c.4A>G, 95% cases)



Genotype-Phenotype Correlations at the Gene Level



Genotype-Phenotype Correlations at the Mutation Level

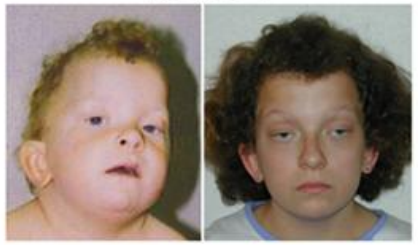
M. Zenker

KRAS

p.V14I

PS, mild learning difficulties, no ectodermal abnormalities, NS-like facial features

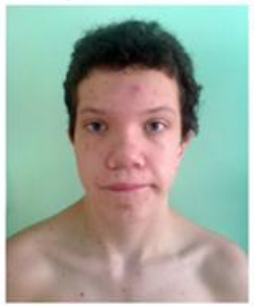
p.D153V



ASD, HCM, moderate MR, ectodermal involvement and facies resembling CFCS

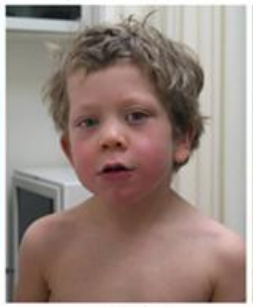
BRAF

p.L245F



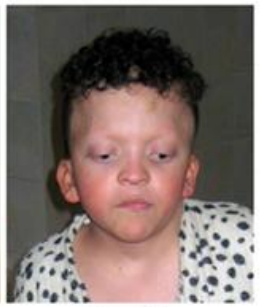
IQ 120

p.G464A



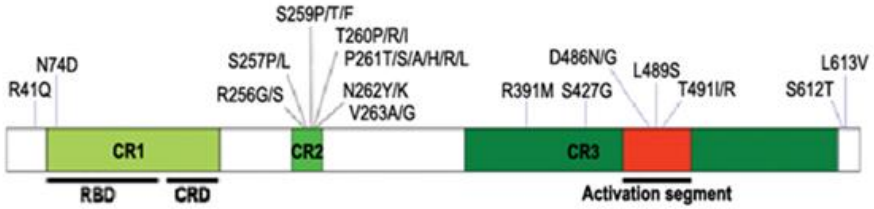
IQ 90

Q257R

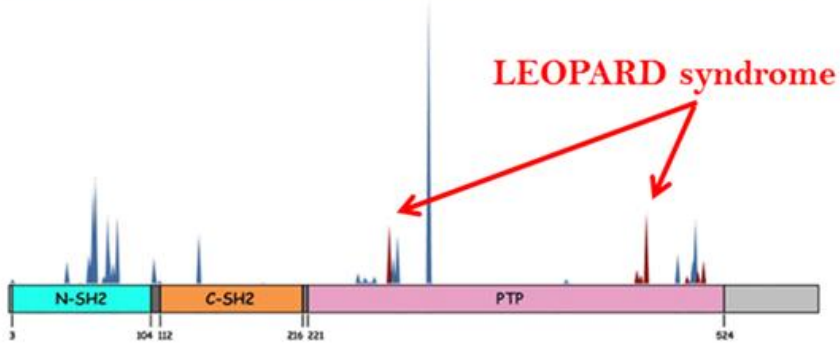


IQ 30

DO NOT POST



RAF1		*PTPN11*	
Domain	HCM	Disorder	HCM
CR2	96%	LS	75%
CR3/C-ter	27%	NS	9%



Pandit *et al.* (2007) *Nat Genet 39:1007-12*
Digilio *et al.* (2009) *Monogr Hum Genet 17:109-18*
Dhandapany *et al.* (2014) *Nat Genet 46:635-9*
Bowen *et al.* (2011) *PLoS Genet 7:e1002050*

› Am J Dis Child. 1968 Oct;116(4):373-80. doi: 10.1001/archpedi.1968.02100020377005.

Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease

J A Noonan

› Am J Dis Child. 1969 Jun;117(6):652-62. doi: 10.1001/archpedi.1969.02100030654006.

Multiple lentigenes syndrome

R J Gorlin, R C Anderson, M Blaw

Case Reports › Am J Med Genet. 1986 Nov;25(3):413-27. doi: 10.1002/ajmg.1320250303.

New multiple congenital anomalies/mental retardation syndrome with cardio-facio-cutaneous involvement--the CFC syndrome

J F Reynolds, G Neri, J P Herrmann, B Blumberg, J G Coldwell, P V Miles, J M Opitz

Case Reports › Aust Paediatr J. 1977 Jun;13(2):114-8. doi: 10.1111/j.1440-1754.1977.tb01135.x.

A new syndrome: mental subnormality and nasal papillomata

J M Costello

Case Reports › Am J Med Genet A. 2003 Apr 30;118A(3):279-86. doi: 10.1002/ajmg.a.10923.

Noonan-like syndrome with loose anagen hair: a new syndrome?

Laura Mazzanti [1], Emanuele Cacciari, Alessandro Cicognani, Rosalba Bergamaschi, Emanuela Scarano, Antonino Forabosco

LETTERS

nature genetics

Germline loss-of-function mutations in *SPRED1* cause a neurofibromatosis 1–like phenotype

Hilde Brems[1,9], Magdalena Chmara[1,2,9], Mourad Sahbatou[3,9], Ellen Denayer[1], Koji Taniguchi[4], Riet Somers[1,5], Ludwine Messiaen[6], Sofie De Schepper[7], Jean-Pierre Fryns[1], Jan Cools[1,5], Peter [illegible], Gilles Thomas[3,8], Akihiko Yoshimura[4] & Eric Legius[1]

ARTICLE

Enhanced MAPK1 Function Causes a Neurodevelopmental Disorder within the RASopathy Clinical Spectrum

Marialetizia Motta,[1,27] Luca Pannone,[1,2,27] Francesca Pantaleoni,[1] Gianfranco Bocchinfuso,[3] Francesca Clementina Radio,[1] Serena Cecchetti,[4] Andrea Ciolfi,[1] Martina Di Rocco,[2,5] Mariet W. Elting,[6] Eva H. Brilstra,[7] Stefania Boni,[8] Laura Mazzanti,[9] Federica Tamburrino,[9] Larry Walsh,[10] Katelyn Payne,[10] Alberto Fernández-Jaén,[11] Mythily Ganapathi,[12] Wendy K. Chung,[13] Dorothy K. Grange,[14] Ashita Dave-Wala,[15] Shalini C. Reshmi,[15,16] Dennis W. Bartholomew,[15] Danielle Mouhlas,[15] Giovanna Carpentieri,[1,2] Alessandro Bruselles,[2] Simone Pizzi,[1] Emanuele Bellacchio,[1] Francesca Piceci-Sparascio,[17] Christina Lißewski,[18] Julia Brinkmann,[18] Ronald R. Waclaw,[19] Quinten Waisfisz,[6] Koen van Gassen,[7] Ingrid M. Wentzensen,[20] Michelle M. Morrow,[20] Sara Álvarez,[21] Mónica Martínez-García,[21] Alessandro De Luca,[17] Luigi Memo,[22] Giuseppe Zampino,[23] Cesare Rossi,[24] Marco Seri,[24] Bruce D. Gelb,[25] Martin Zenker,[18] Bruno Dallapiccola,[1] Lorenzo Stella,[3] Carlos E. Prada,[19,26] Simone Martinelli,[2,28] Elisabetta Flex,[2,28] and Marco Tartaglia[1,28,*]

Original article

Germline mutations of the *CBL* gene define a genetic syndrome with predisposition to juve myelomonocytic leukaemia

B Pérez,[1,2] F Mechinaud,[3] C Galambrun,[4] N Ben Romdhane,[5] B Isidor,[6] J Derain-Court,[7] B Cassinat,[2] J Lachenaud,[1,2] S Kaltenbach,[1] A Salmon, S Pereira,[1] M L Menot,[2] N Royer,[9] O Fenneteau,[10] A Baruchel,[11] C Chomienne, A Verloes,[1,12] H Cavé[1,2]

Germline *CBL* mutations cause developmental abnormalities and predispose to juvenile myelomonocytic leukemia

Charlotte M Niemeyer[1,18], Michelle W Kang[2,18], Danielle H Shin[2,18], Ingrid Furlan[1], Miriam Erlacher[1], Nancy J Bunin[3], Severa Bunda[4], Jerry Z Finklestein[5], Kathleen M Sakamoto[6], Thomas A Gorr[1], Parinda Mehta[7], Irene Schm, Andrea He, Franco Loc, Michael Ol

REPORT

Heterozygous Germline Mutations in the *CBL* Tumor-Suppressor Gene Cause a Noonan Syndrome-like Phenotype

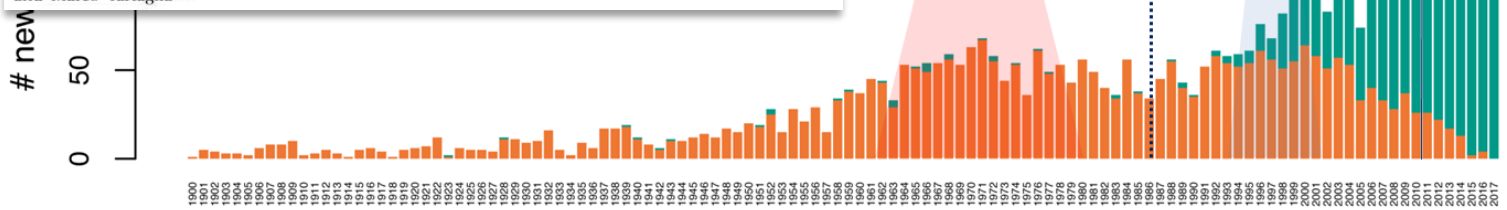
Simone Martinelli,[1] Alessandro De Luca,[2] Emilia Stellacci,[1] Cesare Rossi,[3] Saula Checquolo,[4] Francesca Lepri,[2] Viviana Caputo,[1] Marianna Silvano,[1] Francesco Buscherini,[3] Federica Consoli,[2] Grazia Ferrara,[4] Maria C. Digilio,[5] Maria L. Cavaliere,[6] Johanna M. van Hagen,[7] Giuseppe Zampino,[8] Ineke van der Burgt,[9] Giovanni B. Ferrero,[10] Laura Mazzanti,[11] Isabella Screpanti,[4] Helger G. Yntema,[9] Willy M. Nillesen,[9] Ravi Savarirayan,[12] Martin Zenker,[13] Bruno Dallapiccola,[5] Bruce D. Gelb,[14] and Marco Tartaglia[1,*]

Hypothesis-free

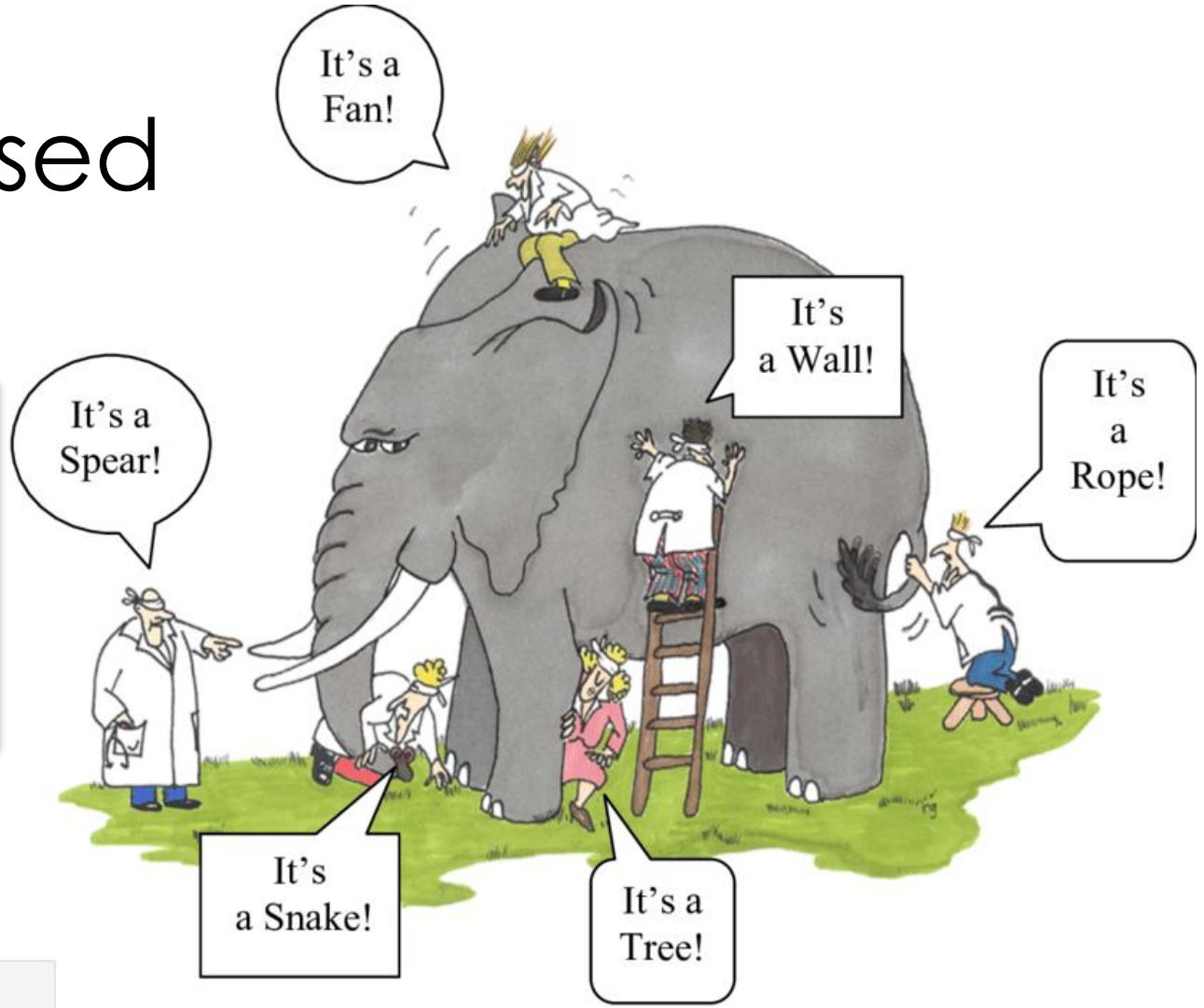
«functional candidacy»

«positional candidacy»

«Golden Age» of Syndrome delineation



Recognizing new RASopathies by unbiased clinical reassessment



ARTICLE

Check for updates

Loss-of-function variants in *ERF* are associated with a Noonan syndrome-like phenotype with or without craniosynostosis

Maria Lisa Dentici[1,25], Marcello Niceta[2,25], Francesca Romana Lepri[3], Cecilia Mancini[2], Manuela Priolo[4], Adeline Alice Bonnard[5], Camilla Cappelletti[2,6], Chiara Leoni[7,8], Andrea Ciolfi[2], Simone Pizzi[2], Viviana Cordeddu[9], Cesare Rossi[10], Marco Ferilli[2], Mafalda Mucciolo[3], Vito Luigi Colona[1], Christine Fauth[11], Melissa Bellini[12], Giacomo Biasucci[12], Lorenzo Sinibaldi[1], Silvana Briuglia[13], Andrea Gazzin[14], Diana Carli[15], Luigi Memo[16], Eva Trevisson[17], Concetta Schiavariello[18], Maria Luca[15], Antonio Novelli[3], Caroline Michot[19], Anne Sweertvaegher[20], David Germanaud[21,22], Emanuela Scarano[18], Alessandro De Luca[23], Giuseppe Zampino[7,8], Martin Zenker[24], Alessandro Mussa[15], Bruno Dallapiccola[2], Helene Cavé[5], Maria Cristina Digilio[1] and Marco Tartaglia[2]✉

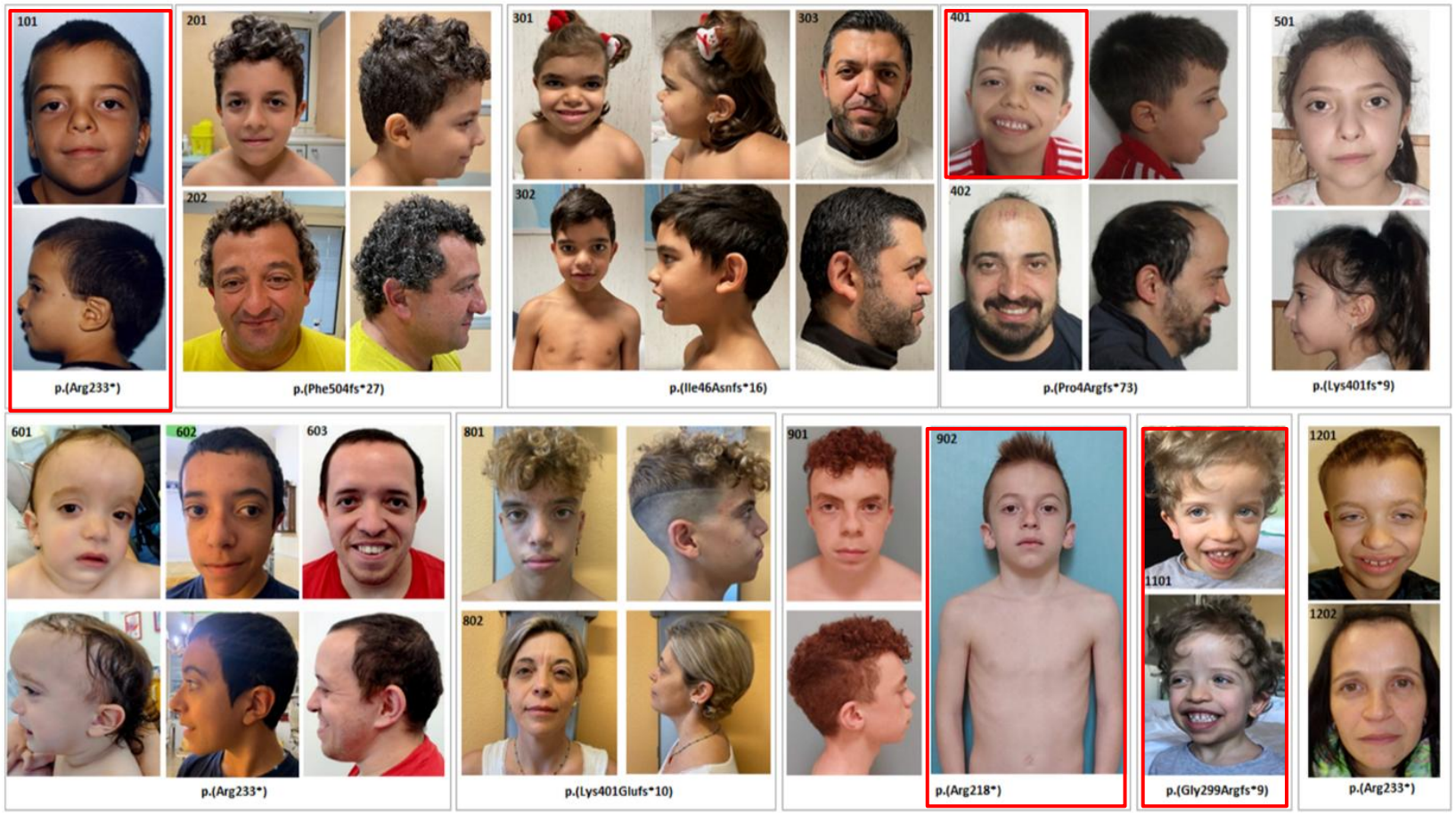
* 611888 **OMIM - Online Mendelian Inheritance in Man**

ETS2 REPRESSOR FACTOR; ERF

Gene-Phenotype Relationships

Location	Phenotype (View Clinical Synopses)	Phenotype MIM number	Inheritance	Phenotype mapping key
19q13.2	Chitayat syndrome	617180	AD	3
	Craniosynostosis 4	600775	AD	3

ERF haploinsufficiency underlies a novel RASopathy

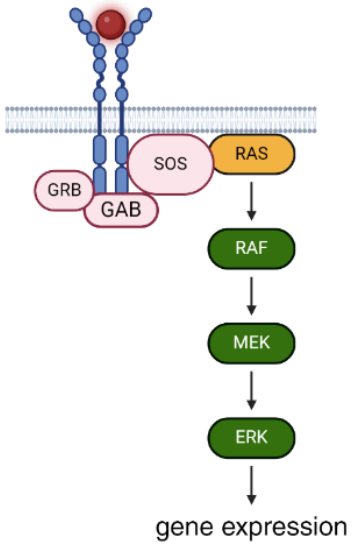


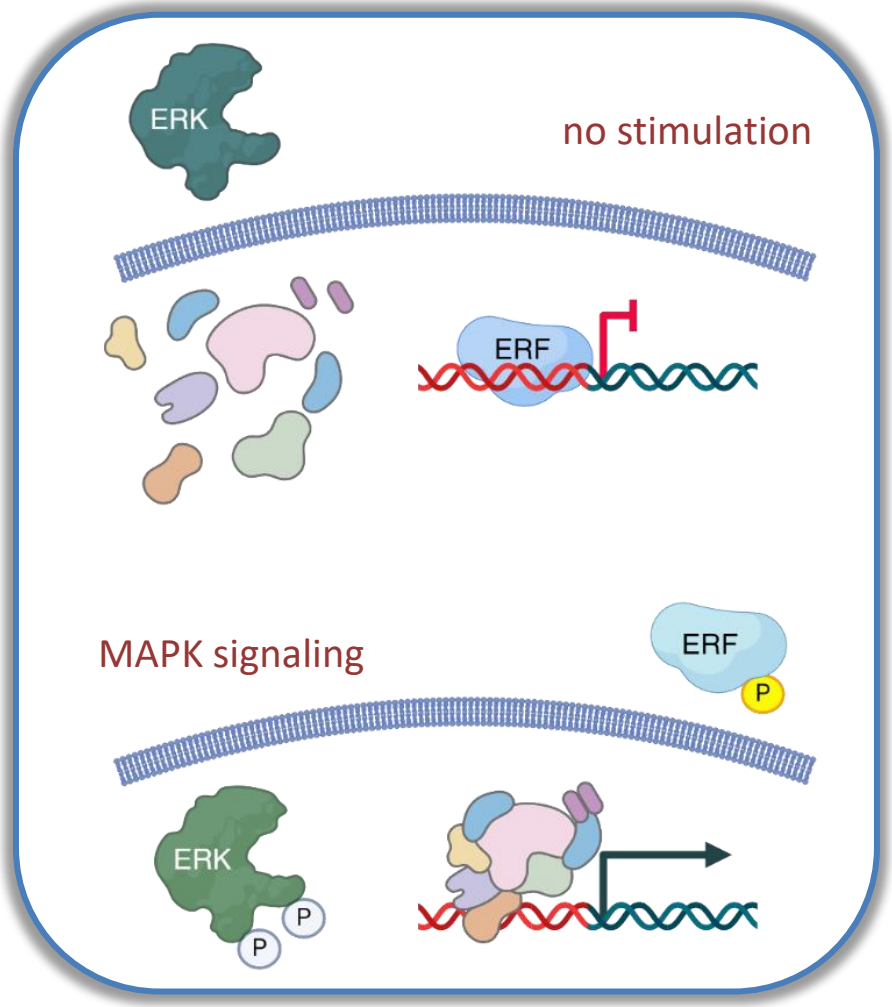
Clinically variable
No subject show cardiac involvement

	Tot (N=26)	CRS4 (N=36)
Short stature (≤3rd centile)	15/26	4/6
DD/ID	13/25[3]	10/30
Speech delay/learning difficulties	19/25	14/30
Behavioural abnormalities	5/26	10/28
Macrocephaly (including relative)	24/26	8/25
Facial features		
high forehead	16/26	29/35
hypertelorism	21/26	33/36
DPF	16/26	23/36
ptosis	16/26	25/36
Wide/depressed nasal bridge	17/26	34/36
thick lips/macrostomia	20/26	22/36
low-set ears	19/26	14/21
posteriorly angulated ears	17/26	15/20
thickened helix	12/26	14/20
Short/webbed neck	15/26	9/14
Low posterior hairline	8/26	11/14
CHD/HCM	1/25	1/1[4]
Pectus abnormalities[1]	9/23	1/1
Ectodermal features		
thin/curly hair	11/26	2/36
sparse eyebrows	6/26	16/36
keratosis pilaris/ulerythema ophryogenes	4/25	NA
dark skin	10/26	NA
cafè-au-laits spots	6/24	NA
lentigines	4/24	NA
nevi	13/24	NA
Craniosynostosis[2]	3 /13	19/25

Dentici *et al., Eur J Hum Genet, 32:954-63.*

ERF & MAPK signaling

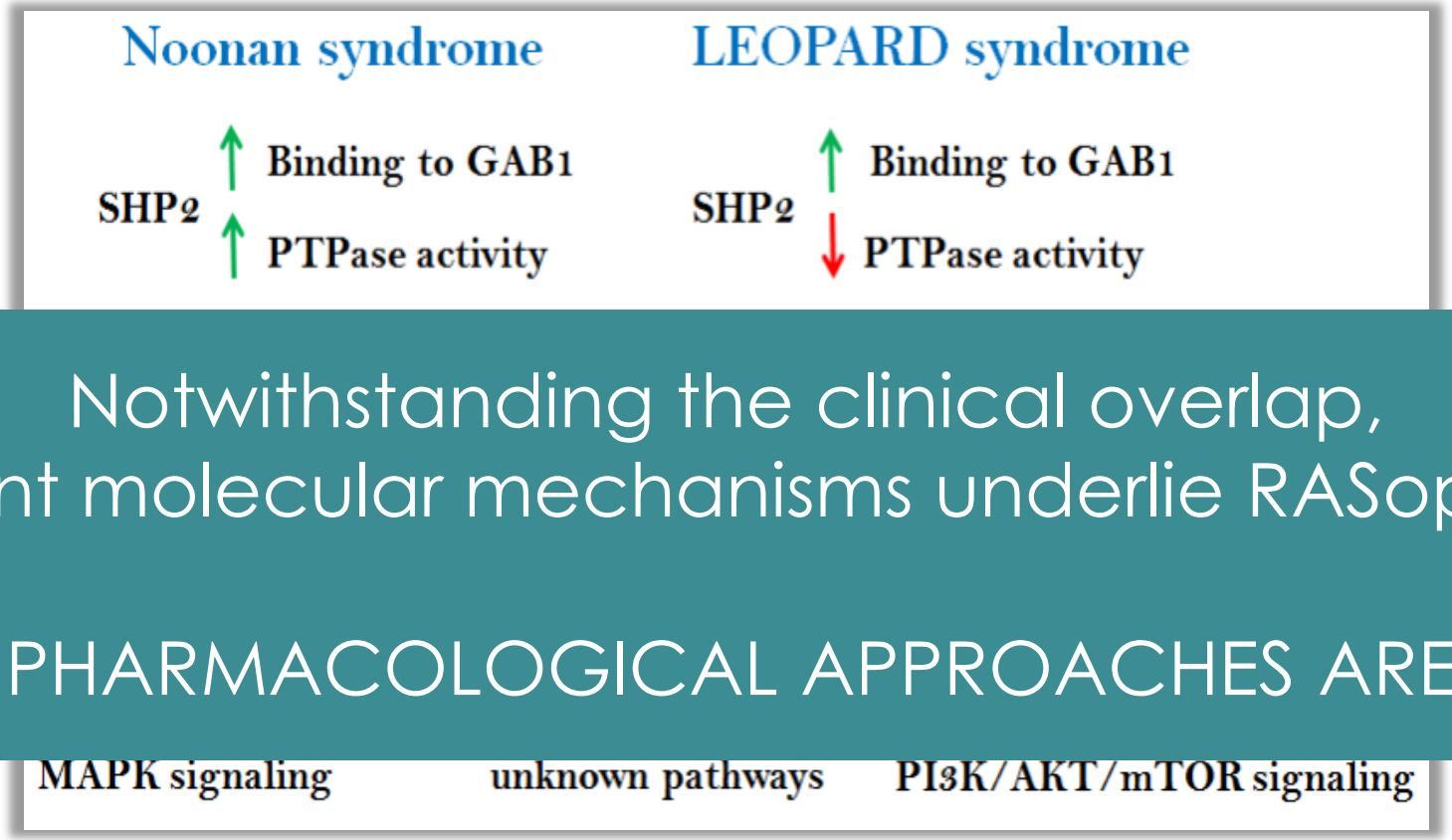




ERF is an ETS domain transcriptional repressor that binds to DNA in a sequence-specific manner to transcriptionally silence target genes

ERF is regulated by ERK phosphorylation via nucleo-cytoplasmic shuttling. ERK-mediated phosphorylation promotes ERF translocation to the cytoplasm, allowing transcription of target genes

Dentici *et al., Eur J Hum Genet, 32(8):954-963.*

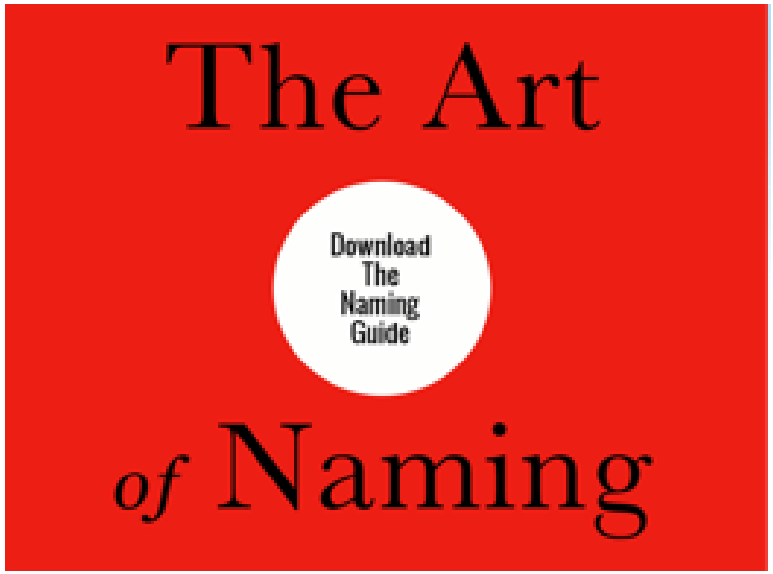


Notwithstanding the clinical overlap,
different molecular mechanisms underlie RASopathies

TARGETED PHARMACOLOGICAL APPROACHES ARE REQUIRED

- *Ptpn11*^{Q79R} e *Raf1*^{L613V} models:
The use of MEK inhibitors allows to rescue multiple clinical features (e.g., reduced growth, HCM)

- *Ptpn11*^{Y279C} model :
Rapamycin, an inhibitor of the PI3K-AKT-mTOR pathway, is effective in blocking HCM progression



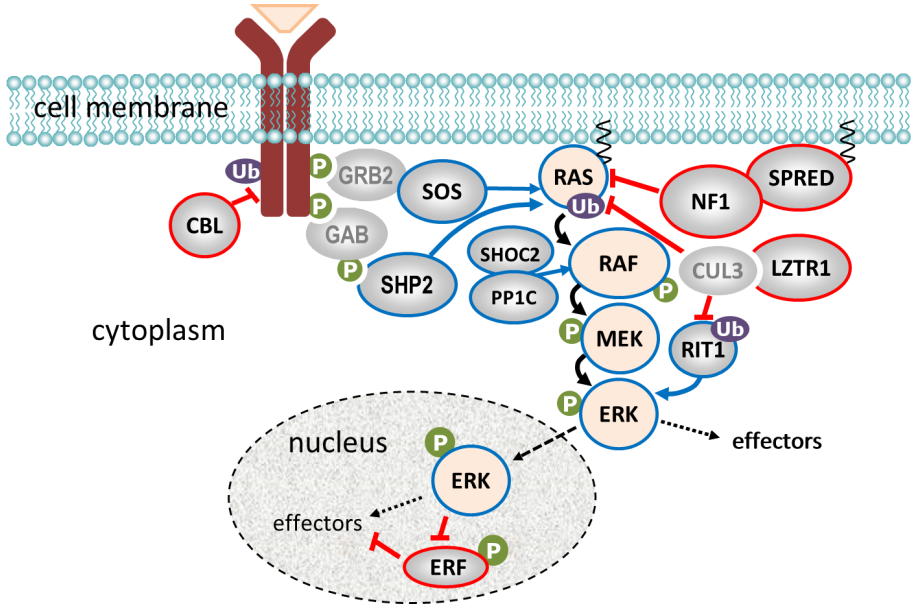
«Noonan syndrome» is not a clinically exhaustive term

the involved gene and pathogenic variant(s) should be taken into account to effectively apply precision medicine and optimize patient management and care.

Take home message (1)

RASopathies share the upregulation of RAS-MAPK signaling as a common pathogenetic mechanism

>25 disease genes identified;
13 implicated in Noonan syndrome



New RASopathies and recessive forms are emerging

Take home message (2)

Mutations may affect protein function by multiple mechanisms and have different consequences on intracellular signaling

Other pathways contribute to the clinical phenotype and phenocopies do exist

RASopathy mutants are weak hypermorphs & mutations do not necessarily predispose to cancer

OPBG

Marialetizia Motta
Clementina Radio
Cecilia Mancini
Luca Mignini
Claudia Compagnucci
Marcello Niceta
Antonella Lauri
Giulia Fasano
Andrea Ciolfi
Mattia Carvetta

ISS

Elisabetta Flex
Simone Martinelli
Viviana Cordeddu
Alessandro Bruselles
Luca Pannone
Valentina Muto
Simona Coppola
Emilia Stellacci
Giovanna Carpentieri
Erika Zara

AIRC

Lorenzo Stella, Gianfranco Bocchinfuso (*Rome*)
Giovanni Chillemi (*Rome*)

Rete Italiana per le RASopatie

Giuseppe Zampino, Chiara Leoni (*Rome*)
Alessandro De Luca (*S. Giovanni Rotondo*)
GiBi Ferrero & Alessandro Mussa (*Turin*)
Laura Mazzanti, Federica Tamburrino, Emanuela Scarano & Cesare Rossi (*Bologna*)
M. Cristina Digilio & Maria Lisa Dentici (*Rome*)
Leonardo Salviati & Eva Trevisson *(Padua)*
Manuela Priolo, Giuseppe Limongelli (Naples)
Daniela Melis (Salerno)
Angelo Selicorni (*Como*)

Ministero della Salute

AISC CRASIA

Associazione Nazionale SINDROME DI NOONAN RASopatie

NSEuroNet

Martin Zenker (*Magdeburg*), Bruce D Gelb (New York), Helene Cavé (*Paris*), Reza Ahmadian (*Dusseldorf*), Jeroen den Hertog (*Utrecht*), Armelle Yart (*Tolouse*), Monika Gos (*Warclaw*)

Topic 2 - Growth Abnormalities and New Therapeutic Perspectives

Thomas Edouard, Professor, MD, PhD, Endocrine, Bone Diseases, and Genetics Unit, Reference centre for rare diseases of growth, FIRENDO network, Endo-ERN

Children's Hospital, Toulouse University Hospital, Toulouse, France

2025

Disclosures

- **Research funding (investigator in clinical trials):** Biomarin, Novo Nordisk, QED therapeutics
- **Advisory board participation:** Biomarin, Novo Nordisk
- **Fees for lecture:** Biomarin, Kyowa Kyrin, Novo Nordisk, Pfizer
- This presentation was developed by the speaker and is sponsored by Novo Nordisk

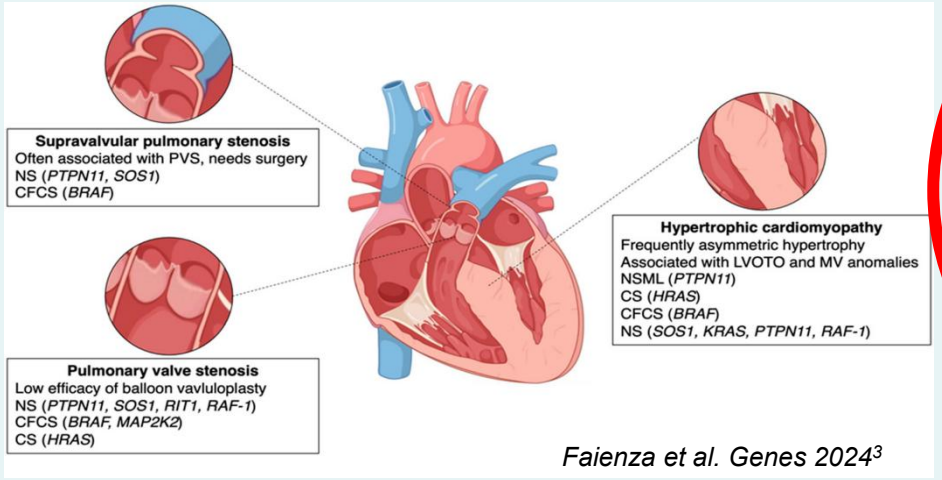
Noonan syndrome (NS)

- Common genetic disorder (1 in 2,000 live births)[1]
- Autosomal dominant (affected parent in ≈1/3)[2]

Distinctive facial features[1]

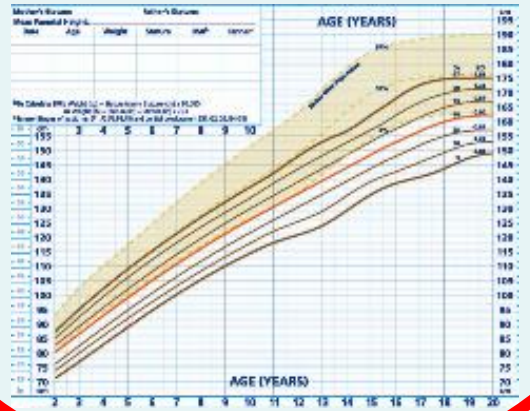
Roberts et al. Lancet 2013[1]

Congenital heart defects (80%)[3]



Faienza et al. Genes 2024[3]

Short stature (50–70%)[4]



Dyscerne 2010[5]

- Many other defects
  - Cryptorchidism in males[6]
  - Skeletal anomalies (*pectus*, scoliosis)[6]
  - Developmental delay and learning disability, hearing and visual impairment[6]
  - Increased risk of cancer (juvenile myelomonocytic leukaemia 3%, brain tumour <1%)[7,8]

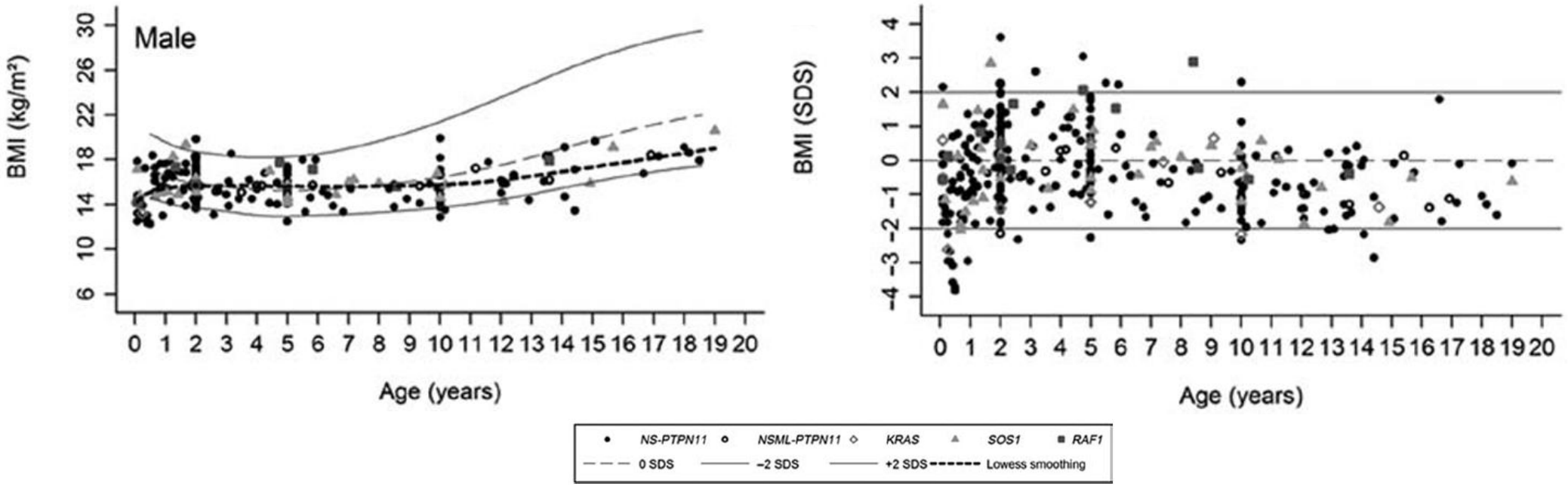
1. Roberts AE et al. Lancet 2013;381:333–42; 2. Zenker M et al. Arch Dis Child 2022;107:1073–8; 3. Faienza MF et al. Genes 2024;15:1015; 4. Edouard T et al. Eur J Med Genet 2022;65:104404; 5. Dyscerne. 2010. NS Clinical Management Guidelines. Available at: https://dyscerne.org/dysc/digitalAssets/0/265_Noonan_Guidelines.pdf. Accessed November 2025; 6. Tajan M et al. Endocr Rev 2018;39:676–700; 7. Protocole National de Diagnostic et de Soins (PNDS). RASopathies: Syndromes de Noonan, cardio-facio-cutané et apparentés. 2021. Available at: https://www.has-sante.fr/upload/docs/application/pdf/2021-10/pnds_rasopathies_texte_sept21_2021-10-01_09-53-19_890.pdf. Accessed October 2025; 8. Perrino MR et al. Clin Cancer Res 2024;30:4834–43.

Nutritional and metabolic aspects

- **Feeding difficulties and failure to thrive** are frequent in newborns and infants (75%)
  - Poor sucking, prolonged feeding times, recurrent vomiting
  - Tube feeding needed in 25%
  - Usually resolves within the first few years of life

- **Lean phenotype** with BMI in the low–normal range

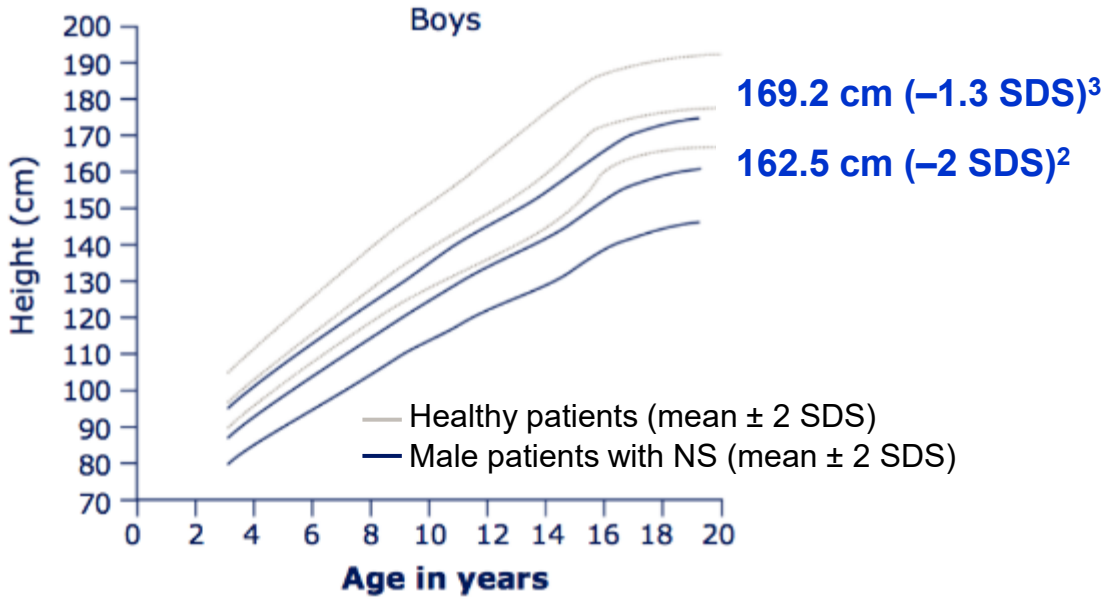
- Aetiology unknown, could be due to increased energy expenditure



Roberts AE et al. Lancet 2013;381:333–42; da Silva FM et al. Am J Med Genet A 2016;170:1525–31; Cessans C et al. Eur J Endocrinol 2016;174:641–50.

Growth and puberty

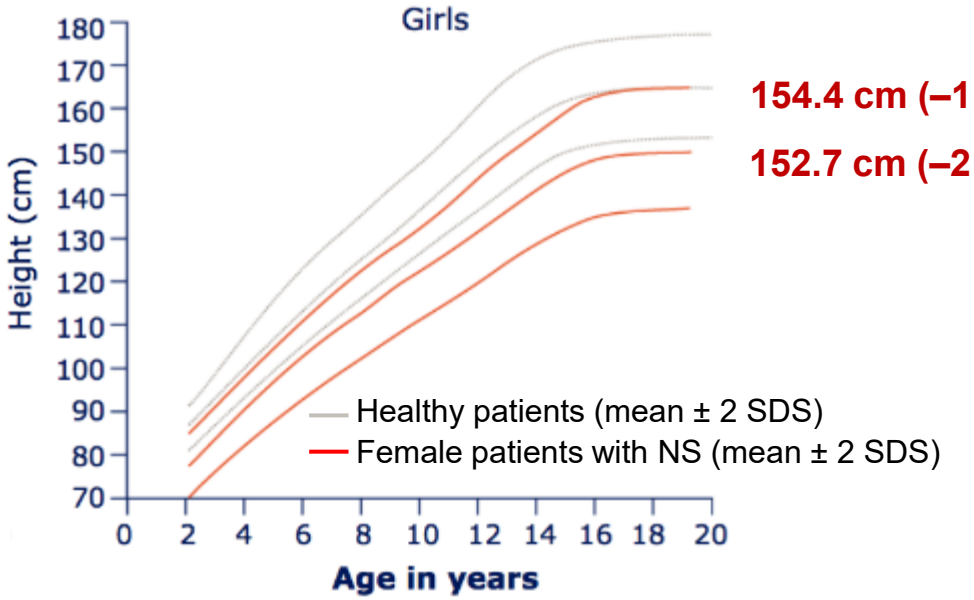
Short stature in 50–70% of patients with NS[1]



169.2 cm (–1.3 SDS)[3]

162.5 cm (–2 SDS)[2]

Adapted from Ranke et al. 1988[2]



154.4 cm (–1.7 SDS)[3]

152.7 cm (–2 SDS)[2]

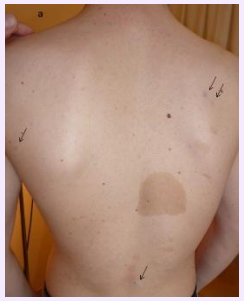
Adapted from Ranke et al. 1988[2]

- Birth length in the lower normal range (25% small for gestational age)
- Decreased growth velocity and short stature by 2 years of age
- Worsening during puberty due to delay
- Bone age typically delayed by about 2 years, allowing for prolonged catch-up growth

1. Edouard T et al. Eur J Med Genet 2022;65:104404; 2. Ranke MB et al. Eur J Pediatr 1988;148:220–7; 3. Binder G et al. J Pediatr 2012;161:501–5.

Noonan syndrome-related disorders

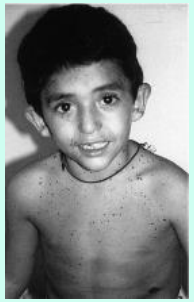
NS / NF1[1]



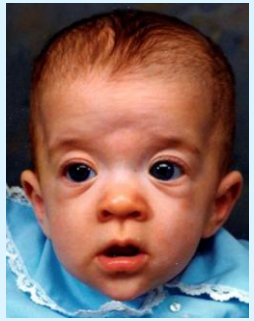
Neurofibromas, café-au-lait spots

NS with multiple lentigines[2]

Lentigines, deafness



Noonan syndrome[3,4]



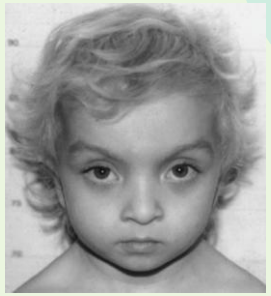
Short stature, pulmonary valve stenosis

Cardiofaciocutaneous syndrome[3]

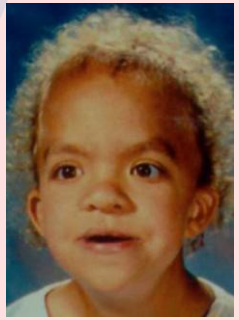
Ectodermal lesions, mental retardation

NS with loose anagen hair[4]

Hairless skin, loose anagen hair



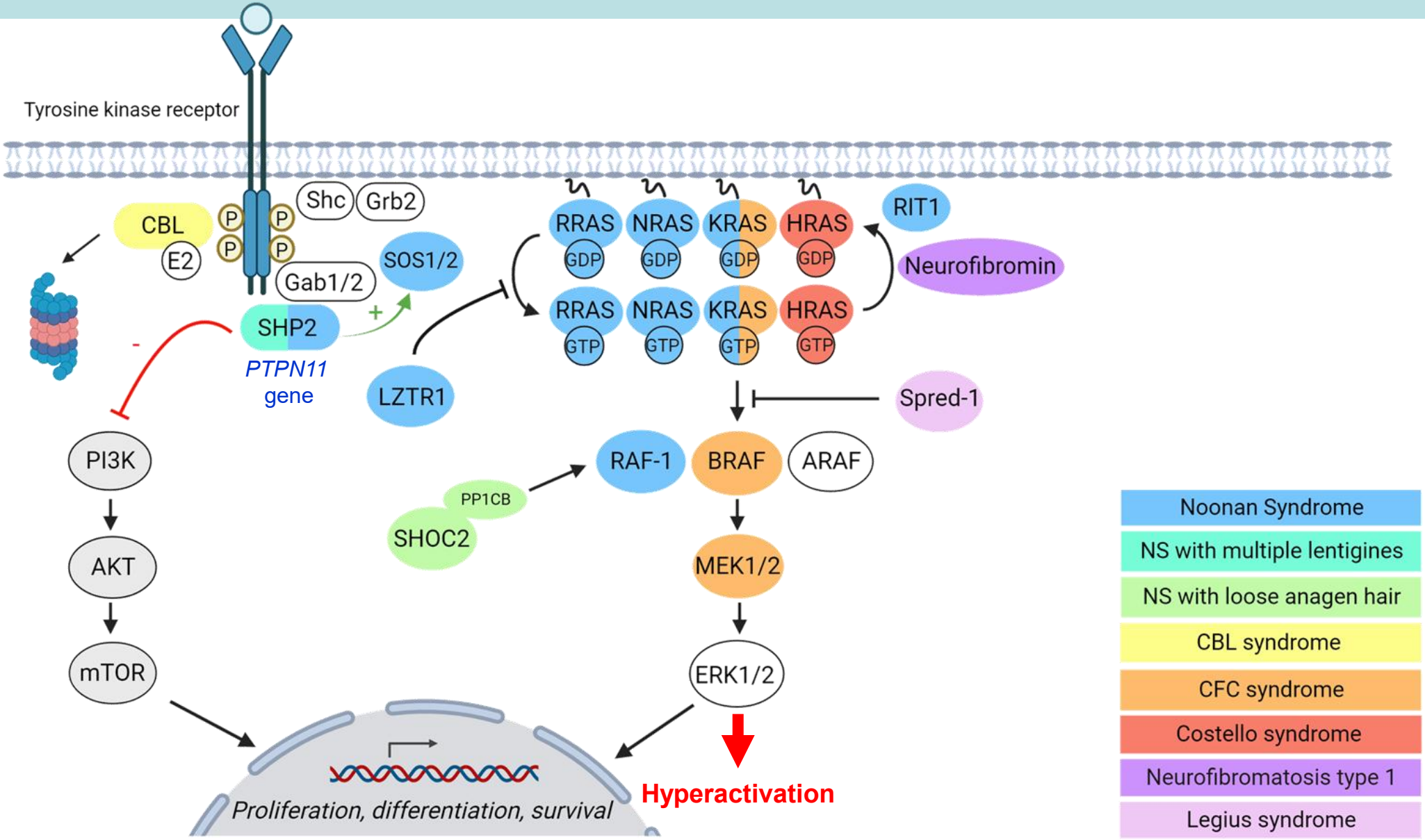
Costello syndrome[3]



HCM, mental retardation, solid tumours (15%)

1. Reig I et al. Dermatol Online J 2011;17:4; 2. Digilio MC et al. Am J Hum Genet 2002;71:389–94;
3. Allanson JE. Am J Med Genet A 2016;170:2570–7; 4. Mazzanti L et al. Am J Med Genet A 2003;118A:279–86.

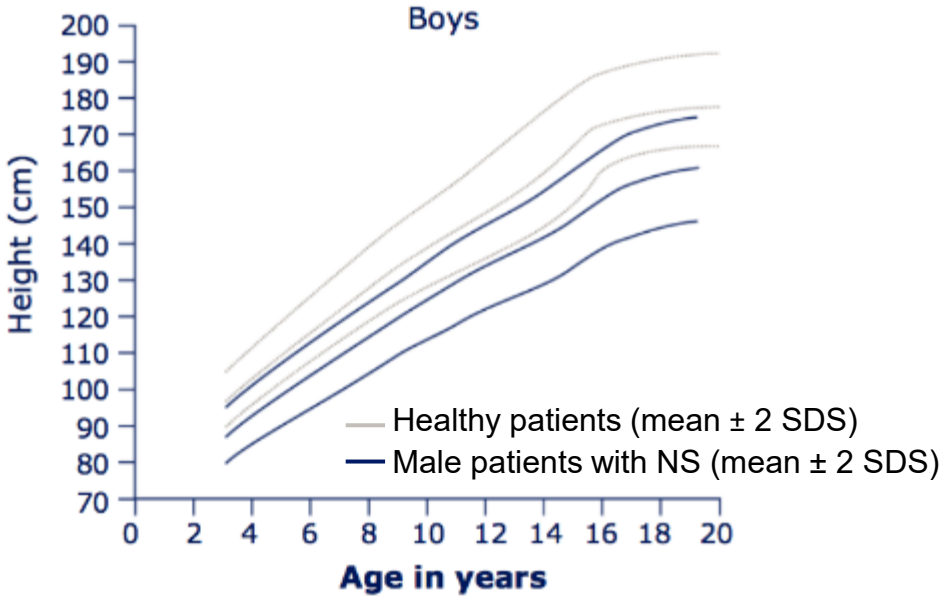
RASopathies



Saint-Laurent C et al. Eur J Pediatr 2024;183:1011–9.

Genotype–phenotype correlations for growth

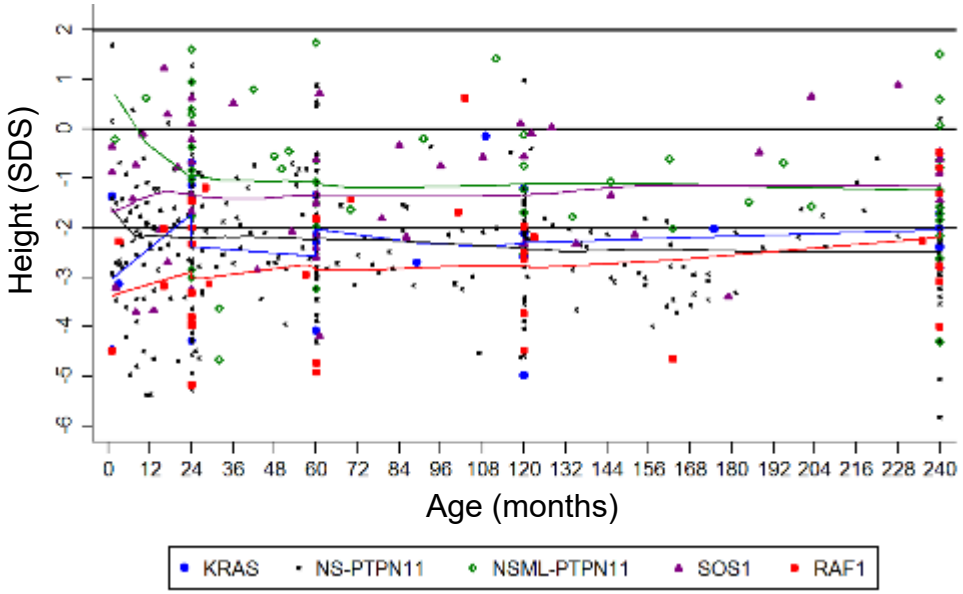
In 144 patients with a clinical diagnosis of NS



Adapted from Ranke et al. 1988[1]

In 420 patients with a confirmed genetic diagnosis of NS

SOS1 > PTPN11 > RAF1

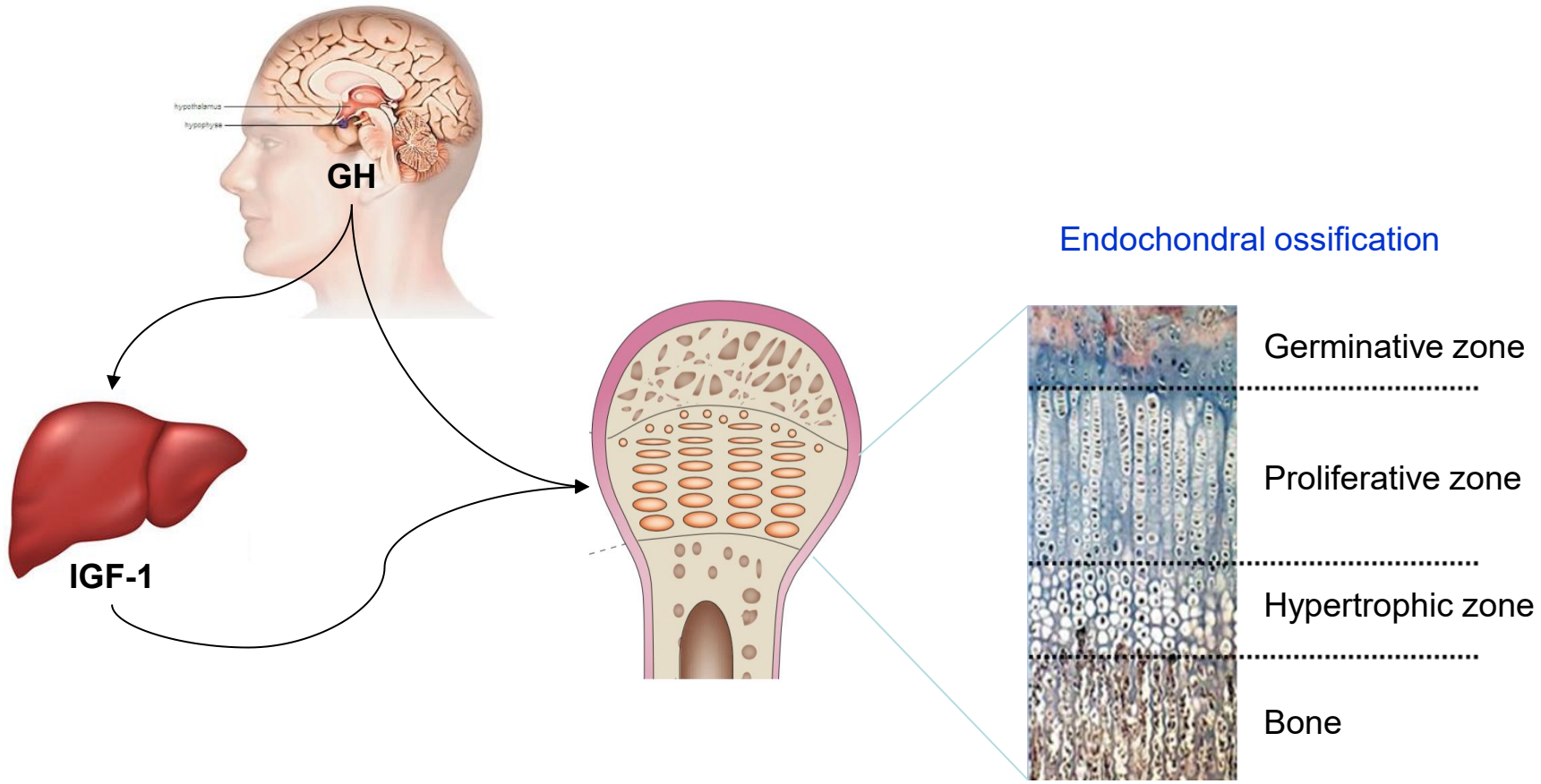


Adapted from Cessans et al. 2016[2]

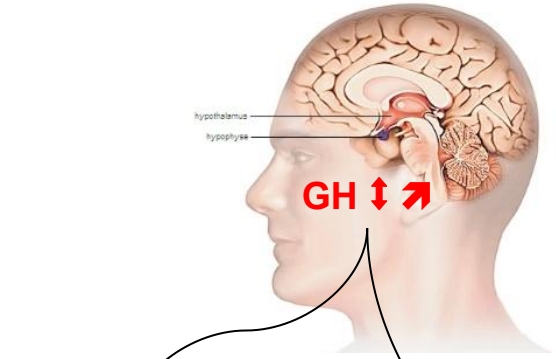
➢ **The severity of short stature is correlated with genotype**

1. Ranke MB et al. Eur J Pediatr 1988;148:220–7; 2. Cessans C et al. Eur J Endocrinol 2016;174:641–50.

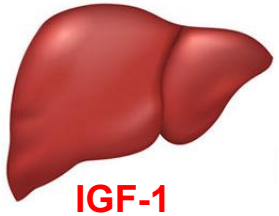
Pathophysiology of short stature (*PTPN11* mutation)

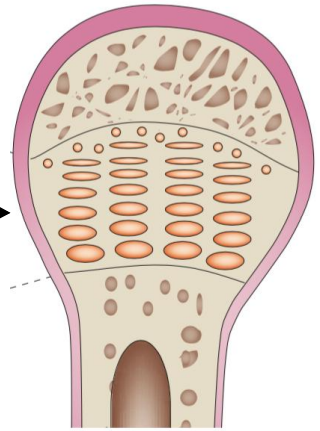


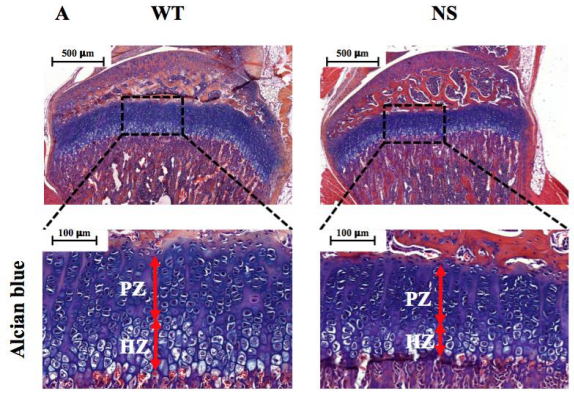
Pathophysiology of short stature (*PTPN11* mutation)



NS mouse model
PTPN11 $^{D61G/+}$







Tajan et al. 2018[2]

RAS/MAPK ↗↗

GH insensitivity[1]

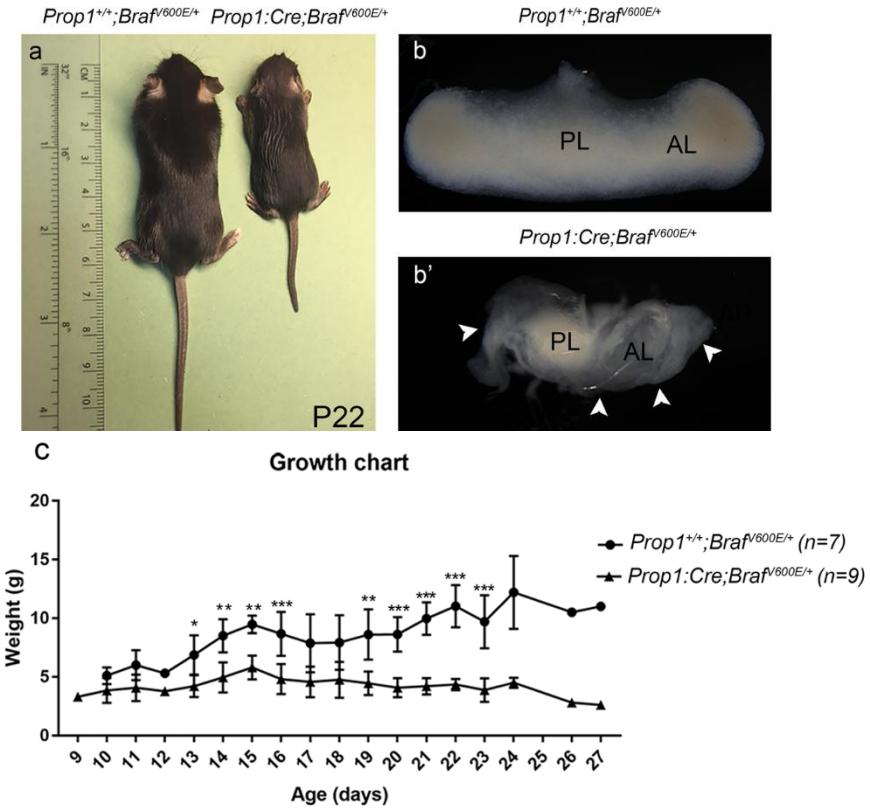
Abnormal chondrocyte differentiation (IGF-1 independent)[2]

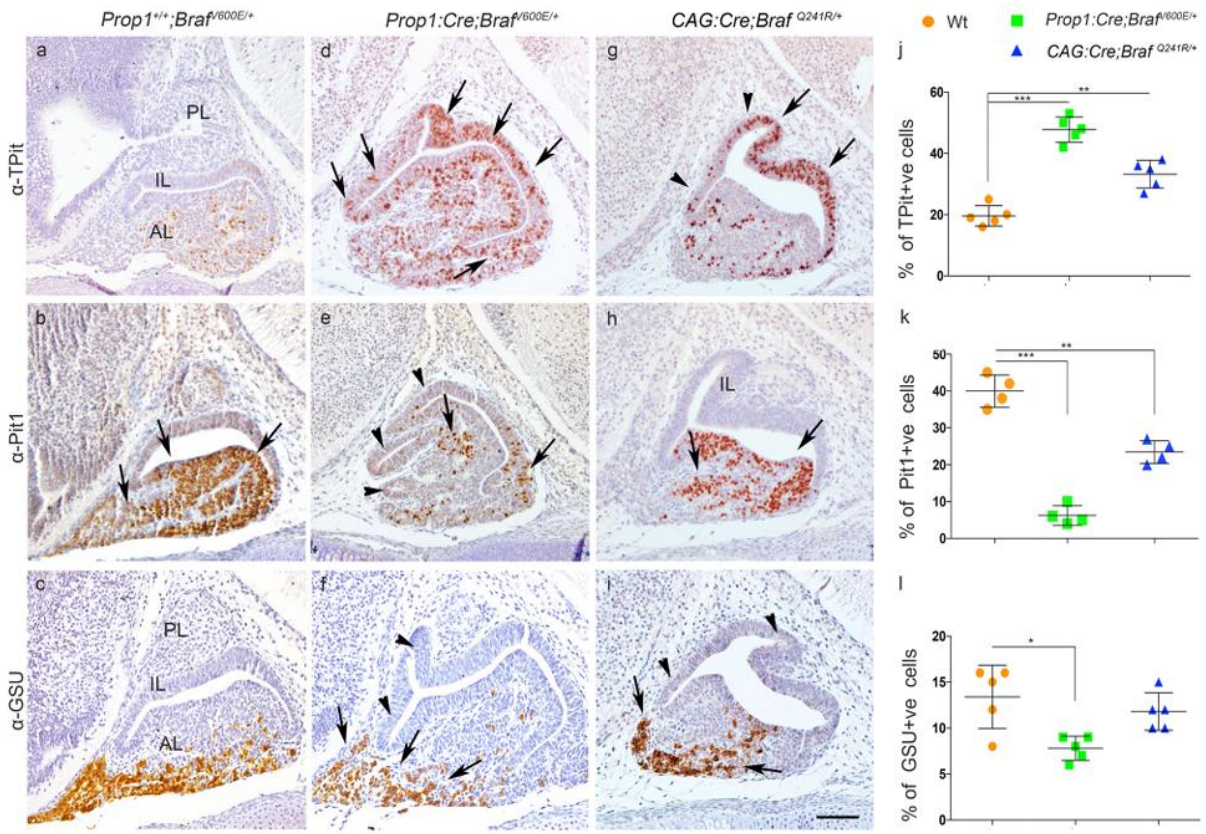
1. De Rocca Serra-Nédélec A et al. Proc Natl Acad Sci USA 2012;109:4257–62; 2. Tajan M et al. Hum Mol Genet 2018;27:2276–89.

Pathophysiology of short stature (*BRAF* mutation)

Activating mutations in BRAF disrupt the hypothalamo-pituitary axis leading to hypopituitarism in mice and humans

Angelica Gualtieri[1,14], Nikolina Kyprianou[1,14], Louise C. Gregory[2,14], Maria Lillina Vignola[1,14], James G. Nicholson[1], Rachael Tan[1], Shin-ichi Inoue[3], Valeria Scagliotti[1], Pedro Casado[4], James Blackburn[1], Fernando Abollo-Jimenez[1], Eugenia Marinelli[1], Rachael E. J. Besser[2], Wolfgang Högler[5,6], I. Karen Temple[7], Justin H. Davies[8,9], Andrey Gagunashvili[10], Iain C.A.F. Robinson[11], Sally A. Camper[12], Shannon W. Davis[13], Pedro R. Cutillas[4], Evelien F. Gevers[1], Yoko Aoki[3], Mehul T. Dattani[2,14] & Carles Gaston-Massuet[1,14]✉



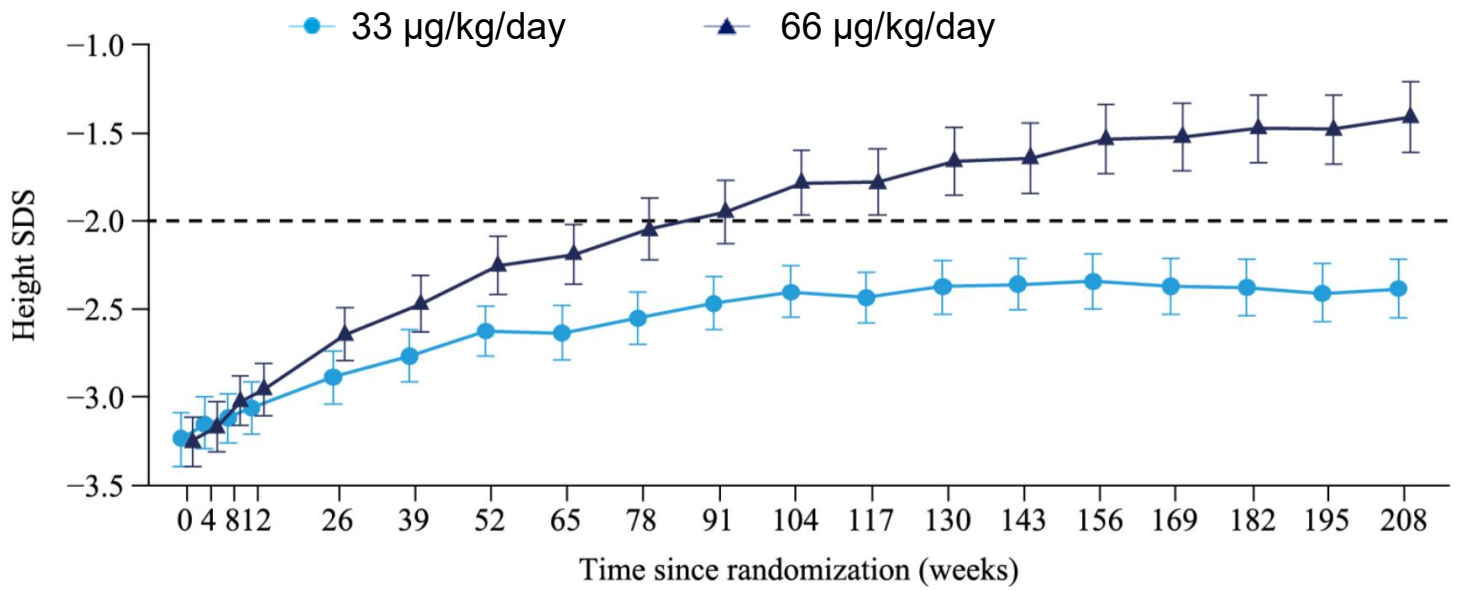


Gualtieri A et al. Nat Commun 2021;12:2028.

Short- to medium-term response to growth hormone treatment

In 51 patients with NS and short stature,

treatment **over 4 years** with somatropin 33 µg/kg/day vs 66 µg/kg/day



P < 0.0001

➢ **Good cardiac and metabolic tolerance**

Horikawa R et al. Endocr J 2020;67:803–18.

Weekly Somapacitan is Effective and Well-Tolerated in Children with Noonan Syndrome: Randomised Phase 3 Trial

Alexander A. L. Jorge[1], Assunta Albanese[2], Michael Højby[3], Kamil Soltysik[3], Thomas Edouard[4, 5], Anna Grandone[6], Michael Tansey[7], Jun Mori[8]

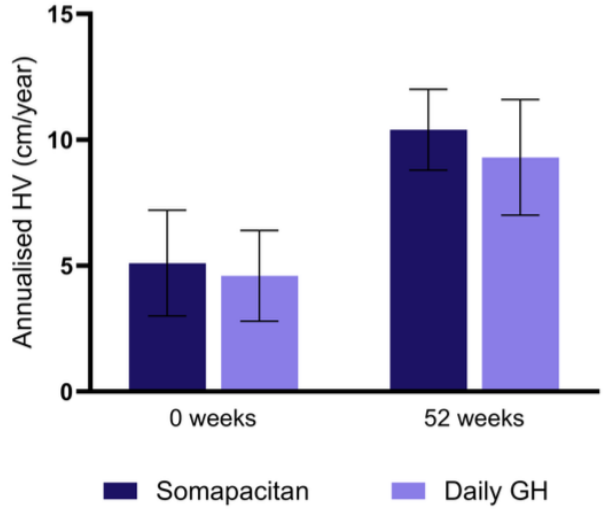
ABSTRACT CODE: LB91

In 77 patients with NS and short stature,

treatment over 1 year with daily somatropin (50 µg/kg/day) or

weekly somapacitan (0.24 mg/kg/week)

Figure 2 - Observed height velocity from baseline to week 52.



Error bars represent SD.

Table 2 - Statistical analyses of in-study efficacy endpoints at week 52

	somapacitan 0.24 mg/kg/wk estimated mean	daily GH 0.050 mg/kg/d estimated mean	ETD (95% CI)
Annualised HV, cm/y	10.4	9.2	1.2 (0.32 to 2.03)
Change in HSDS from baseline	1.07	0.75	0.32 (0.16 to 0.48)
Change in HVSDS from baseline	6.30	5.24	1.06 (0.01 to 2.10)
Change in IGF-I SDS from baseline	2.35	1.51	0.84 (0.36 to 1.31)
Change in BA/CA ratio	0.02	0.03	-0.01 (-0.06 to 0.03)

Full analysis set (all randomised participants).

Jorge A et al. Presented at the Joint Congress of ESPE and ESE 2025; 10-13 May 2025; Copenhagen, Denmark. Poster LB91.

Still many unanswered questions related to rhGH treatment for NS…

- What is the long-term efficacy of rhGH treatment on adult height?
- How safe is the treatment in patients with hypertrophic cardiomyopathy?
- Could there be genotype–phenotype correlations for rhGH treatment efficacy and safety?

- Is a GH stimulation test necessary in children with short stature?
- Should a brain MRI be performed before initiating rhGH treatment?
- What is the optimal age to start rhGH therapy?
- What height threshold should be used when considering rhGH treatment?
- Could rhGH have a beneficial effect on muscle function and motor development?

➢ **Consensus guidelines for Noonan syndrome spectrum disorders**

(currently being developed and validated in association with ESPE and ERN-ITHACA)

The Endocrine working group:

Atilano Carcavilla (Spain)

Laura Mazzanti and Stefano Cianfarini (Italy)

Kees Noordam (Netherlands)

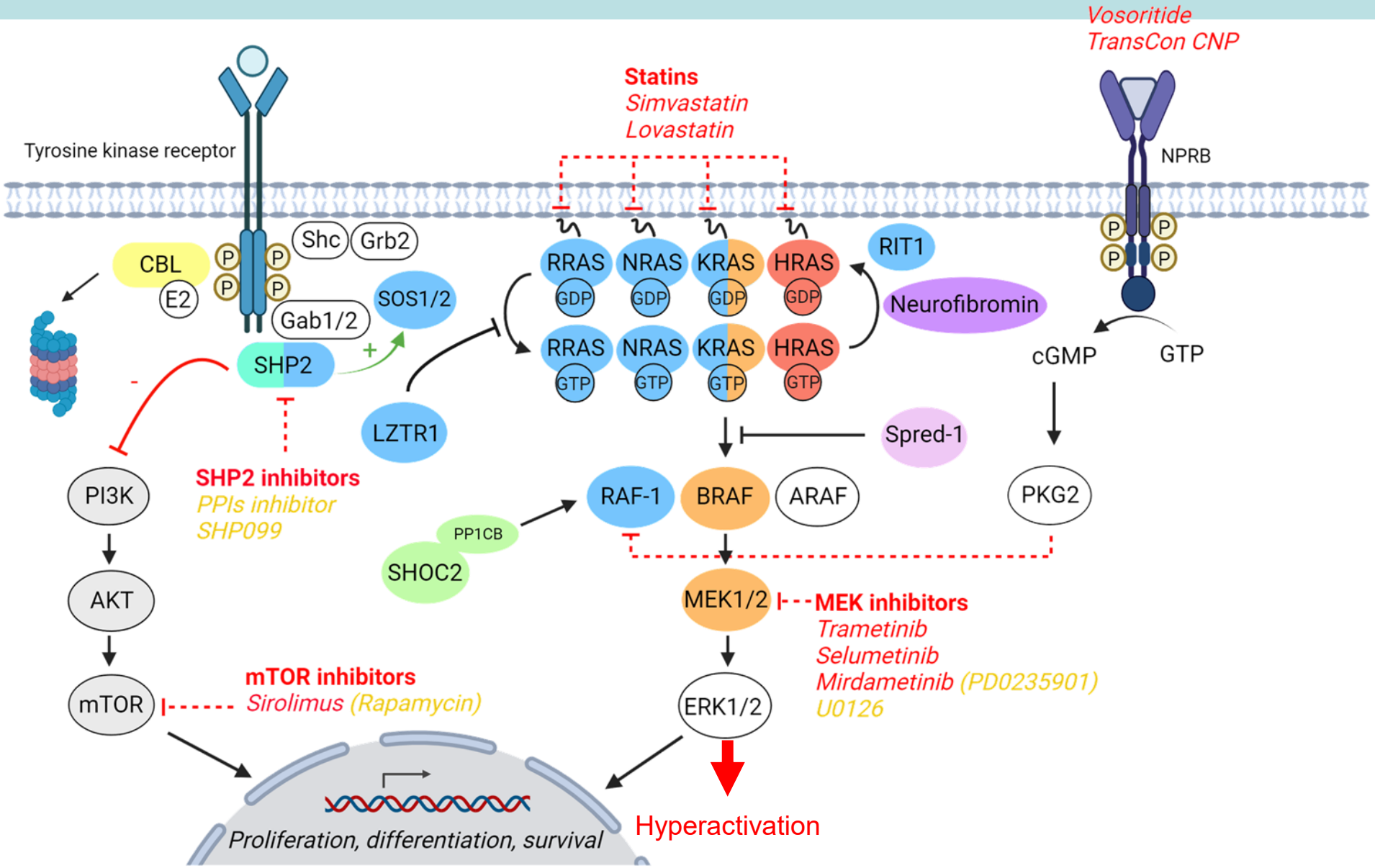
Mehul Dattani and Guftar Shaikh (UK)

Jan Lebl (Czech Republic)

Alexander Jorge (Brazil)

Thomas Edouard (France)

Novel therapeutic perspectives

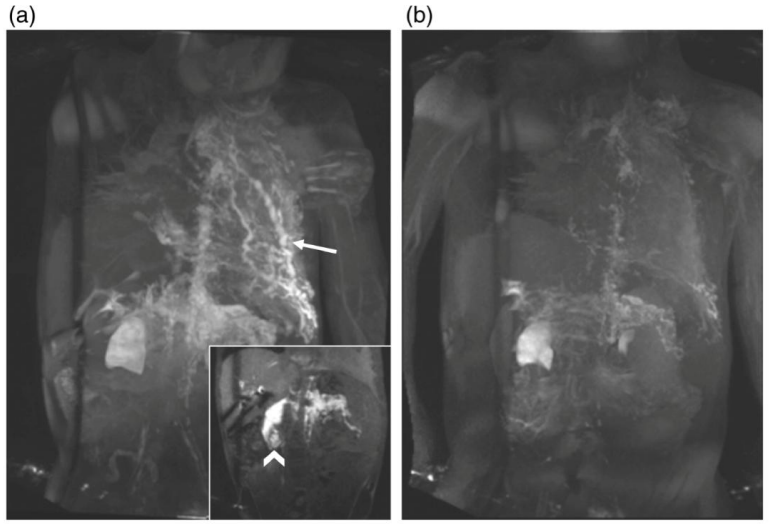


Saint-Laurent C et al. Eur J Pediatr 2024;183:1011–9.

MEK inhibitors (trametinib)

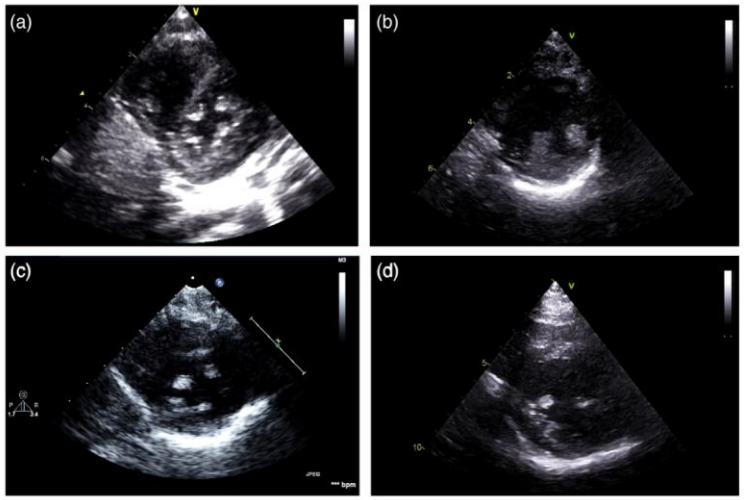
Patients with NS

Effect on lymphovascular anomalies[1]

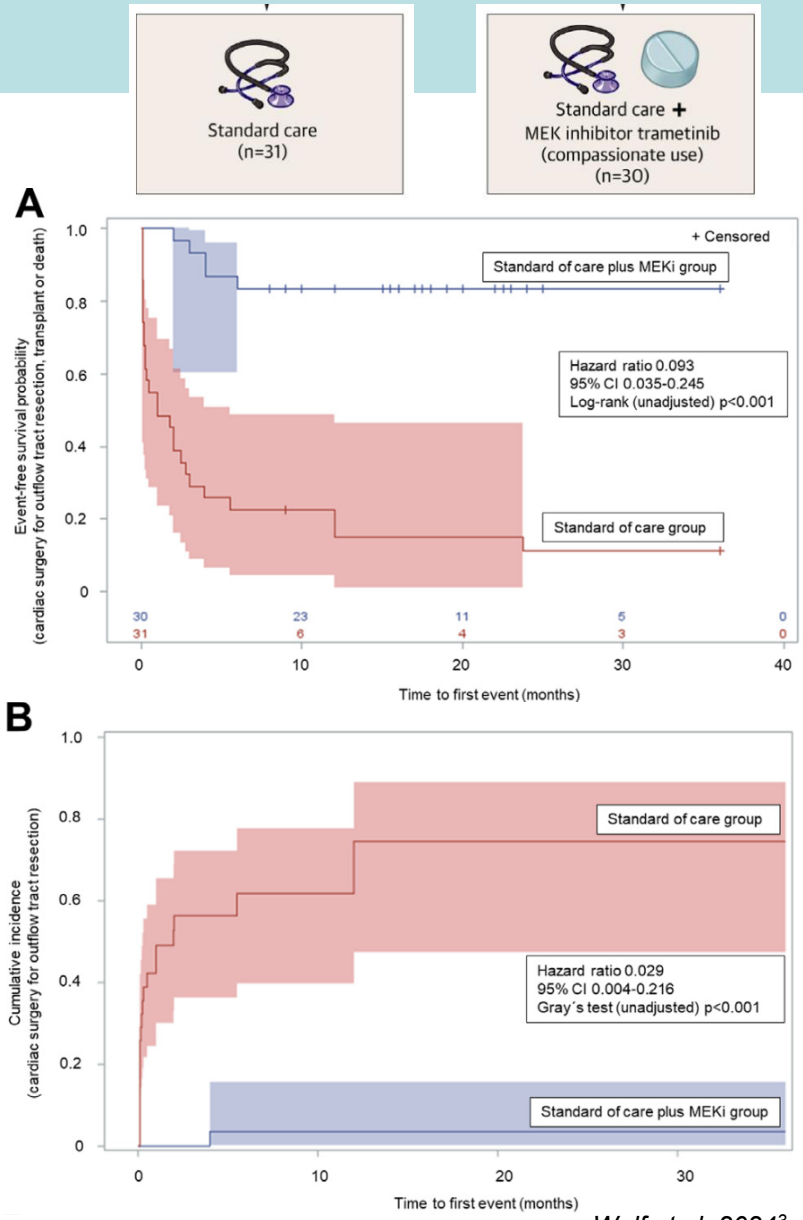


Dori et al. 2020[1]

Effect on hypertrophic cardiomyopathy[2,3]



Gelb et al. 2022[2]



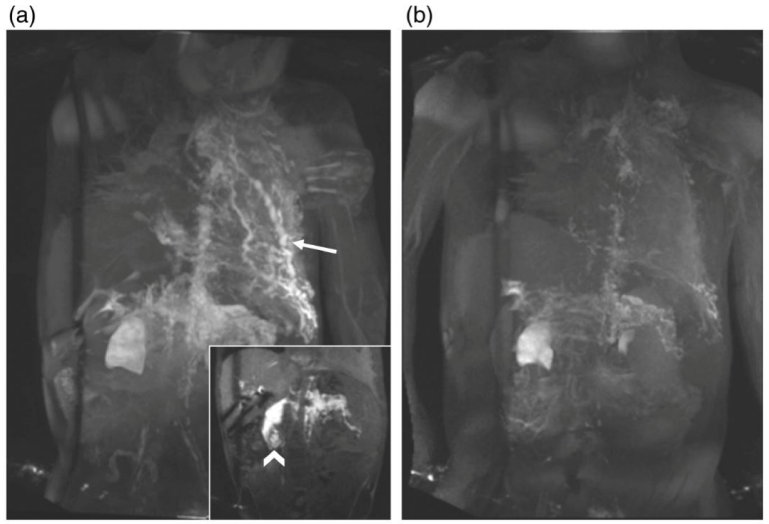
Wolf et al. 2024[3]

1. Dori Y et al. Pediatrics 2020;146:e20200167; 2. Gelb BD et al. Am J Med Genet C Semin Med Genet 2022;190:541–60; 3. Wolf CM et al. JACC Basic Transl Sci 2025;10:152–66.

MEK inhibitors (trametinib)

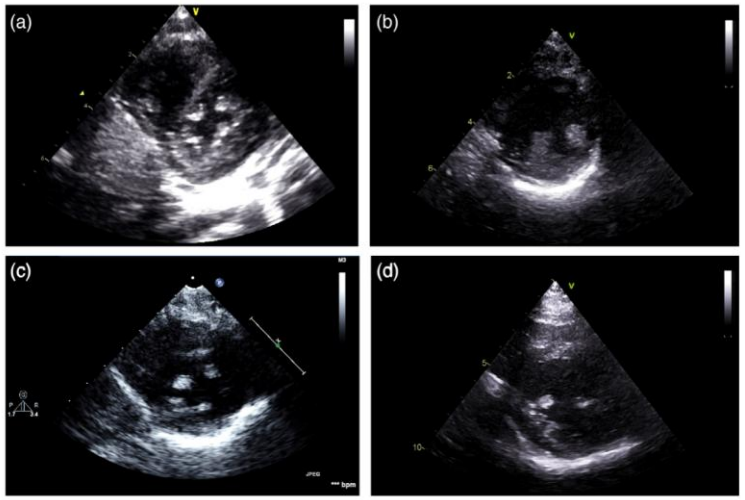
Patients with NS

Effect on lymphovascular anomalies[1]



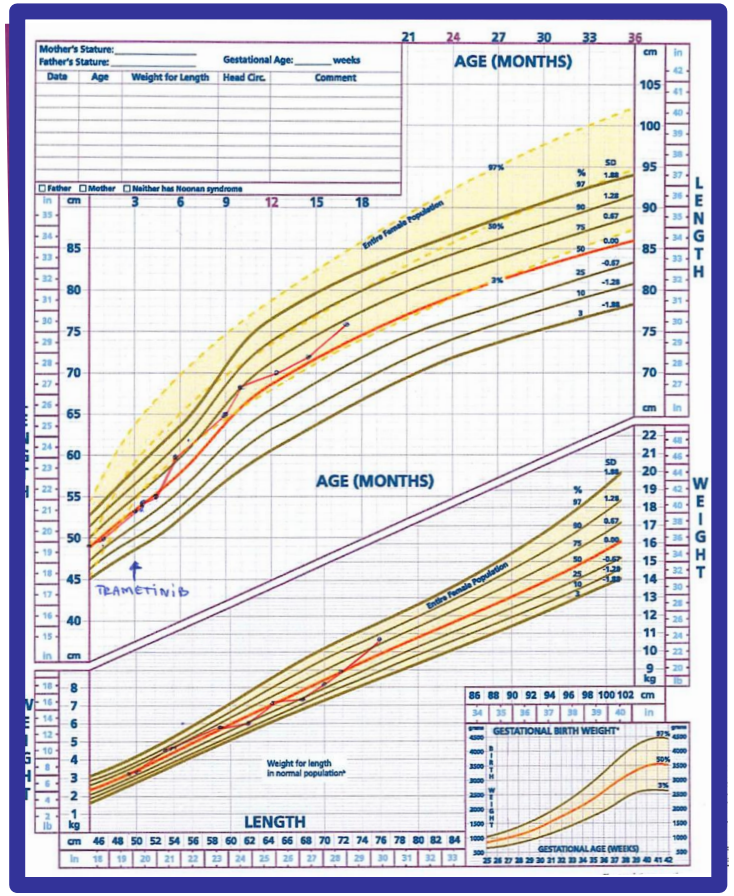
Dori et al. 2020[1]

Effect on hypertrophic cardiomyopathy[2,3]



Gelb et al. 2022[2]

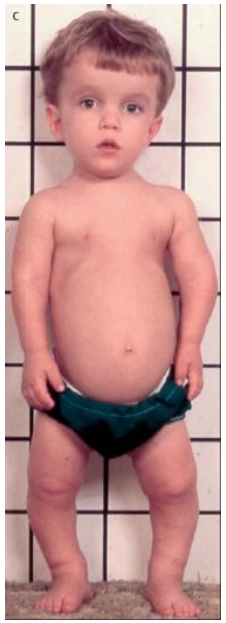
Effect on growth

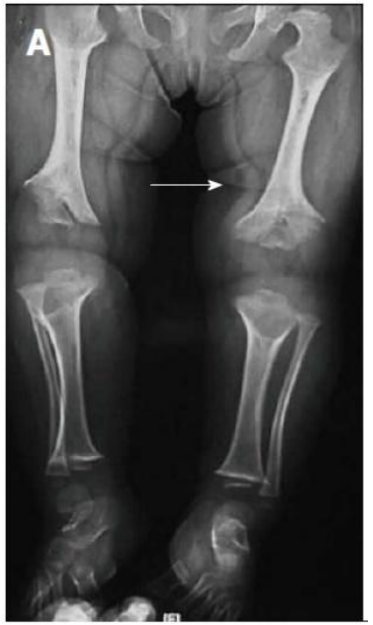


Growth chart image courtesy of Dr MA Delrue.

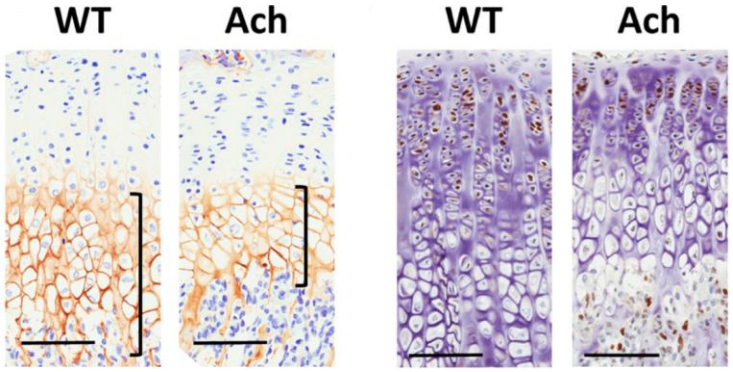
1. Dori Y et al. Pediatrics 2020;146:e20200167; 2. Gelb BD et al. Am J Med Genet C Semin Med Genet 2022;190:541–60; 3. Wolf CM et al. JACC Basic Transl Sci 2025;10:152–66.

CNP analogues and achondroplasia

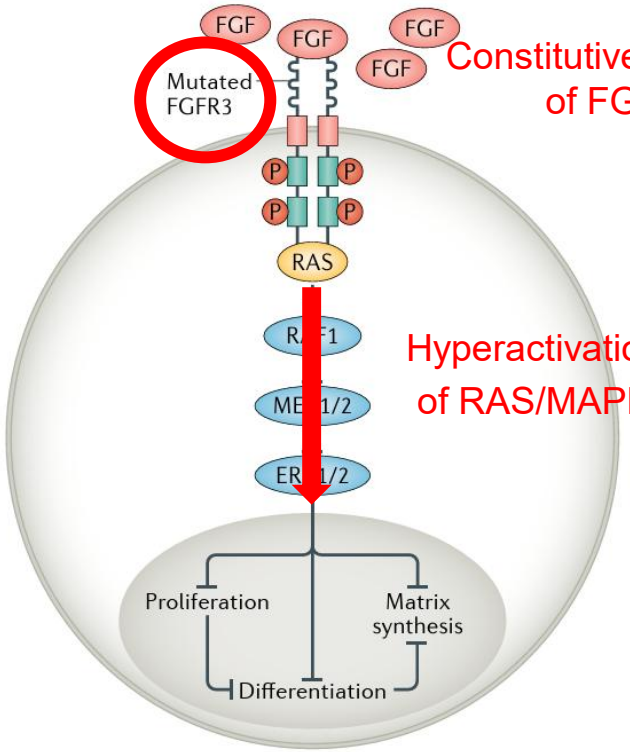




Horton et al. 2007[1]



Shazeeb et al. 2018[2]



Constitutive activation of FGFR3

Hyperactivation of RAS/MAPK

Abnormal endochondral ossification

Savarirayan et al. 2022[3]

Tyrosine kinase inhibitors

Infigratinib (QED therapeutics)
Orally once daily

CNP analogues

Vosoritide (Biomarin)
Subcutaneous once daily

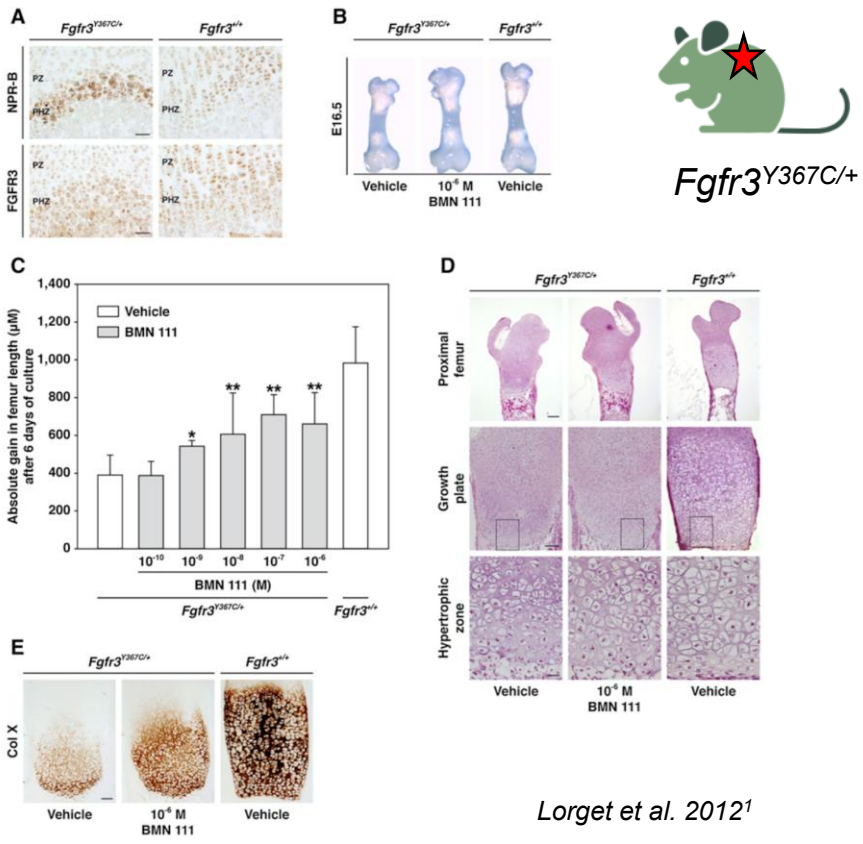
TransconCNP (Ascendis Pharma)
Subcutaneous once daily

1. Horton WA et al. Lancet 2007;370:162–72; 2. Shazeeb MS et al. Sci Rep 2018;8:469; 3. Savarirayan R et al. Nat Rev Endocrinol 2022;18:173–89.

CNP analogues and achondroplasia

Evaluation of the Therapeutic Potential of a CNP Analog in a *Fgfr3* Mouse Model Recapitulating Achondroplasia

Florence Lorget,[1] Nabil Kaci,[2] Jeff Peng,[1] Catherine Benoist-Lasselin,[2] Emilie Mugniery,[2] Todd Oppeneer,[1] Dan J. Wendt,[1] Sean M. Bell,[1] Sherry Bullens,[1] Stuart Bunting,[1] Laurie S. Tsuruda,[1] Charles A. O'Neill,[1] Federico Di Rocco,[2] Arnold Munnich,[2] and Laurence Legeai-Mallet[2,*]



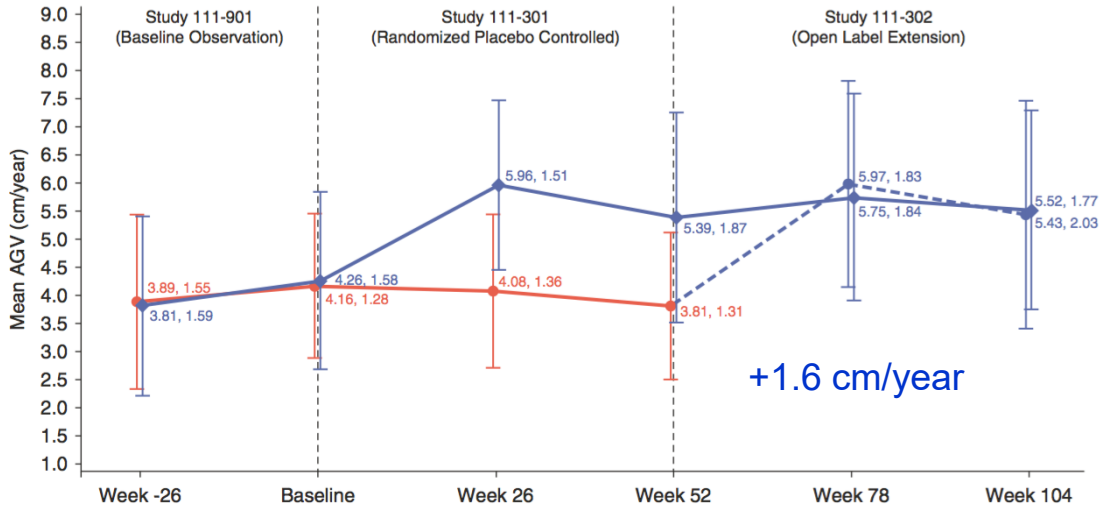
Fgfr3$^{Y367C/+}$

Lorget et al. 2012[1]

BRIEF COMMUNICATION

Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study

Ravi Savarirayan[1✉], Louise Tofts[2], Melita Irving[3], William R. Wilcox[4], Carlos A. Bacino[5], Julie Hoover-Fong[6], Rosendo Ullot Font[7], Paul Harmatz[8], Frank Rutsch[9], Michael B. Bober[10], Lynda E. Polgreen[11], Ignacio Ginebreda[12], Klaus Mohnike[13], Joel Charrow[14], Daniel Hoernschemeyer[15], Keiichi Ozono[16], Yasemin Alanay[17], Paul Arundel[18], Yumiko Kotani[19], Natsuo Yasui[19], Klane K. White[20], Howard M. Saal[21], Antonio Leiva-Gea[22], Felipe Luna-González[22], Hiroshi Mochizuki[23], Donald Basel[24], Dania M. Porco[25], Kala Jayaram[25], Elena Fisheleva[26], Alice Huntsman-Labed[26] and Jonathan R. S. Day[26]



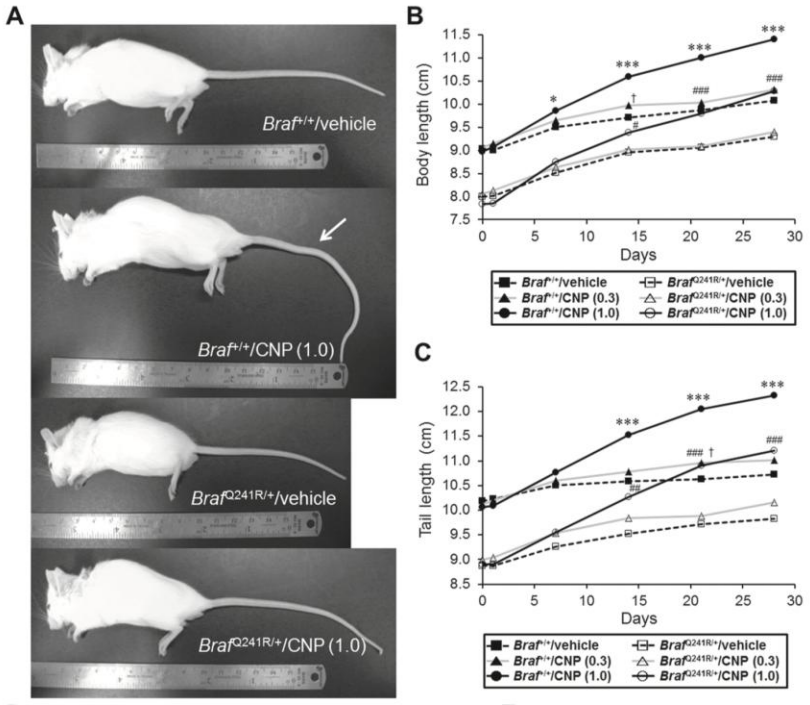
Savarirayan et al. 2021[2]

1. Lorget F et al. Am J Hum Genet 2012;91:1108–14; 2. Savarirayan R et al. Genet Med 2021;23:2443–7.

CNP analogues and RASopathies

Braf $^{Q241R/+}$

Improvement of growth retardation
in a CFC mouse model



Inoue et al. 2019[1]

Active, not recruiting

Vosoritide for Selected Genetic Causes of Short Stature [2]

ClinicalTrials.gov ID NCT04219007

Sponsor Andrew Dauber

Information provided by Andrew Dauber, Children's National Research Institute (Responsible Party)

Last Update Posted 2024-02-06

Recruiting

A Phase 2 Basket Study of Vosoritide in Children With Turner Syndrome, SHOX Deficiency and Noonan Syndrome With an Inadequate Response to Human Growth Hormone [3]

ClinicalTrials.gov ID NCT06668805

Sponsor BioMarin Pharmaceutical

Information provided by BioMarin Pharmaceutical (Responsible Party)

Last Update Posted 2025-08-06

1. Inoue SI et al. Hum Mol Genet 2019;28:74–83; 2. ClinicalTrials.gov. 2024. Available at: https://clinicaltrials.gov/study/NCT04219007. Accessed October 2025;
3. ClinicalTrials.gov. 2025. Available at: https://clinicaltrials.gov/study/NCT06668805. Accessed October 2025

Take-home messages

- **NS is a common genetic disorder** that is now well described in childhood

- NS and related disorders are caused by **mutations in the RAS/MAPK signalling pathway**
  - ➢ The hyperactivation of this pathway is responsible for the different defects

- **Genotype–phenotype correlations** have been established

- **To date, only symptomatic treatments are available** (rhGH for short stature)
  - – Improves growth velocity and height SDS and increases IGF-1 levels in the medium term
  - – Some issues have to be resolved (adult height, patients with HCM, genotype–phenotype correlations…)

- **RAS/MAPK inhibitors or modulators** (i.e. MEK inhibitors, CNP analogues) are currently being assessed

Hôpital des Enfants

CHU TOULOUSE

UNIVERSITÉ TOULOUSE III PAUL SABATIER FACULTÉ DE SANTÉ

CRESCENDO
Centre de Référence des Maladies Endocriniennes Rares de la Croissance et du Développement
https://crescendo.aphp.fr

FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES

Instituts thématiques

Inserm
Institut national de la santé et de la recherche médicale

Endocrine, Bone Diseases and Genetics Unit, Children's Hospital, Toulouse University Hospital

Isabelle Oliver
Audrey Cartault
Béatrice Jouret
Gwenaelle Diene
Alice Clerc
Charlotte Garczynski
Valérie Porquet Bordes
Shirley Vera-Marquez

Maithé Tauber
Jean Pierre Salles

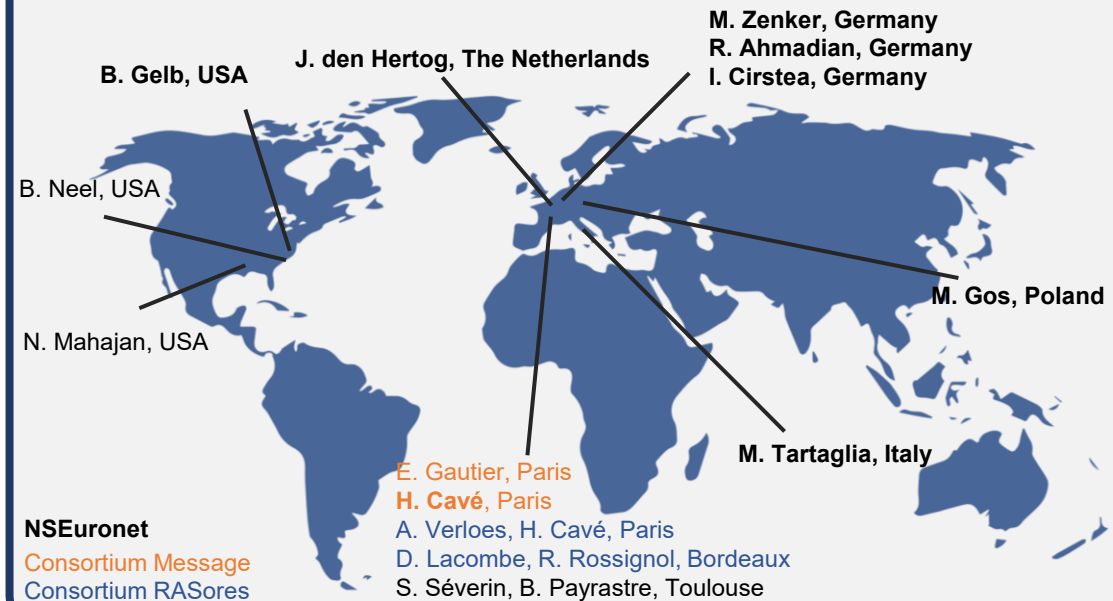
INSERM UMR 1301
Metabolink team
RESTORE Institute

Armelle Yart

Céline Saint-Laurent
Laurène Mazeyrie

Speaker's own images.

Collaborations



NSEuronet
Consortium Message
Consortium RASores

E. Gautier, Paris
H. Cavé, Paris
A. Verloes, H. Cavé, Paris
D. Lacombe, R. Rossignol, Bordeaux
S. Séverin, B. Payrastre, Toulouse

Grants and supports

EUROPEAN JOINT PROGRAMME RARE DISEASES
Fondation pour la Recherche Médicale
InsermTransfert Your partner in health innovation
FONDATION Maladies Rares
anr
MINISTÈRE DE LA SANTÉ ET DE LA PRÉVENTION
EHRC-N Programme hospitalier de recherche clinique national
La Région Occitanie Pyrénées · Méditerranée
UNIVERSITÉ TOULOUSE III PAUL SABATIER
ASSOCIATION NOONAN

Topic 3 - Puberty in RASopathies

Federica Tamburrino , MD, PhD, Rare Disease Unit, Department of Pediatrics, IRCCS Policlinico di Sant'Orsola, Bologna, Italy

PUBERTY

Puberty is a process that marks the transition from childhood to adulthood, and influences the development of secondary sexual characteristics, reproductive organs, growth velocity and final height (FH), and self-esteem

OUTLINE

- The challenge of puberty in RASopathies
- Noonan syndrome as a model
- Extending to other conditions
- What we know about the mechanisms
- What clinicians should do
- What still needs to be learned
- Take home messages

1. The Challenge of Puberty in RASopathies

What is known from the literature regarding puberty in RASopathies?

- Delayed Puberty is frequent
- Pubertal Onset is usually spontaneous
- Sex Differences
- Impact on Final Height and Psychosocial well-being
- Hormonal Alterations affecting fertility

European Reference Networks ITHACA

2. Noonan syndrome as a model

⏱️ 🔹 Delayed Puberty

- **Pubertal onset:** typically delayed by ~2 years (not in all patients)
- **Growth during puberty:** secondary peak growth rate lower than general population (GP)
- Multiple cases of **delayed puberty** described **and primary amenorrhea** reported in some cases
- **Puberty progression:** in some patients, **onset is within normal range** but **progression is slow**

Shaw AC et al, 2007
Romano AA et al, 2009
Rezende et al, 2022
Libraro et al. 2021

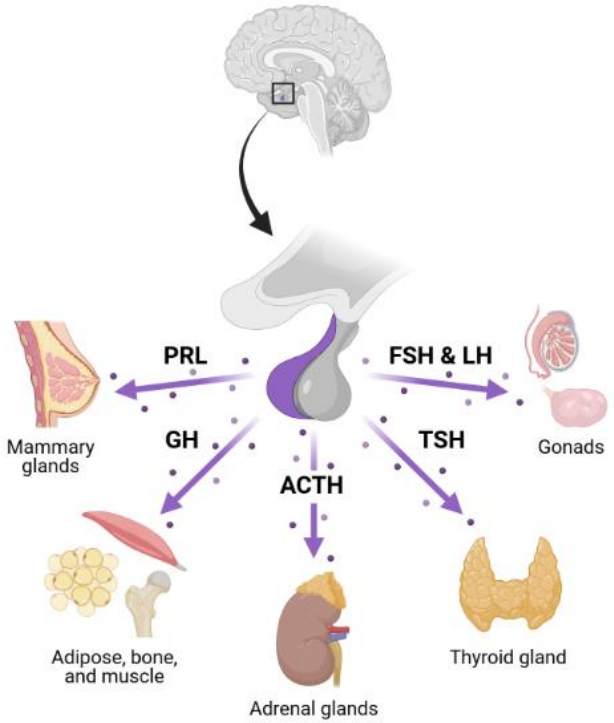
	Age at start puberty			
	Males		Females	
	Age	% delay	Age	% delay
Shaw et al., 2007	14.5 yrs (10-18)		14 yrs (10-18)	
Romano et al., 2009	> 13.5 yrs	35%	> 13 yrs	44%
Libraro et al., 2021	12.1±2.3 yrs	10%	12.1±1.3 yrs	45%
Rezende et al., 2022	12.5±1.7 yrs	27.9%	11.9±1.9 yrs	49.1%
Patti et al., 2024	12.3 yrs±2.7 DS		13.3±0.8 yrs	
Tamburrino et al., 2025	11.96±0.17 yrs	2.6%	12.92±0.25 yrs	23%

🔔🔹 Pubertal Onset

- Despite the delay**, puberty begins spontaneously** in most NS patients, indicating normal hypothalamic-pituitary function
- Consider:
  - mild alteration in GnRH pulsatility
  - partial pituitary resistance to GnRH

↓

delay in HPG axis maturation



Sex differences

Females

- **Puberty onset:** more often delayed compared to males
- **Fertility:** generally preserved

Males

- **Puberty onset:** may be delayed
- **Cryptorchidism:** present in 60–77% of patients
    - Similar frequency in normal and delayed puberty groups
    - **Impact on puberty:** minimal
    - **Impact on fertility:** can impair spermatogenesis
- **Fertility:** reduced (not limited to pts with cryptorchidism); exact prevalence unknown

Rezende et al., 2022
Tamburrino et al., 2025

📈 🔹 Impact on Final Height and Psychosocial Development

- The **age of onset** and the **duration** of pubertal development significantly **influence** the **growth spurt and near adult height** in RASopathies, exacerbating the typical growth deficits associated with these conditions.

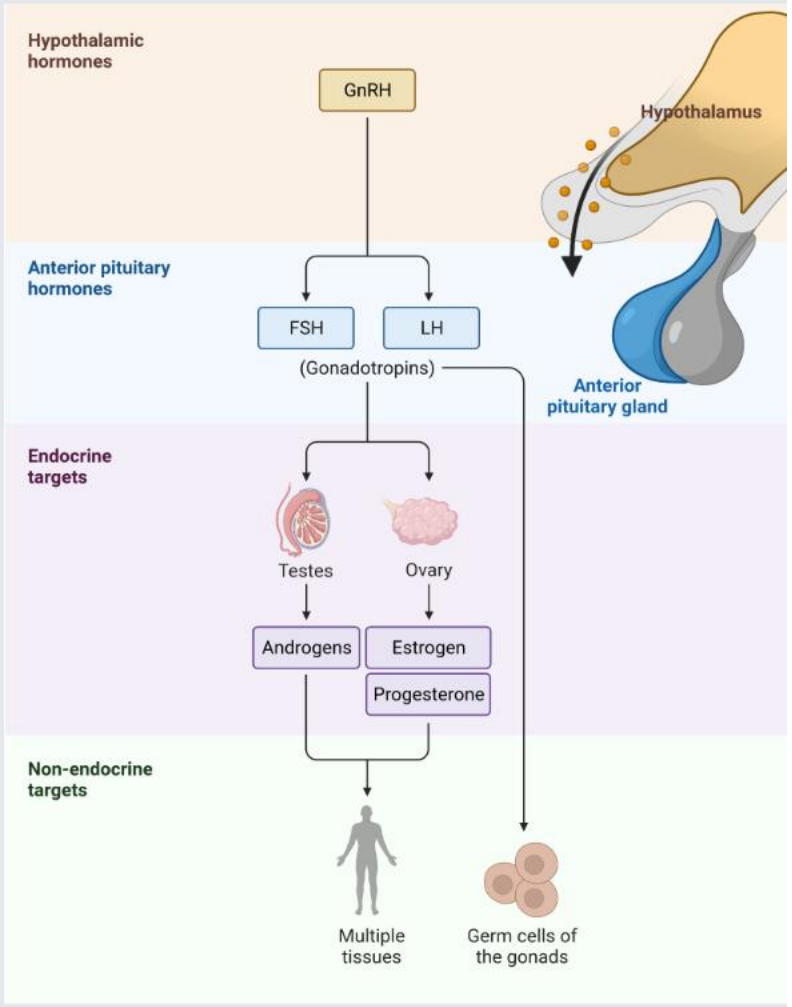
- In RASopathies, **delayed pubertal development and inadequate pubertal catch-up growth** could contribute to the observed **reduced adult height**

- **Emotional** and **social challenges** due to delayed development

Hormonal Alterations

- Altered levels of LH, FSH, and sex steroids reported in several studies

- Notably, in **males** with NS, **fertility** appears to be **reduced**, probably due to
  - the high incidence (60–77%) of cryptorchidism
  - primary alterations in the activity of Sertoli and Leydig cells



Ankarberg-Lindgren C et al 2011
Moniez S et al, 2018

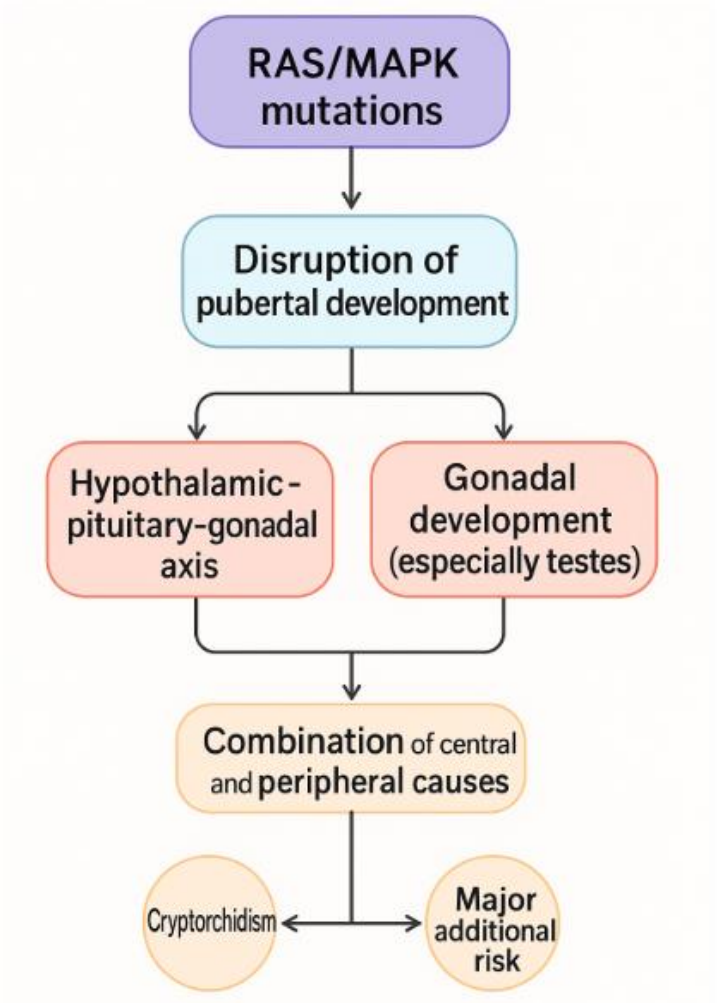
3. Extending to other conditions

Syndrome	Delayed Puberty	Precocious Puberty	Notes / Evidence
NSML	Possible / scarce data	Rare / unknown	Very limited case reports
Costello	Reported	Anecdotal	Mixed pattern, mostly delayed
CFC	Reported	Anecdotal	Possible hypogonadism, limited evidence

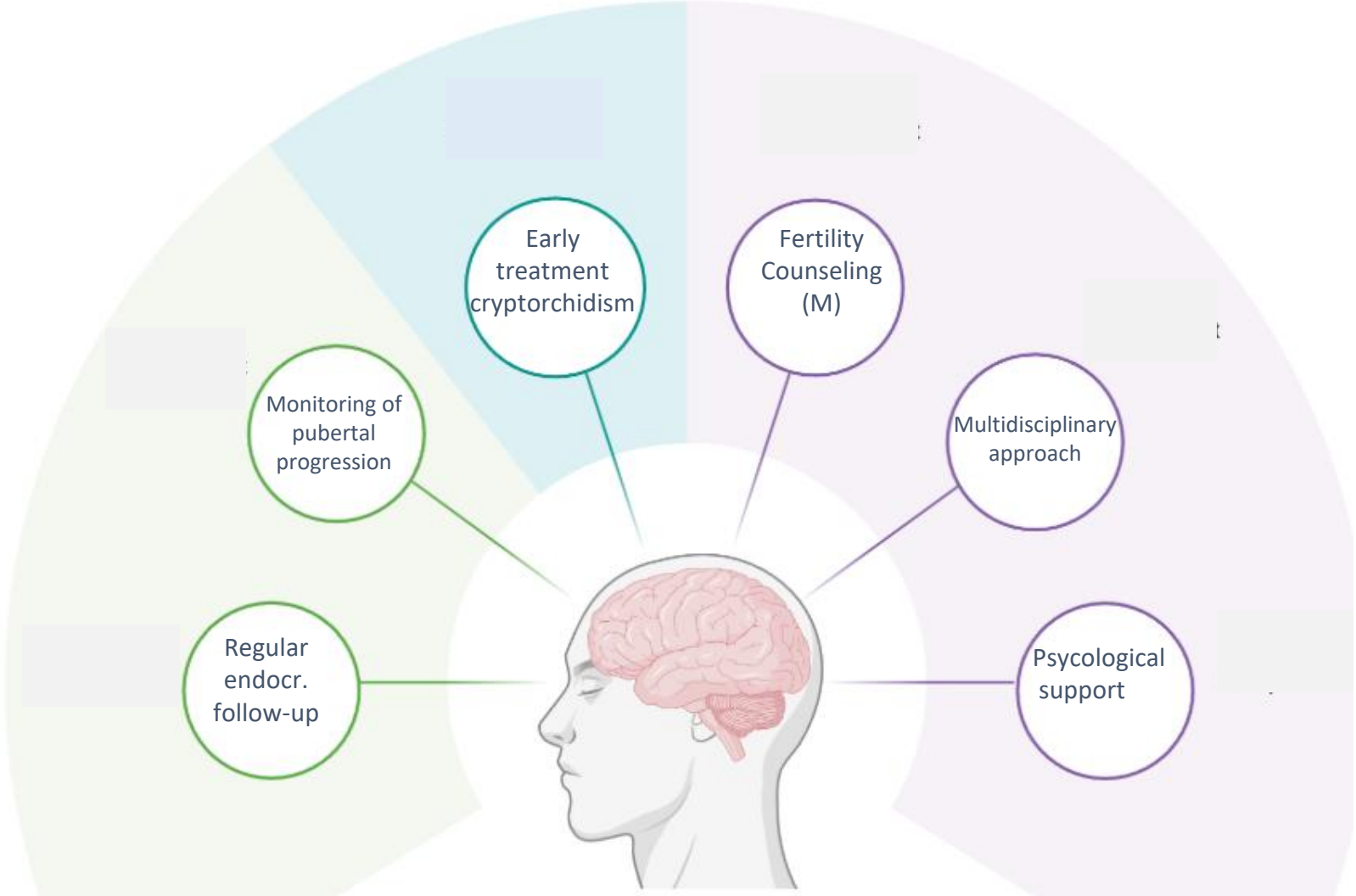
(Arnold-Chiari malformation, hyperprolactinemia, or GHD)

European Reference Networks ITHACA

4. What We Know About the Mechanisms

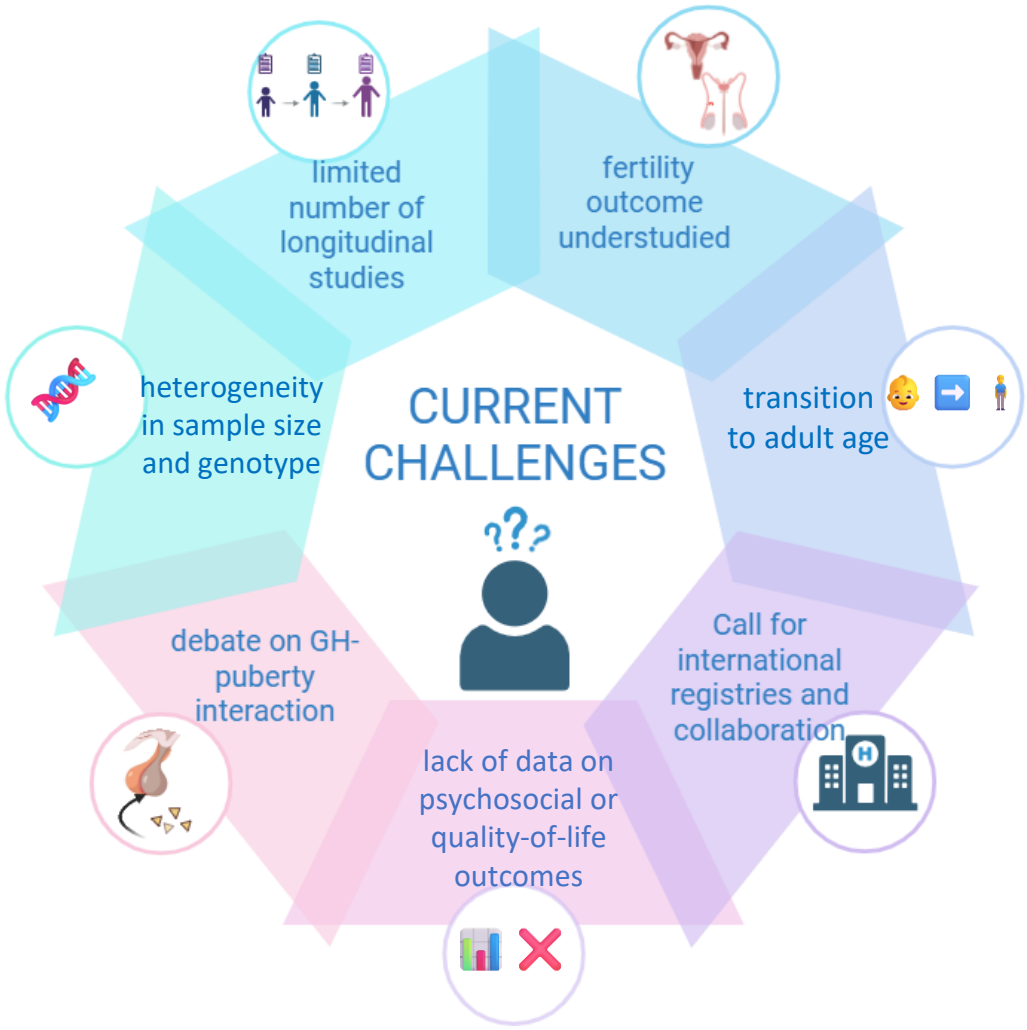


5. What Clinicians Should Do



European Reference Networks ITHACA

6. What still need to be learned



Personal data

Impact of pubertal timing on growth progression and final height in subjects affected by RASopathies

Federica Tamburrino[1*†], Laura Mazzanti[2†], Dino Gibertoni[3], Concetta Schiavariello[1], Annamaria Perri[1], Eleonora Orlandini[4], Cesare Rossi[5], Marco Tartaglia[6], Marcello Lanari[1] and Emanuela Scarano[1]

Frontiers in Endocrinology (2025)

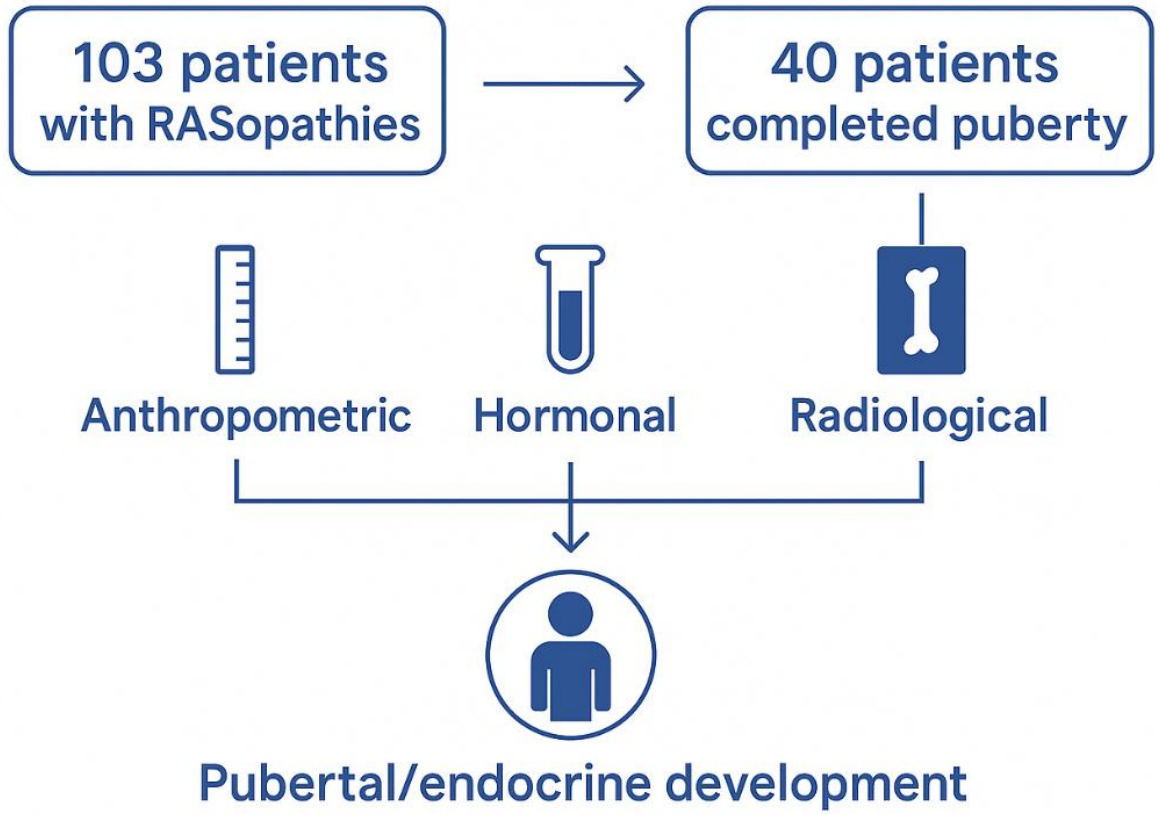


TABLE 1A Subgrouping of the studied RASopathy cohort by genotype.

	Entire cohort	
Genotype	n	%
Noonan syndrome	30	75.0
PTPN11	24	80.0
KRAS	2	6.7
RAF1	2	6.7
RIT1	1	3.3
SOS1	1	3.3
Noonan syndrome with multiple lentigines		
PTPN11	1	2.5
Cardiofaciocutaneous syndrome		
BRAF	1	2.5
Mazzanti syndrome		
SHOC2	7	17.5
Legius syndrome		
SPRED1	1	2.5
Total	40	100.0

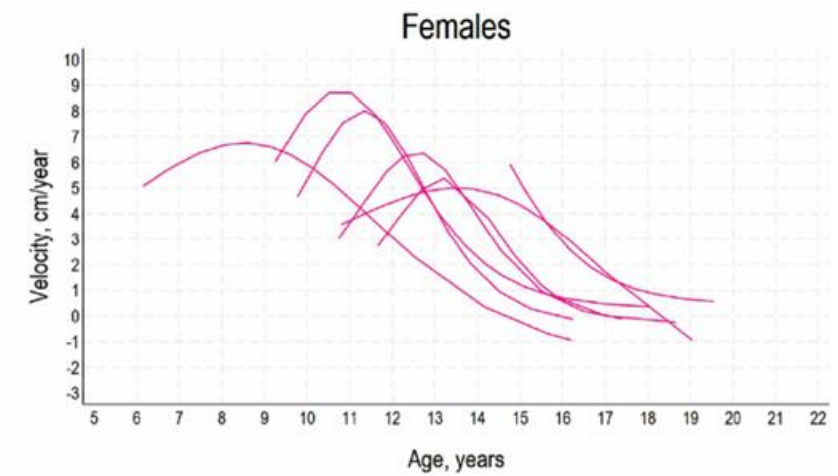
n, number of patients.

TABLE 2 Comparison of pubertal data of the study cohort with the general population (GP).

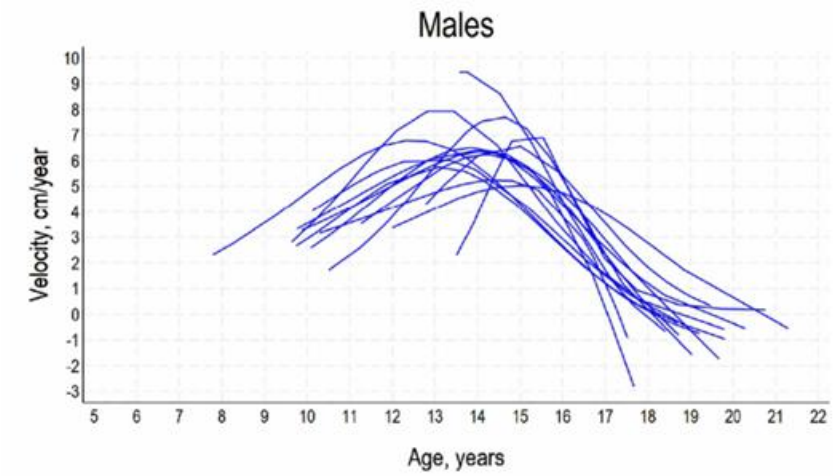
	Study cohort (mean ± SDS)	GP (mean ± SDS)	test; p-value
Age at onset of puberty (years)			
M	11.96 ± 0.17	12.05 ± 0.85	-0.5; 0.586
F	12.92 ± 0.25	10.3 ± 0.95	10.7; <0.001
Age at PHV (years)			
M	14.28 ± 0.18	13.91 ± 0.84	2.1; 0.035
F	12.86 ± 0.23	11.89 ± 0.90	4.2; <0.001
PHV (cm/years)			
M	8.30 ± 0.22	8.80 ± 1.05	-2.3; 0.021
F	5.89 ± 0.20	8.13 ± 0.78	-11.1; <0.001
Spurt gain (cm)			
M	25.98 ± 0.91	27.56 ± 3.54	-1.7; 0.084
F	13.80 ± 1.25	25.25 ± 4.14	-9.2; <0.001

Data referring to the GP are from (5).
PHV, peak of height velocity.

a. Individual height velocity curves for females according to chronological age



b. Individual height velocity curves for males according to chronological age



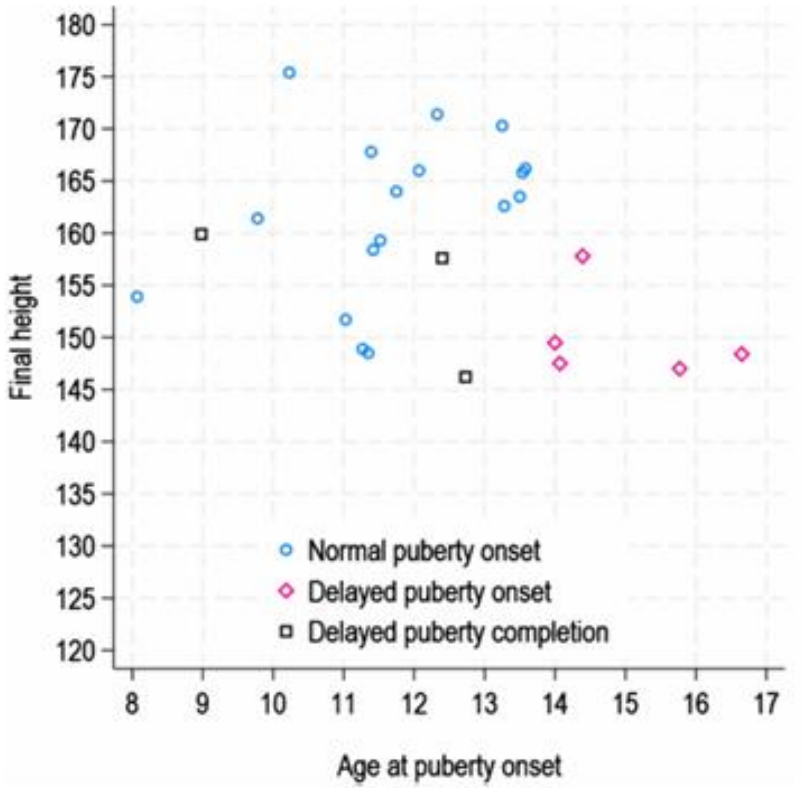
Tamburrino et al., Front Endocrinol 2025

TABLE 3 Comparison of pubertal data by genotype (*PTPN11* vs *SHOC2* patients).

PUBERTAL CLINICAL PARAMETERS	*PTPN11* (n=25) Median [IQR]	*SHOC2* (n=7) Median [IQR]	p-value
Age at puberty onset (yrs)	12.33 [11.32-13.25]	12.73 [11.42-14.07]	0.469
Height at puberty (cm)	135.55 [131.95-140.8]	133.9 [129.5-143.5]	0.686
Spurt duration (yrs)	6.64 [5.43-7.75]	5.665 [3.23-7.995]	0.764
PHV (cm)	7.86 [6.60-8.33]	6.19 [5.43-6.34]	0.070
Spurt gain (cm)	20.6 [19.6-26.2]	14.25 [3.40-29.95]	0.531
Age at menarche (yrs)	14.45 [12.28-16.40]	19.4 [14.64-19.41]	0.066
Final height (cm)	159.3 [151.7-165.8]	149.5 [148.4-158.4]	0.256

PHV, peak of height velocity.

Final Height according to pubertal timing



Tamburrino et al., Front Endocrinol 2025

TABLE 4 Comparison of clinical and pubertal features by GH-therapy in the studied RASopathy cohort.

PARAMETERS	GH-treated patients (23 pts) Median [IQR]	Untreated GH patients (5 pts) Median [IQR]	p-value
Age at 1st evaluation (yrs)	5.26 [3.09, 9.25]	6.09 [4.85, 7.66]	0.976
Height at 1st evaluation SDS	-2.9 [-3.5, -2.1]	-1.2 [-2.0, -0.4]	0.032
Age at PHV (yrs)	14.2 [12.6, 15.4]	13.4 [12.7-13.9]	0.529
Height at PHV (cm)	145.9 [141.1-154.1]	152.2 [135.6-154.4]	0.787
Spurt duration (yrs)	6.2 [5.4, 7.3]	8.1 [3.8-9.6]	0.407
Spurt gain (cm)	21.5 [15.7, 25.4]	25.7 [16.9-33.4]	0.286
Final height (cm)	157.8 [148.5-165.8]	159.9 [154.4-164.0]	0.653
Final height SDS	-2.2 [-2.6, -1.5]	-1.7 [-2.3, -0.7]	0.286
Target height (cm)	166.5 [160.0, 171.0]	161.75 [158.0-167.5]	0.417
Pubertal timing, n (%)			0.118 ^
■ normal	15 (71.4%)	3 (60.0%)	
■ delayed onset	5 (23.8%)	0	
■ delayed completion	1 (4.8%)	2 (40.0%)	

GH, growth hormone; pts, patients; PHV, peak of height velocity, yrs, years.
Mann-Whitney test except ^ (Fisher's exact test).

Take Home Messages: Puberty and Growth in RASopathies

Delayed puberty onset
- negatively affects final height; insufficient pubertal growth spurt

Puberty generally starts spontaneously

Careful monitoring of growth and pubertal progression
- to optimize therapeutic interventions and improve final height outcomes

Research gaps remain
- need for further studies

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico
POLICLINICO DI SANT'ORSOLA

Centro Hub Regionale Malattie Rare Pediatriche
SS-UO Malattie Rare Congenito-Malformative
U.O.Pediatria-Lanari
IRCCS Azienda Ospedaliero-Universitaria Sant'Orsola
Tel 051 2143723
Email ambulatorio.malattie.rare@aosp.bo.it

E. Scarano, F. Tamburrino, C. Schiavariello, E. Orlandini
Case Manager M. Guidetti, IP C. Mazzari, S. Malaguti
Membro ERN-ITHACA, HCP F. Tamburrino, Laura Mazzanti, Emanuela Scarano
Membro ENDO-ERN
Psicologhe: M. Foresti, S.Palmeira, F. Stortoni

Founder of the Rare Disease Center
Laura Mazzanti, Professor of Alma Mater

European Reference Networks ITHACA

Topic 4 - Metabolic Profile in Patients with Noonan Syndrome

Alexander A L Jorge, Associate Professor at the University of São Paulo (USP), Head and Principal Investigator of the Genetic Endocrinology Unit at Hospital das Clínicas, University of São Paulo, São Paulo, Brazil

2025

Disclosures

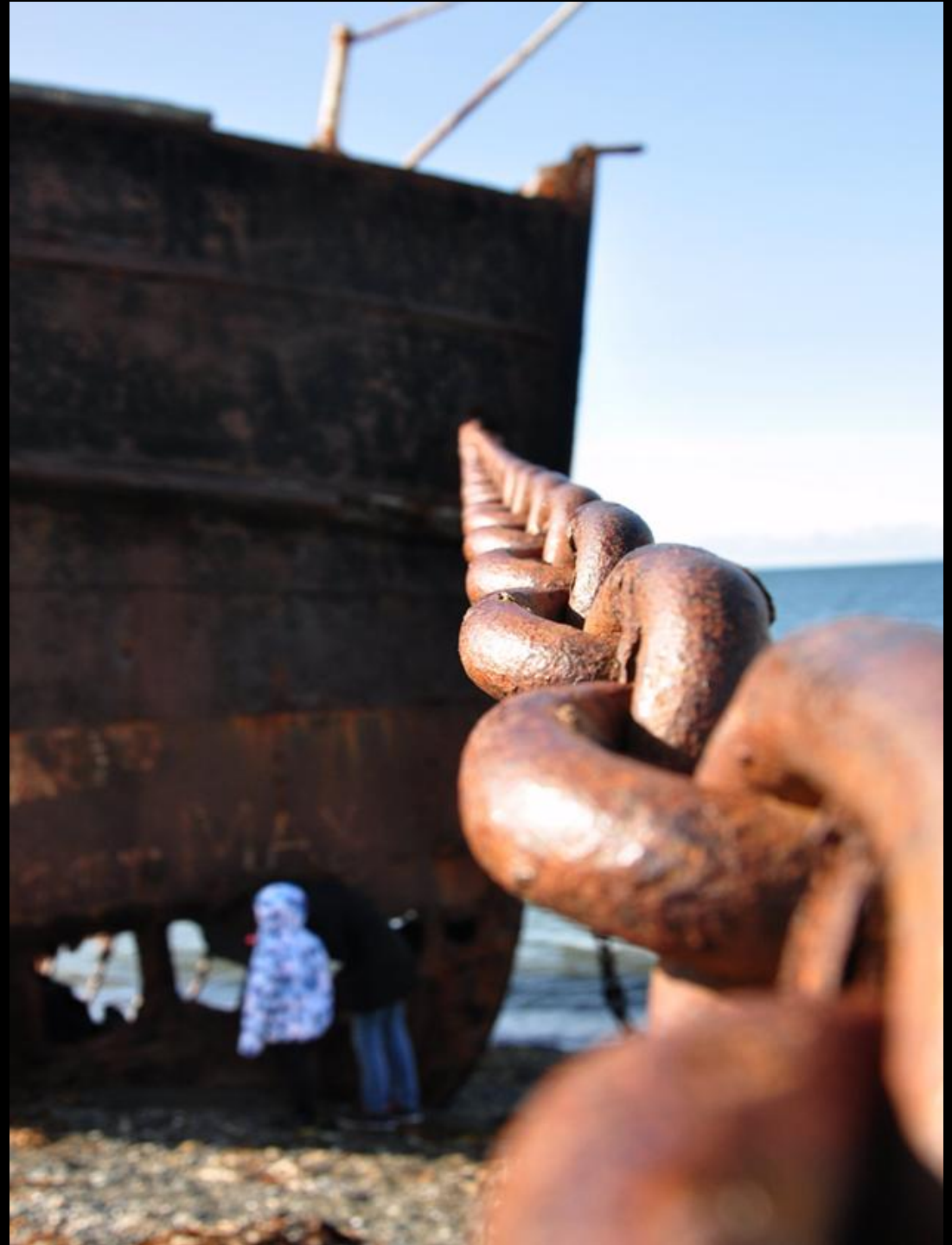
No potential conflicts of interest in relation to this presentation

In the past 12 months, received speaker fees from Pfizer, Sandoz, BioMarin and NovoNordisk

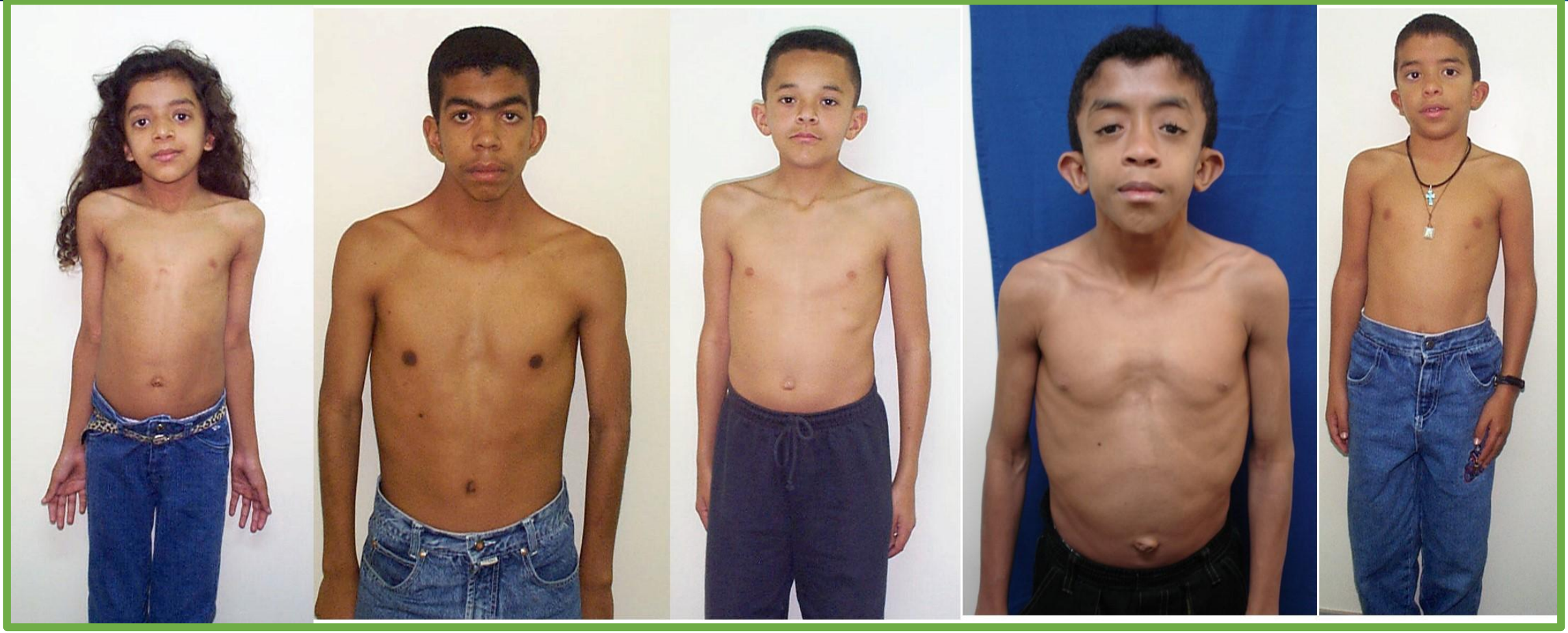
Member of advisory board and clinical trial of NovoNordisk

Independent research grant from BioMarin

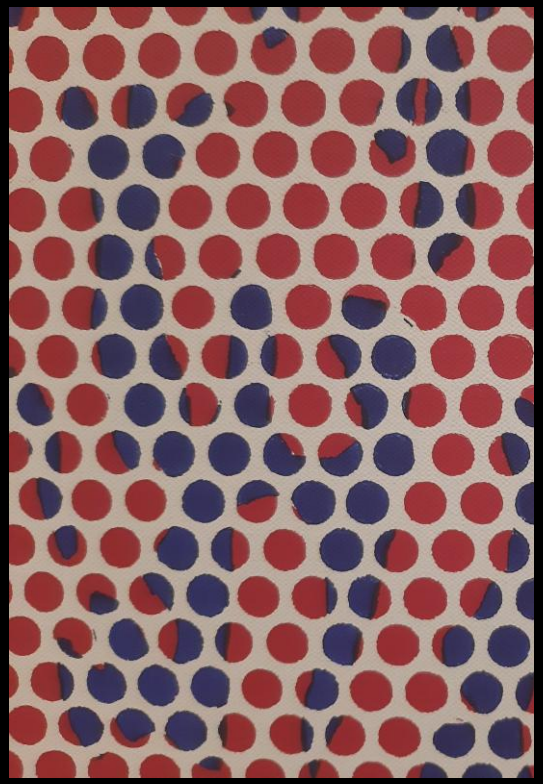
Patients or their guardians have given permission to use the photos for this lecture

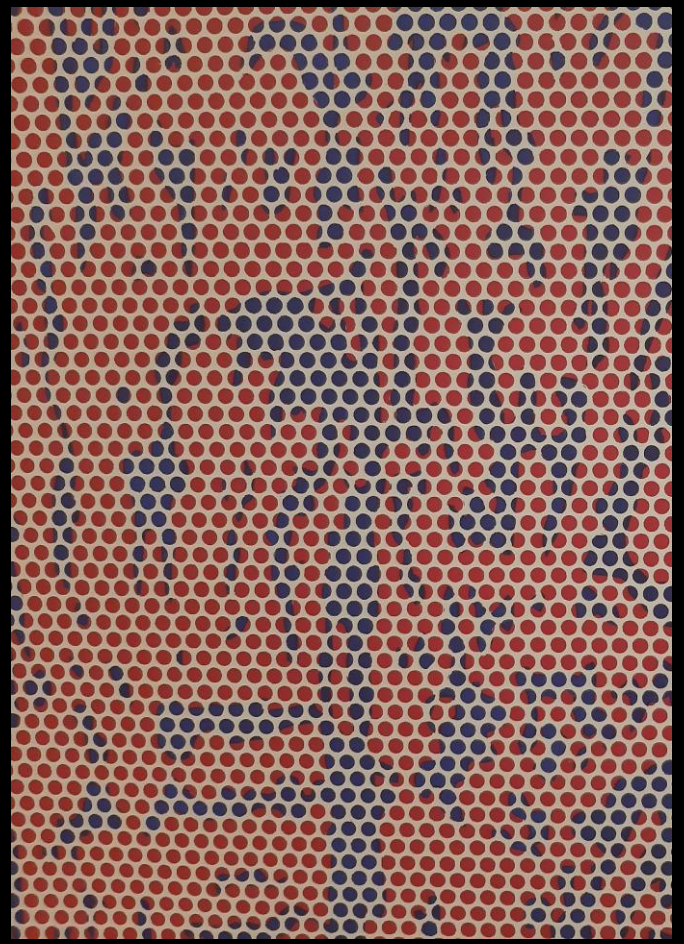


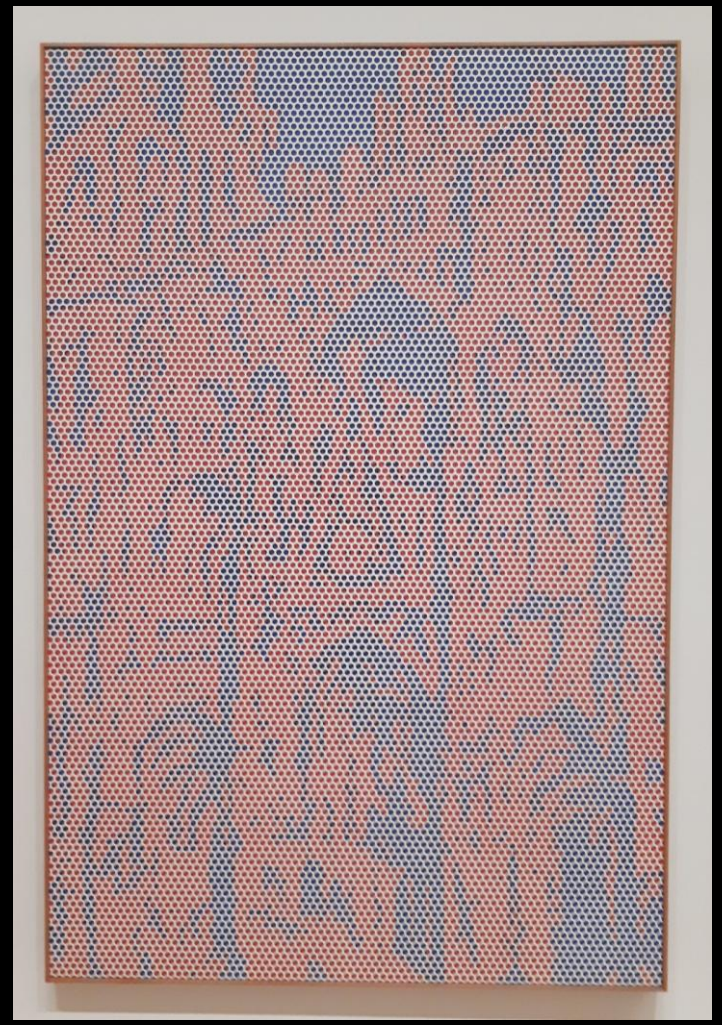
Picture from speaker's personal archive



Picture from speaker's personal archive







Picture from speaker’s personal archive

Post-natal growth in NS

Age	Height SDS
1mo – 2y	-1.9 ± 1.6
2y - 5y	-2.0 ± 1.2
5y – 10y	-2.1 ± 1.1
12y - 18y	-3.2 ± 1.3

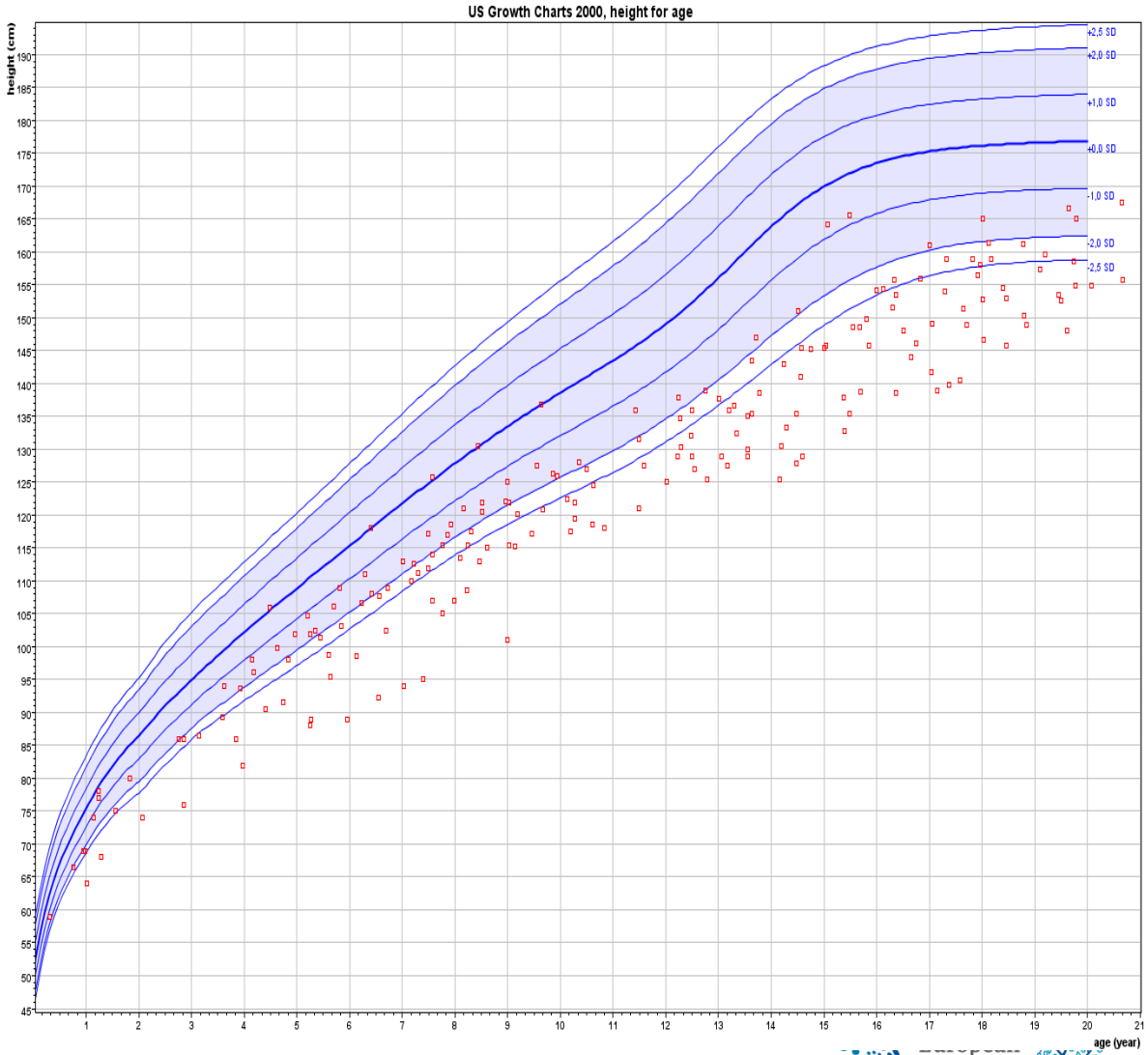
Total of 137 patients

Adult height (n = 60)

Males = 157.2 ± 7.5 cm

Females = 150.6 ± 7.7 cm

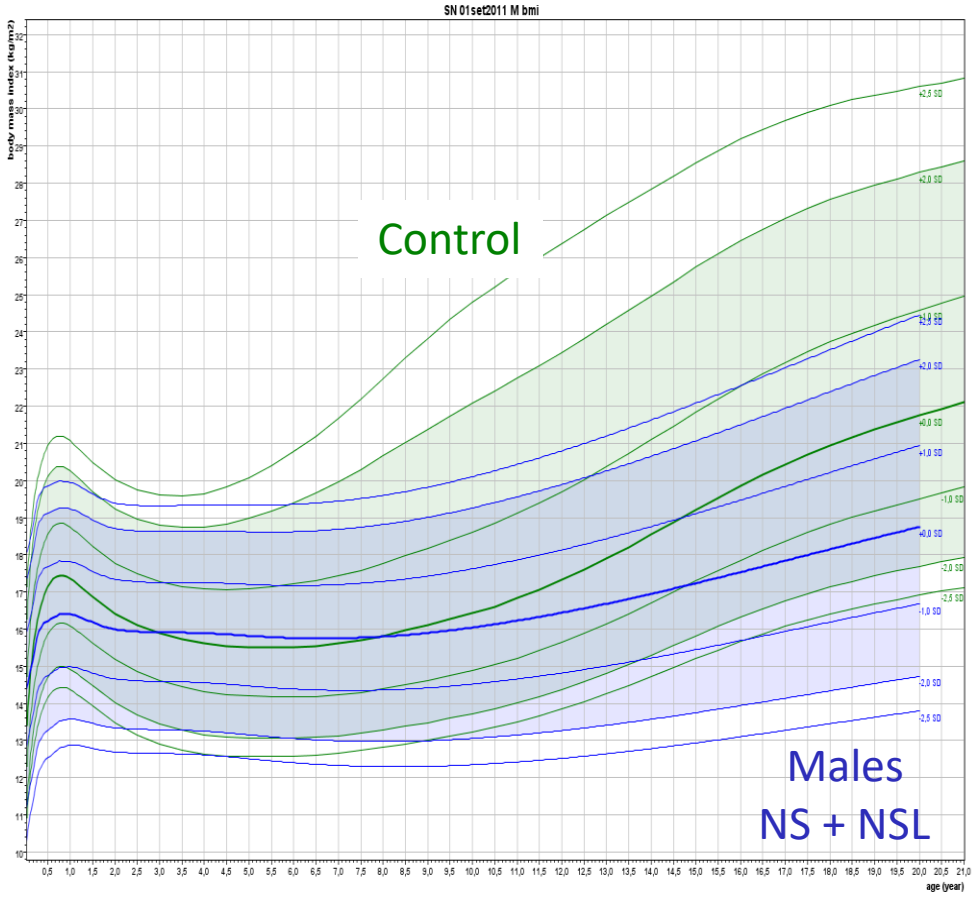
Our cohort was shorter in stature than the average normal Brazilian population, corresponding to a height SDS of **-2.6** and **-2.0** for males and females, respectively.

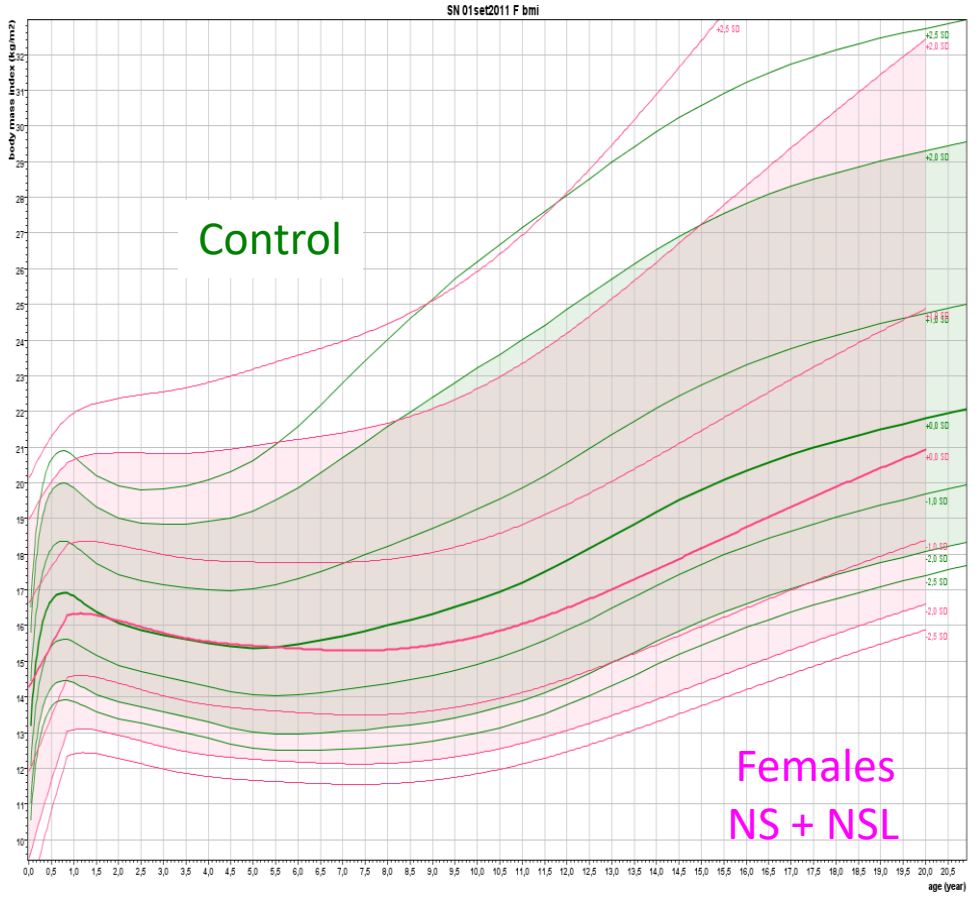


Malaquias *et al*. Am J Med Genet A. **2012** PMID: **22887833**

Post-natal growth curves in NS

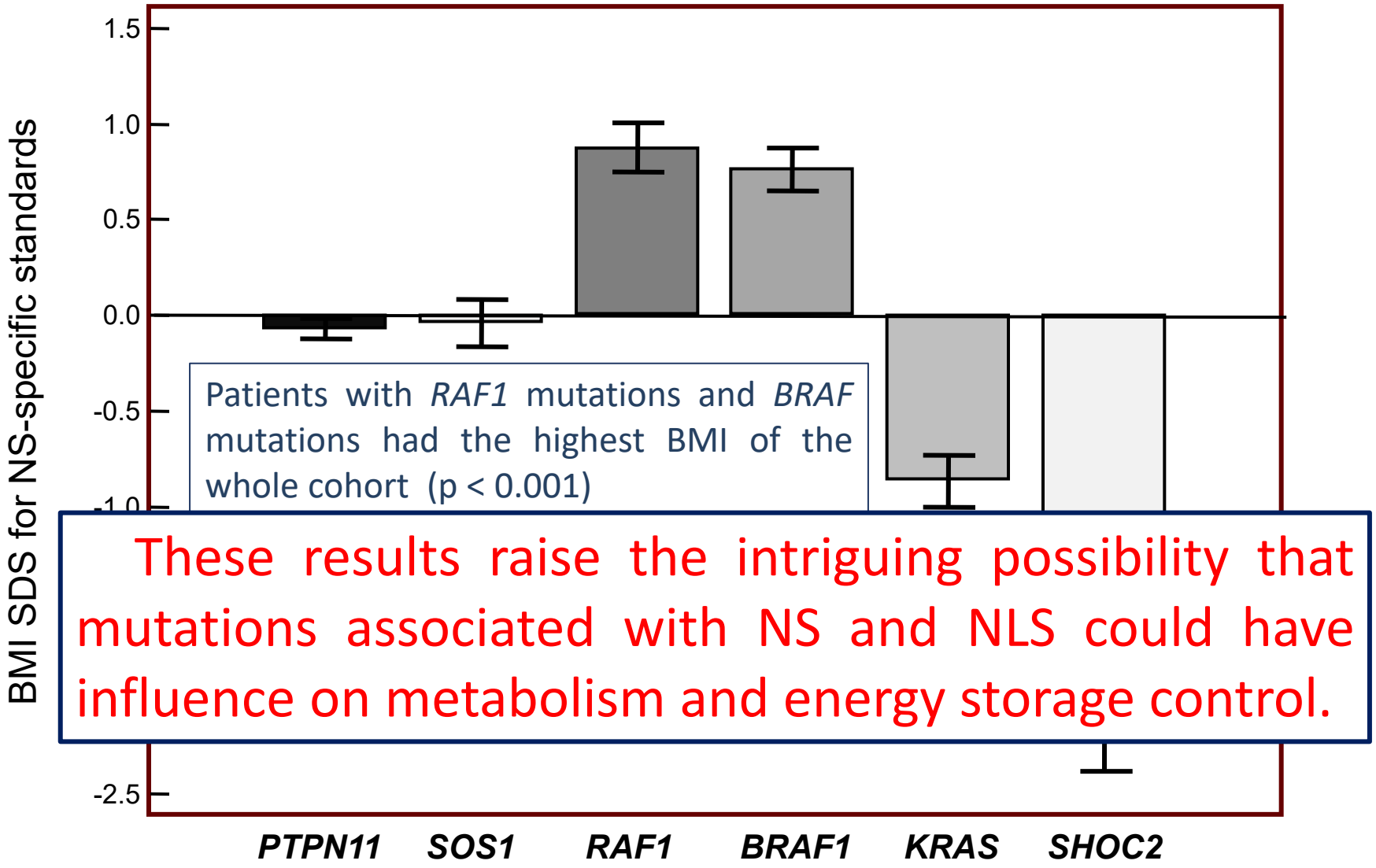
The mean BMI observed values correspond to -1.2 and -0.7 SDS for Brazilian healthy men and women, respectively





Malaquias *et al*. Am J Med Genet A. **2012** PMID: **22887833**

NS genotype influence on BMI



These results raise the intriguing possibility that mutations associated with NS and NLS could have influence on metabolism and energy storage control.

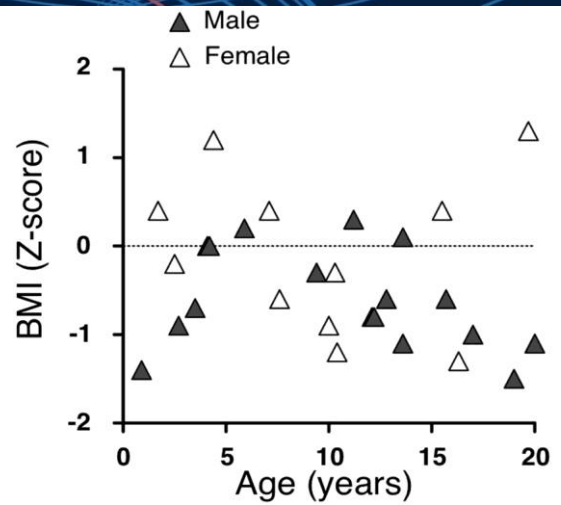
Malaquias *et al*. Am J Med Genet A. **2012** PMID: **22887833**

European Reference Networks ITHACA

Low BMI as NS-phenotype

One study evaluated 45 adults with NS and observed a lower incidence of overweight or obesity than observed in the general population (mainly among men).

Binder *et al.* J Pediatr **2012**; 161(3): 501-505

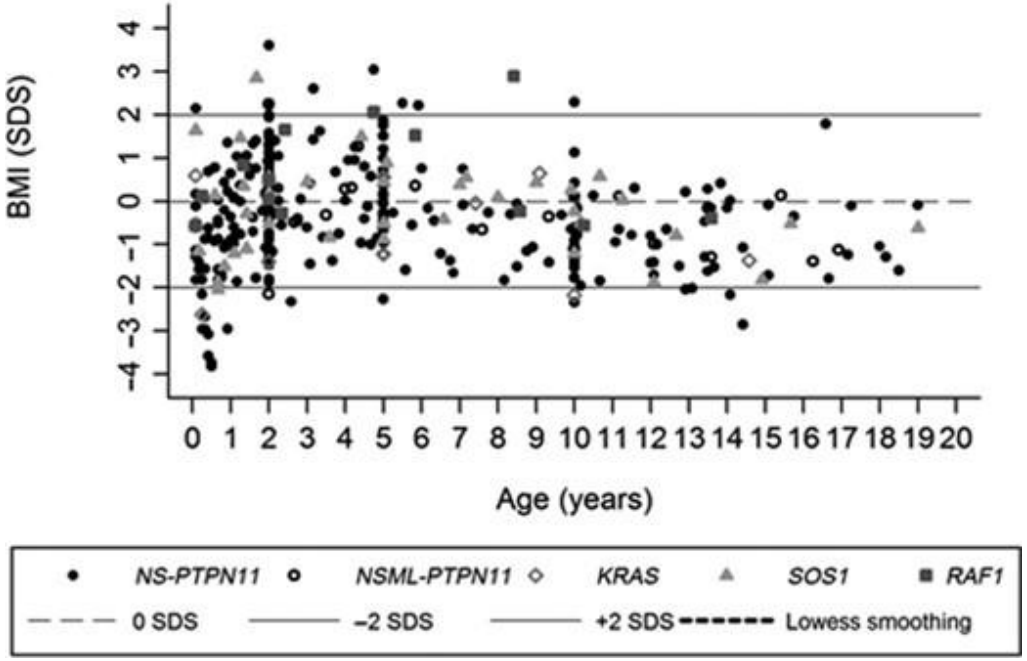


420 patients (176 females and 244 males)

- NS-PTPN11 n= 244
- NSML-PTPN11 n = 25

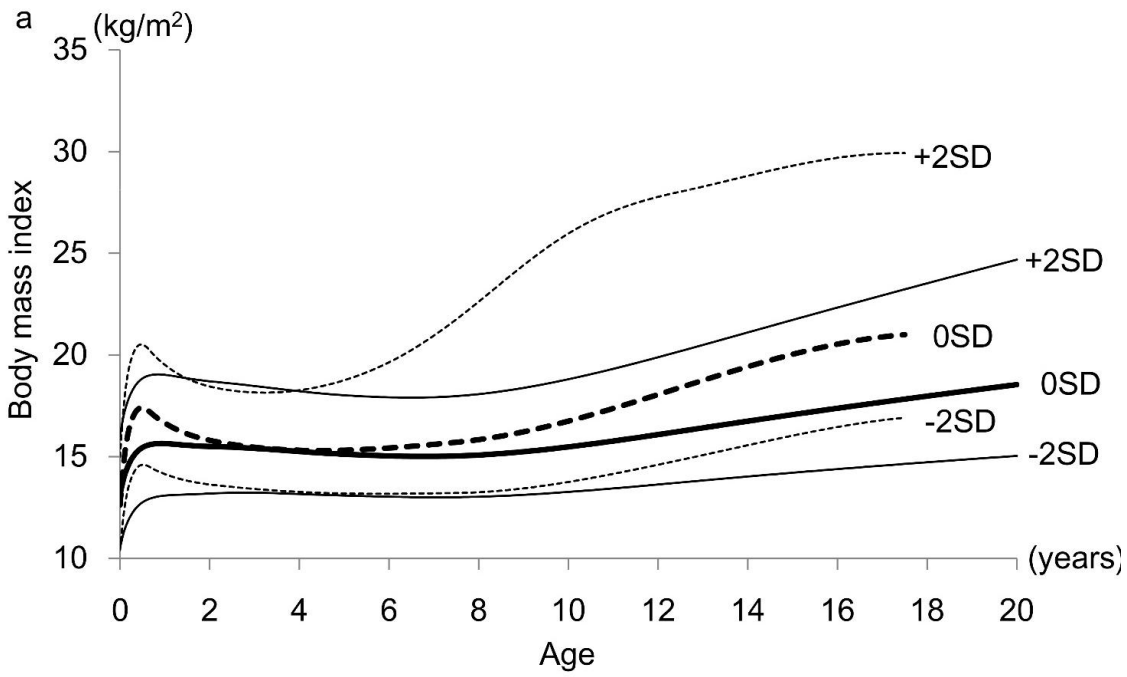
Patients with NS had lower BMI at 10 years.
No difference between genotypes was demonstrated

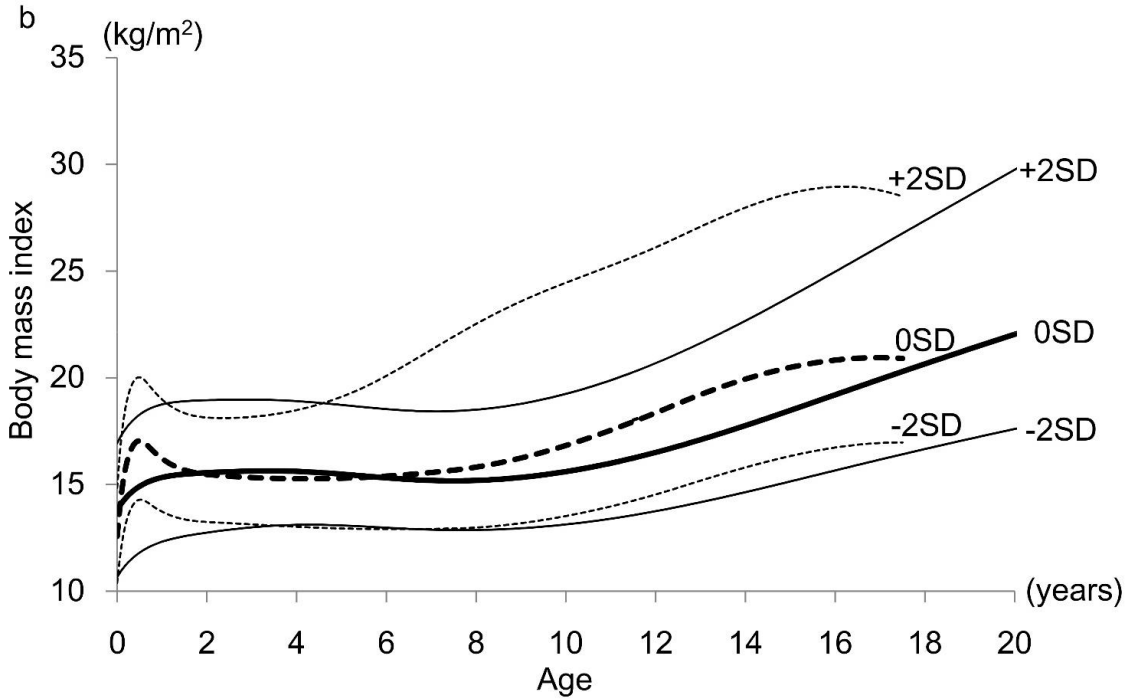
Cessans et al. Eur J Endocrinol. **2016**; PMID: 26903553



New BMI curves in patients with NS

308 subjects (males: 159 and females: 149)





Isojima et al. Pediatr Res. **2016**. PMID: 26650342

Additional BMI curves in patients with NS

190 patients

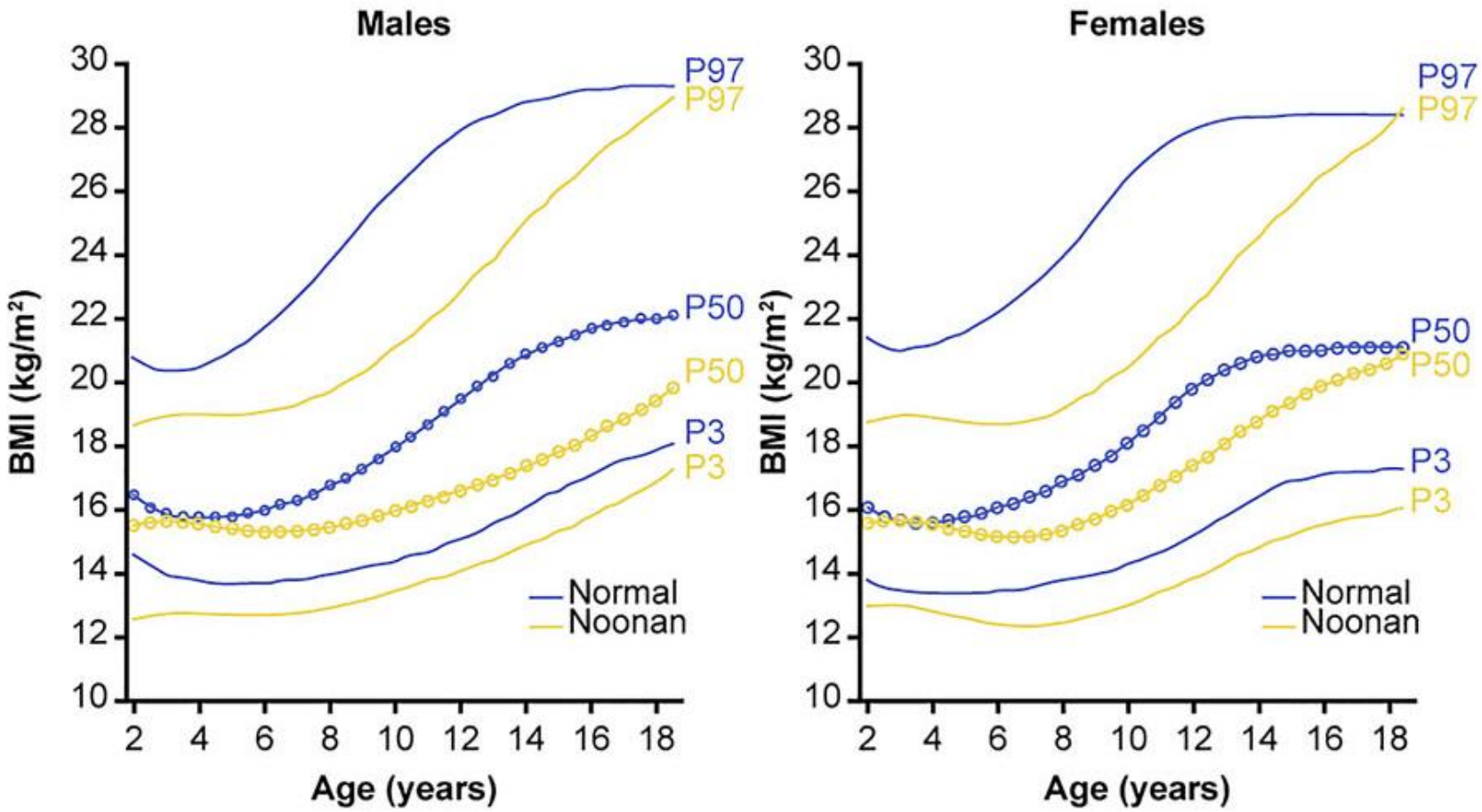
106 males : 84 females

66% *PTPN11*

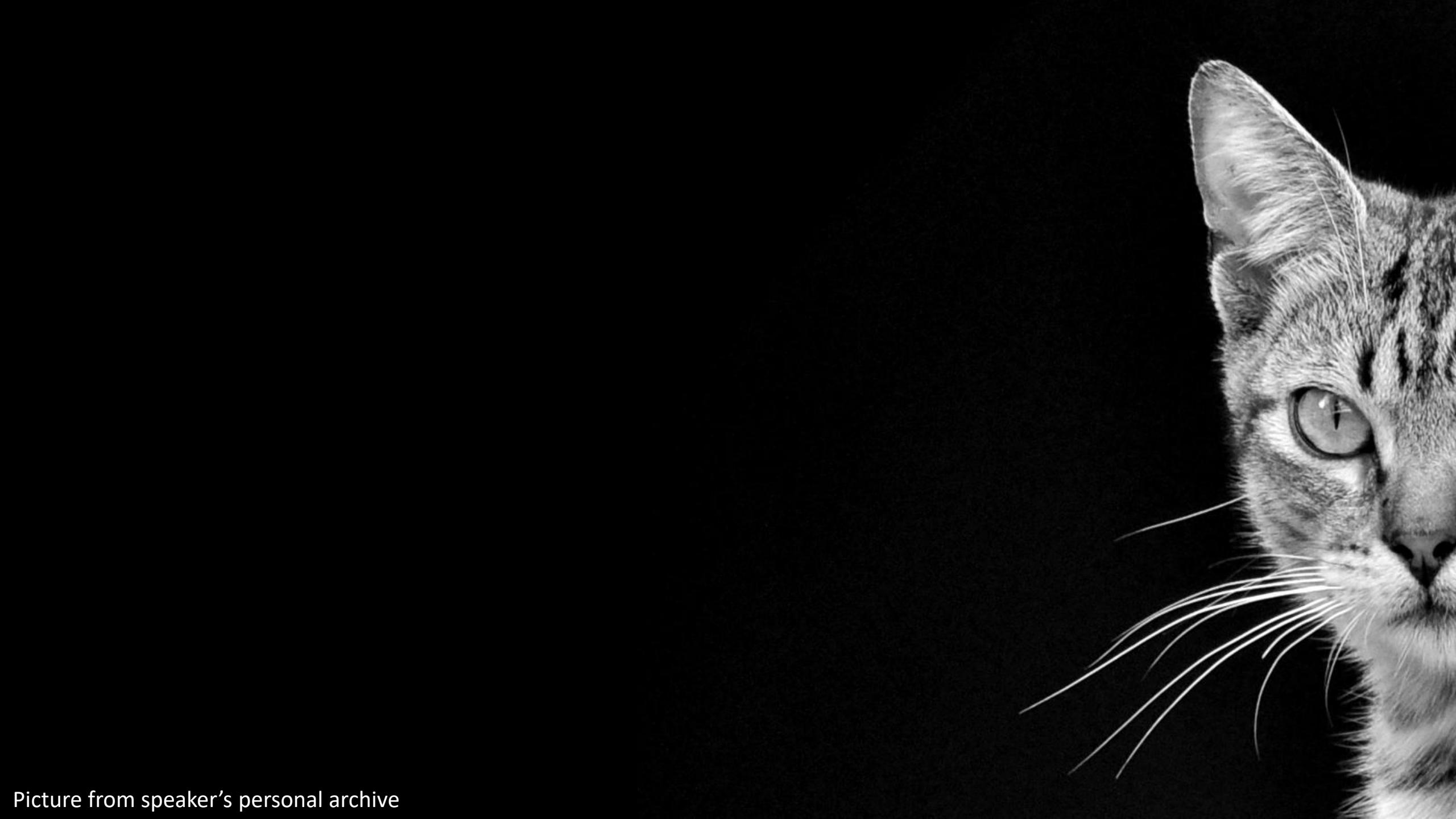
BMI for both females and males with NS was below the reference curve for the general Italian population.

This trend was seen up to approximately 12 years of age, after which patients seemed to progressively gain weight.

Both females and males with *PTPN11* mutations had lower BMIs than those with “other mutations”,



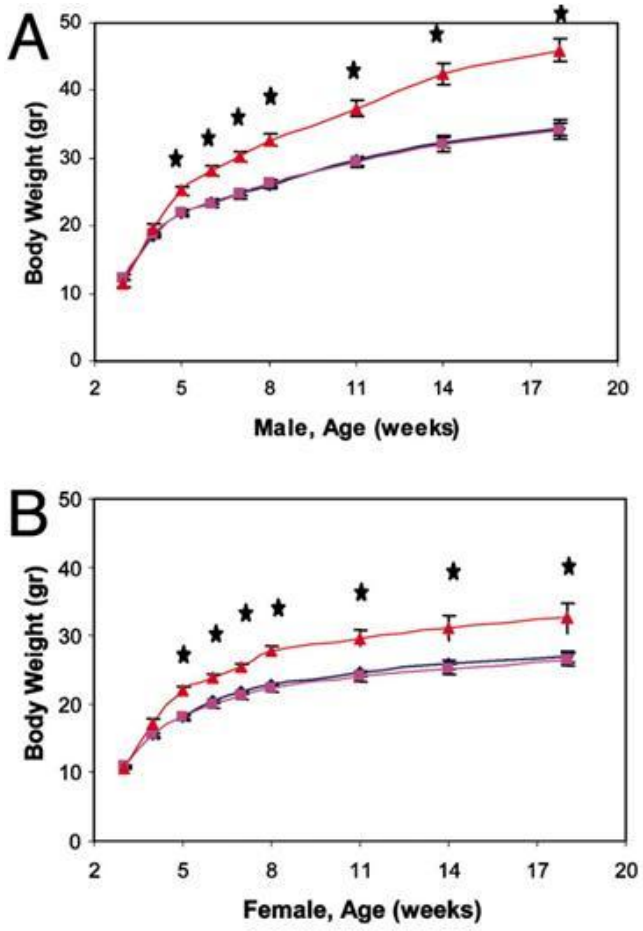
Cappa et al. Horm Res Paediatr. **2024;** PMID: 38964306

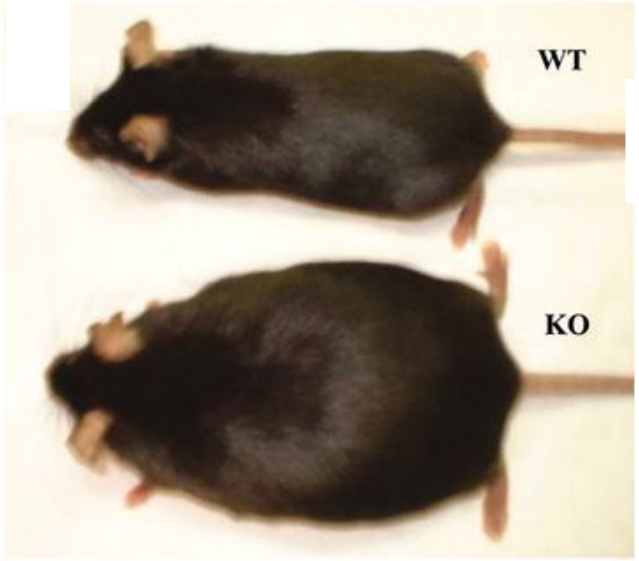


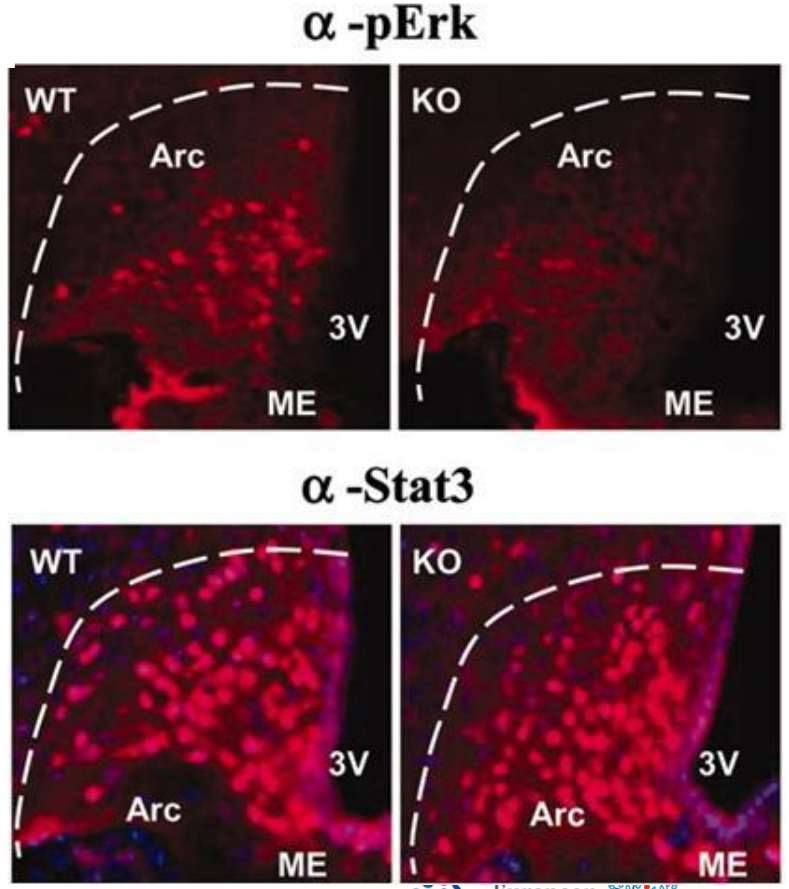
Picture from speaker’s personal archive

SHP2 controls energy balance and metabolism

Mice with selected deletion of Shp2 in forebrain neurons developed early-onset obesity, due to the decrease of leptin-stimulated Erk (MAPK) pathway







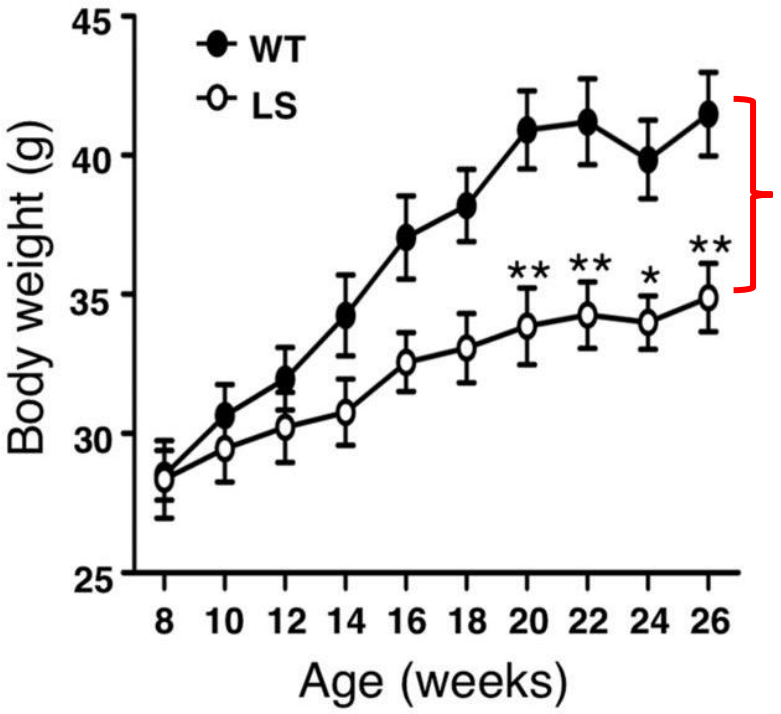
Zhang *et al.* PNAS **2004**; PMID: 15520383

Animal model with SHP-2 (*PTPN11*) mutation

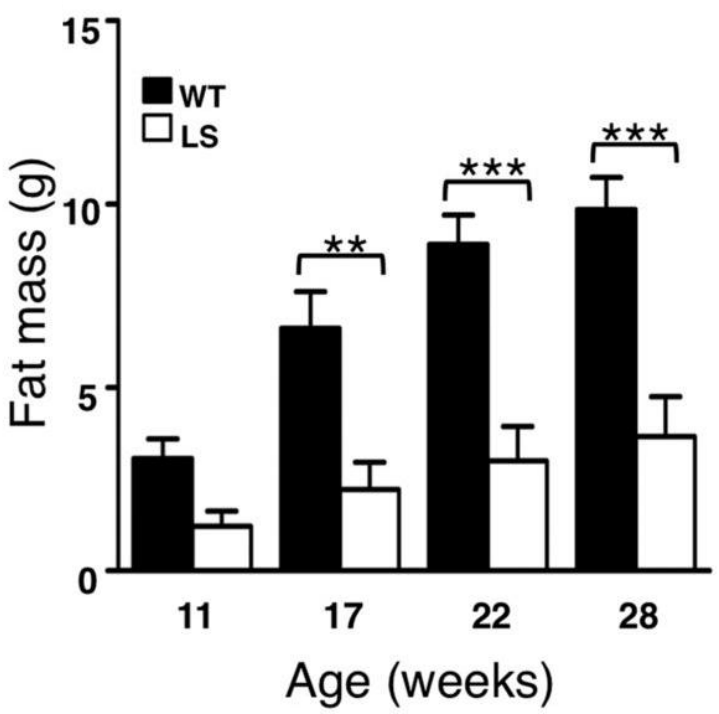
Knock-in mouse model carrying the T468M mutation (SHP2 mutations in Leopard syndrome/NSML patients)

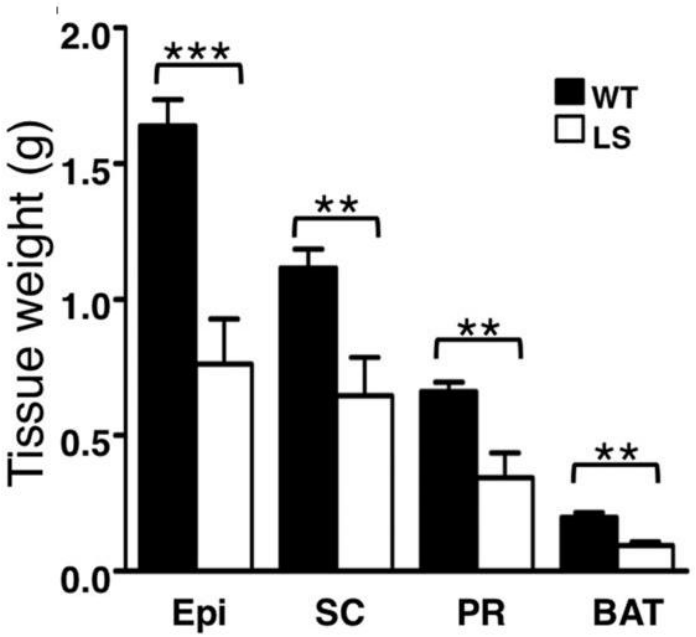
NS variants: **SHP2 gain-of-function → ↑RAS–MAPK**;
LS/NSML variants : **catalytically impaired (dominant-negative) SHP2 → PI3K–AKT/mTOR-shifted signaling**

Regular diet



Impaired adipocyte differentiation

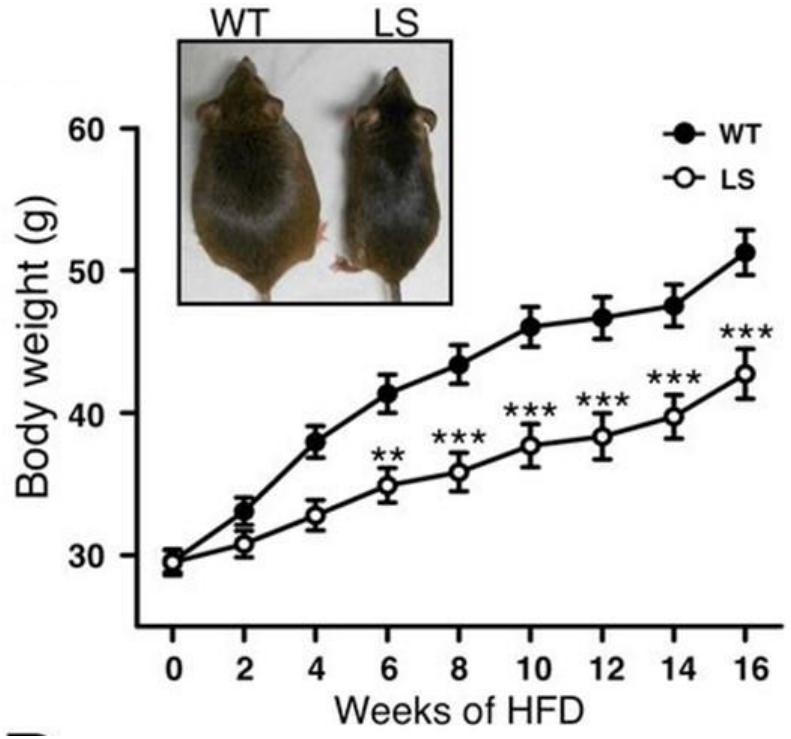




Tajan *et al.* PNAS **2014**; PMID: 25288766

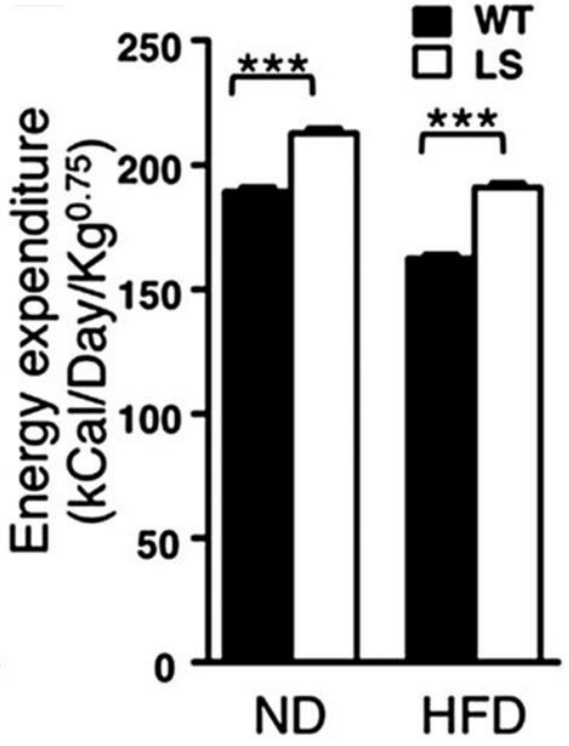
Animal model with SHP-2 (*PTPN11*) mutation

High fat diet



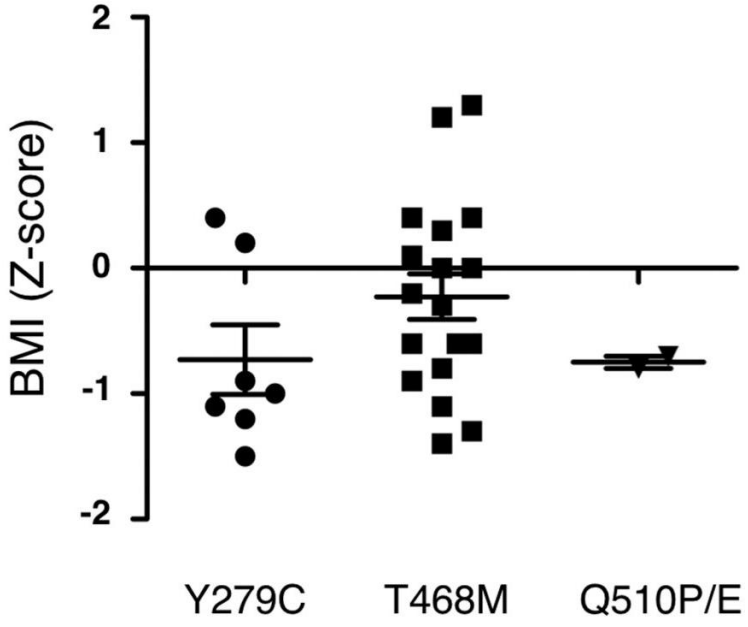
LS Mice Are Resistant to HFD-Induced Obesity

Caloric expenditure



28 adults with NSML

Z-score of adipose tissue between -2.4 to -1.8



Tajan *et al.* PNAS **2014**; PMID: 25288766

Unfavorable metabolic profile in Noonan syndrome

185 patients (112 prepubertal children and 73 adults)

NS (n = 178) and CFCS (n = 7)

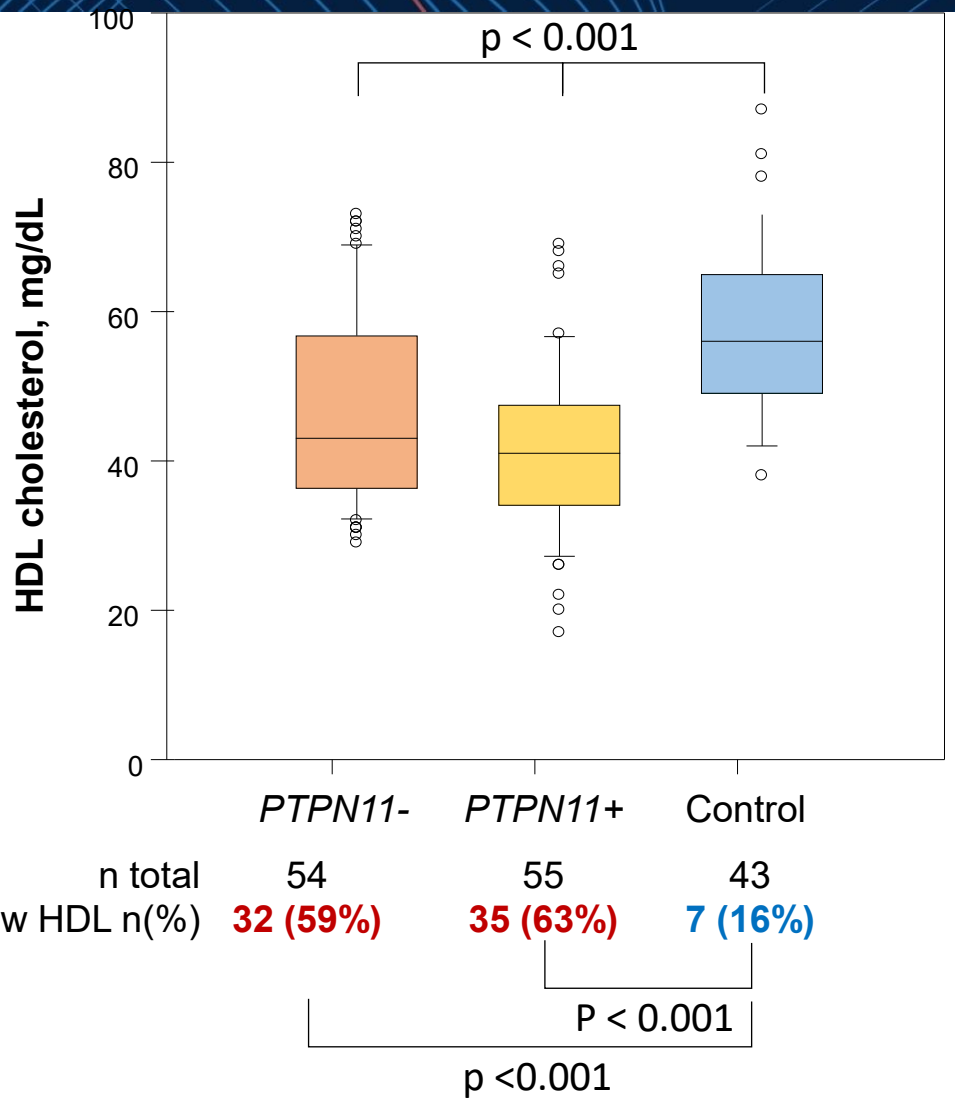
Exclusion criteria: Medications that interfere with glucose or lipid homeostasis, chronic disease malnutrition, and a positive familial history of dyslipidemia and diabetes mellitus.

Control group (n = 43) : healthy children from the same community as the patients.

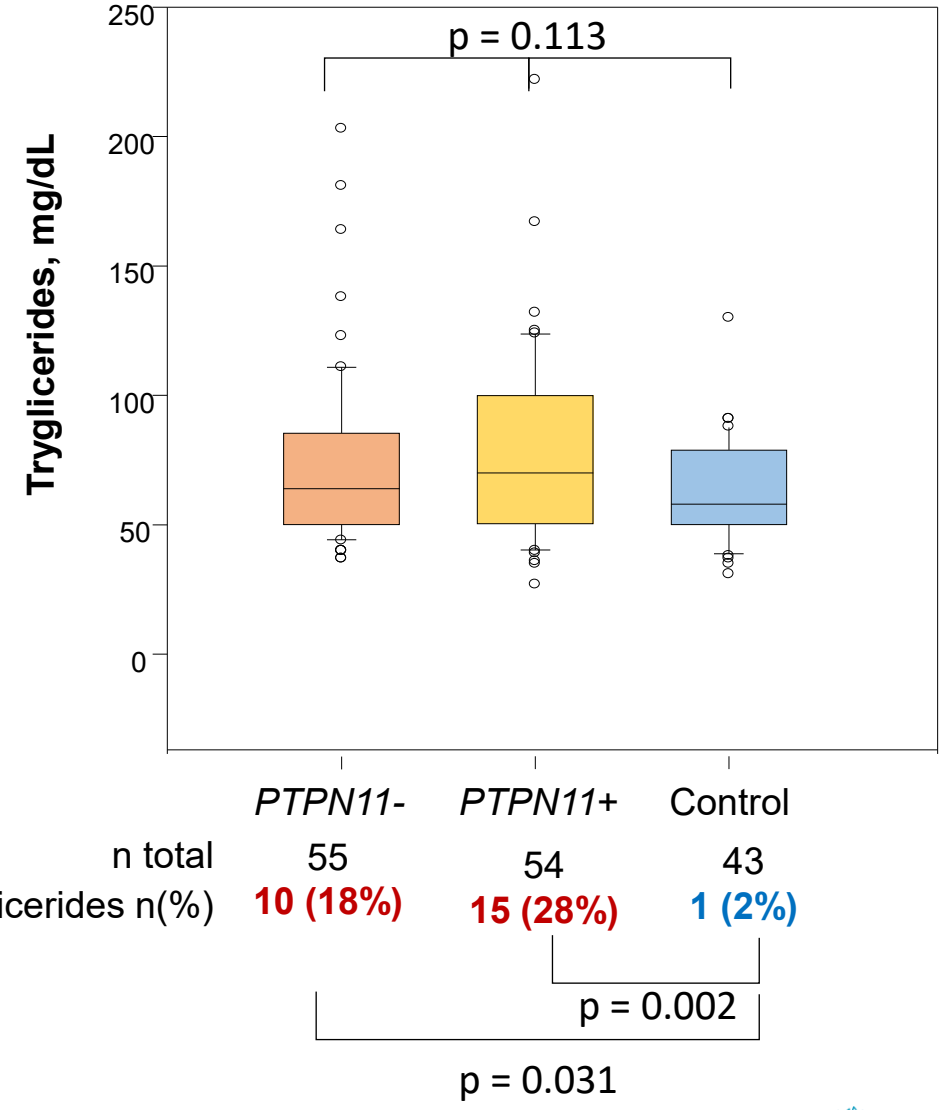
	NS (Total) n:112	NS (PTPN11 +) n:57	NS (PTPN11 -) n:55	Controls n:43	p (NS vs control)	p (PTPN11 + vs -)
Sex (F:M)	46:66	19:38	27:28	19:24	0.865	0.133
CA, years	7.7 (2.6 to 16)	7.1 (4.1 to 16)[a]	8.4 (2.6 to 14.4)[a]	9.7 (7.2 to 12.6)	<0.001	0.221
Height SDS	-2.2 ± 1.2	-2.3 ± 1.1 [a]	- 2.1 ± 1.3[a]	0.9 (-1.7 to 2.1)	<0.001	0.459
BMI SDS	-0.4 (-4.7 to 2.4)	-0.5 (-3.2 to 1.3)	- 0.3 (-4.7 to 2.4)	-0.4 (-2.0 to 1.7)	0.293	0.777

Noronha et al. Am J Med Genet A. **2021** PMID: **33382187**

Low HDL-cholesterol



Elevated triglycerides levels

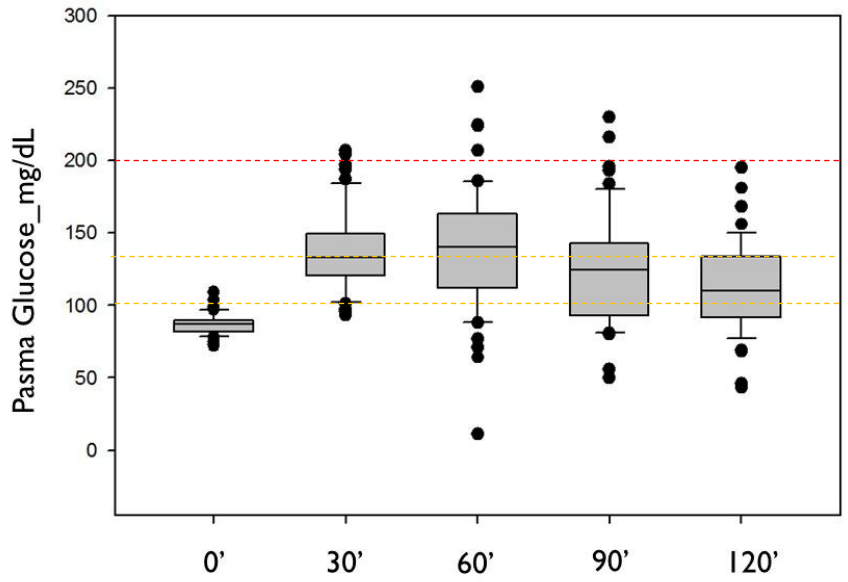


Noronha et al. Am J Med Genet A. **2021** PMID: **33382187**

Frequency of Glucose Intolerance in Noonan Syndromes

54 patients with NS
(31 females / 22 males)
CA = 14.5 to 61.2 years.

75g OGTT



Ten patients (18%) had impaired glucose tolerance (IGT)

Abnormal OGTT

5 males and 5 females

***PTPN11* (6x)**,
RIT1, *LZTR1*, *RAF1*, *SHOC2*

Age: 26.5 ± 5.6 y (17.8 to 37.7 y)

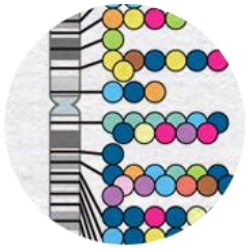
BMI: 21 ± 3 kg/m^2

- 2 underweight
- 7 appropriate weight
- 1 overweight

Low HDL-cholesterol 50%

Noronha et al. Am J Med Genet A. **2021** PMID: **33382187**

Association studies



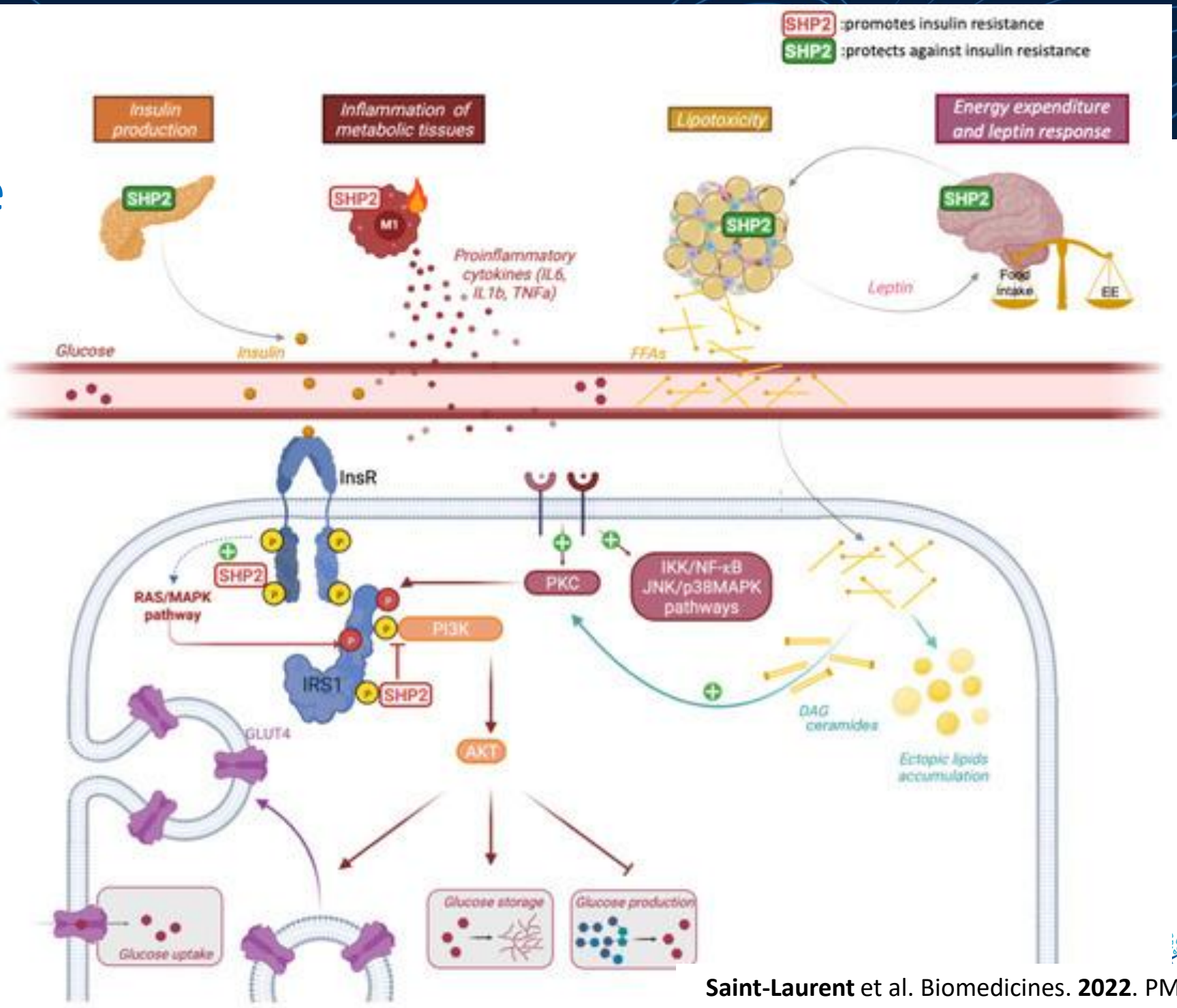
GWAS Catalog

SNPs in *PTPN11* associated with:

- Low LDL-cholesterol levels (5 associations)
- Low HDL-cholesterol levels (4 associations)
- Triglycerides (2 associations)

Diagnosis of Metabolic Syndrome	
Adult Criteria 3+ criteria	**Pediatric Criteria 2+ criteria**
WC > 102 cm (men) or 88 cm (women)	WC ≥ 90th percentile for age and gender
Triglycerides ≥ 150 mg/dL	Triglycerides ≥ 150 mg/dL
HDL-C < 40 (men) or < 50 (women)	HDL-C < 40 mg/dL
Systolic BP > 130 mmHg or > 85 mmHg diastolic	Systolic BP ≥ 130 or diastolic ≥ 85 mmHg
Fasting glucose ≥ 100 mg/dL Or known T2DM	Fasting glucose ≥ 100 mg/dL Or known T2DM

SHP-2 (*PTPN11*) and Insulin Resistance



Saint-Laurent et al. Biomedicines. **2022**. PMID: **36140242**

Lipid profile in Noonan syndrome: Italian cohort

N = 93
CA = 9.5 ± 6.2 years
BMI SDS = -0.3 ± 1.2
52.7% *PTPN11*

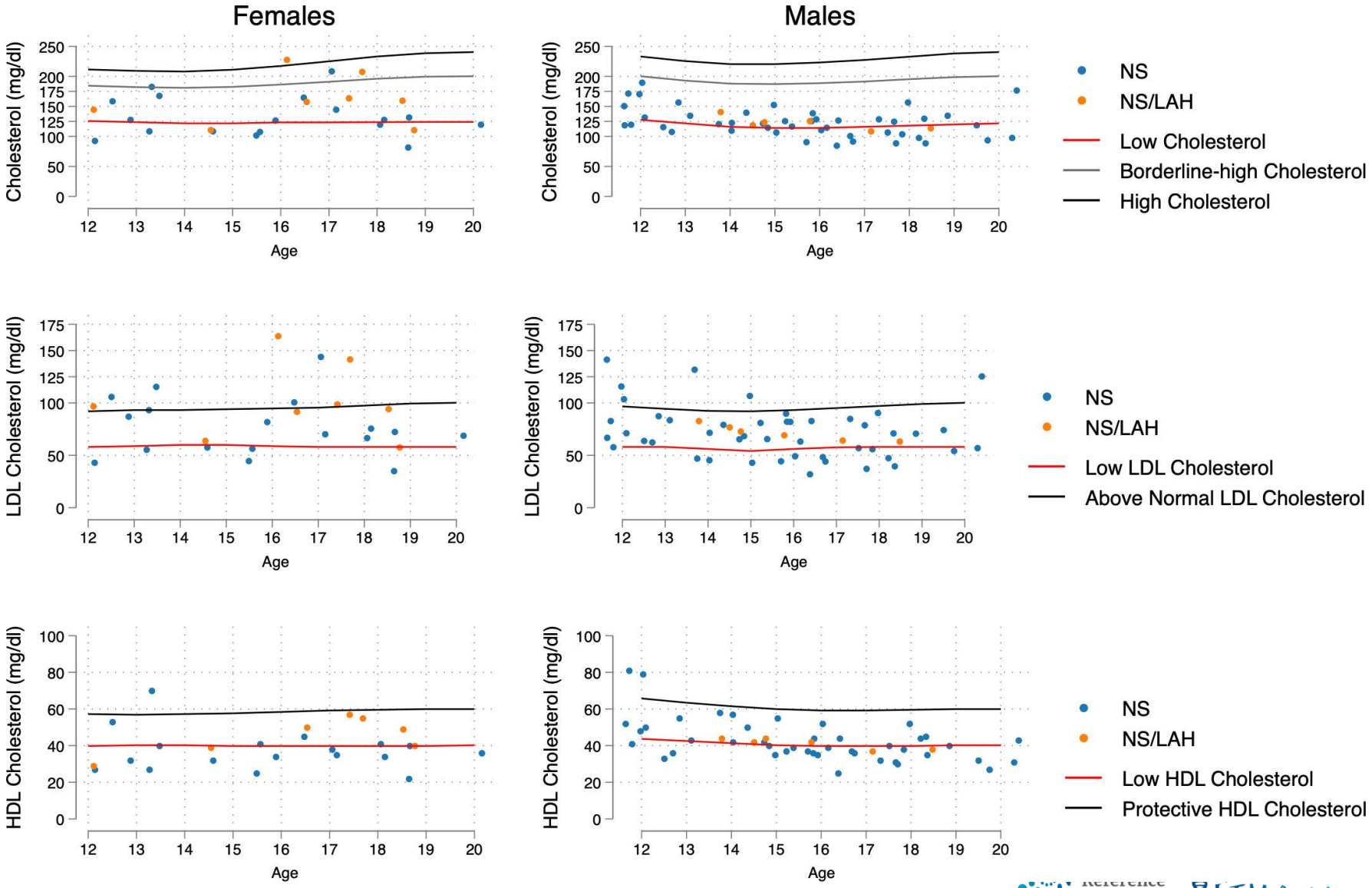
Low

- Total cholesterol
- HDL-cholesterol

(in particular in *PTPN11*)

Triglycerides showed an increasing trend with age only in NS females.

Normal glucose metabolism (HOMA-IR)



Tamburrino et al. Front Endocrinol (Lausanne). **2023** PMID: **37588986**

Take home message

Patients with NS, especially those with *PTPN11*, exhibit resistance to weight gain

- Low BMI is frequently observed in childhood, but in adulthood it is a phenotype more commonly seen in men with Noonan syndrome.

There appears to be a metabolic profile in patients with Noonan syndrome characterized by:

- Resistance to weight gain
- Low total cholesterol and HDL cholesterol
- Tendency toward elevated triglycerides

European Reference Networks ITHACA

Take home message

In our clinic, we currently have 81 adult patients with NS under annual follow-up

- None have developed diabetes or had a cardiovascular event.

(70% women, median age 31 years)

Long-term, large cohort studies are needed to define the clinical significance of these findings in terms of:

- Cardiovascular risk
- Risk for diabetes

Acknowledgment

Debora Bertola

Alexsandra Malaquias

Lize Ferreira

Renata Noronha

European Reference Networks ITHACA

Picture from speaker's personal archive

AlexJ
@endogenetica

alexj@usp.br

Time for questions and discussion

- Time for questions

- Satisfaction Survey :
- https://forms.office.com/e/FYeG2sTkPC
- Website :
  - https://ern-ithaca.eu
  - https://ern-ithaca.eu/webinars/

Thank you for your participation