XI CONGRESSO NAZIONALE
FIMP 2017

Insieme ai Bambini, insieme Noi

fimp Federazione Italiana Medici Pediatri

AIM GROUP INTERNATIONAL

Angelo Selicorni

La genetica nel quotidiano

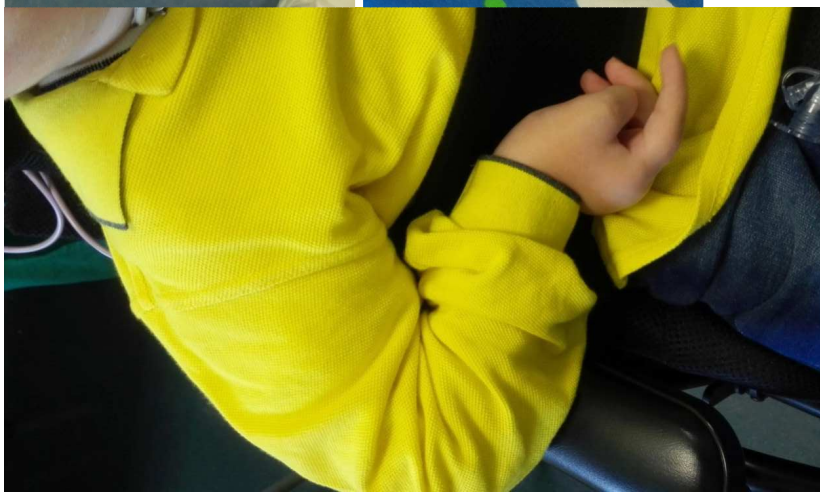
Snodi del percorso

- Inquadramento diagnostico
- Follow-up assistenziale
- Terapia ?

Snodi del percorso

- Inquadramento diagnostico

Barbieri



MALATTIE SENZA DIAGNOSI

Sono malattie genetiche sconosciute: senza un nome, senza una causa biologica nota, senza nessuno che le studi.
Non si sa come evolveranno e se esiste una terapia.

Accedi ora al programma "Malattie Senza Diagnosi"

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Genotipo rilevato

L'analisi eseguita ha evidenziato le seguenti variazioni in eterozigosi composta nel gene TOR1A sul cromosoma 9q34.11 :

Allele	Gene	Coord. hg.19	variante	proteina	zigosità
Paterno	*TOR1A*	Chr9: 132586345	NM_000113: c.19_20insGGCCG (esone 1)	p.V7fs	Het
Materno	*TOR1A*	Chr9: 132580927	NM_000113: c.621-1G>A (esone 4)	splicing	Het

Interpretazioni e conclusioni

L'analisi ha evidenziato le seguenti varianti patogenetiche nel gene *TOR1A*: c.19_20insGGCCG, p.V7fs nell'esone 1; c.621-1G>A nell'esone 4. Le varianti, presenti in eterozigosi composta, sono state confermate mediante sequenziamento Sanger. La variante nell'esone 1 è presente, in eterozigosi, nel padre [redacted] 22/06/1985 e la variante nell'esone 4 è presente, in eterozigosi, nella madre [redacted]

Il referto è compatibile con la diagnosi di **sindrome complessa con artrogriposi.**

I risultati delle analisi e la loro interpretazione si basano sulle attuali conoscenze e sulla tecnologia molecolare che è in continua evoluzione. Per ogni ulteriore quesito sulle indagini effettuate, e per altre eventualmente effettuabili, è possibile contattare il laboratorio.

Vincenzo Nigro

Vincenzo Nigro
prof ordinario di genetica medica

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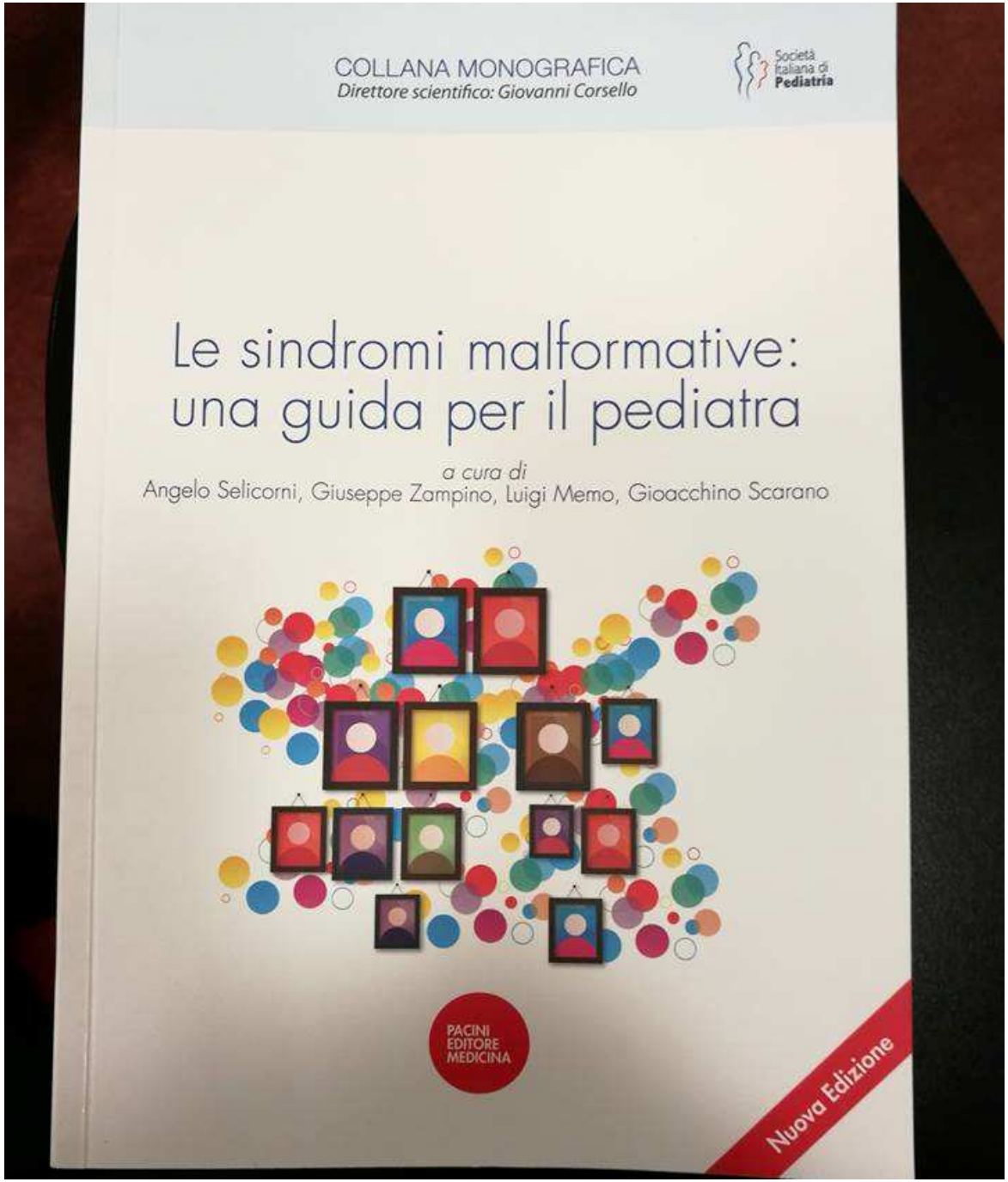
respectively. The pregnancy was complicated by intrauterine growth restriction, reduced fetal movements, and arthrogryposis. Invasive prenatal genetic testing was declined, and no teratogenic exposures or maternal illnesses were reported. Following delivery, examination was notable for contractures in all extremities and skeletal anomalies, including bilateral hip dislocations, bilateral clubfeet, 11 sets of ribs, and scoliosis (figure). He developed restrictive lung disease requiring tracheostomy with ventilator support, and a G-tube was placed for swallowing discoordination. Brain MRI at 3 weeks of age was unremarkable (figure). He is currently 7 months old and has no spontaneous or involuntary movements, although he responds to voices and makes eye contact.

l developmental
The family has
s sibling.



Storia naturale e follow-up

Terapia ?

Il caso

di **Luigi Ippolito**

«Oggi a Charlie sarà staccata la spina» I genitori del neonato: noi lasciati soli

Londra, la rara malattia a 10 mesi. La coppia voleva portarlo negli Usa, il no dei giudici

DAL NOSTRO CORRISPONDENTE

LONDRA Oggi il piccolo Charlie Gard si addormenta per sempre. Ma non potrà farlo nella sua culla: i medici di Londra che hanno deciso di staccare la spina al bambino inglese malato hanno negato ai genitori il permesso di farlo morire in casa.

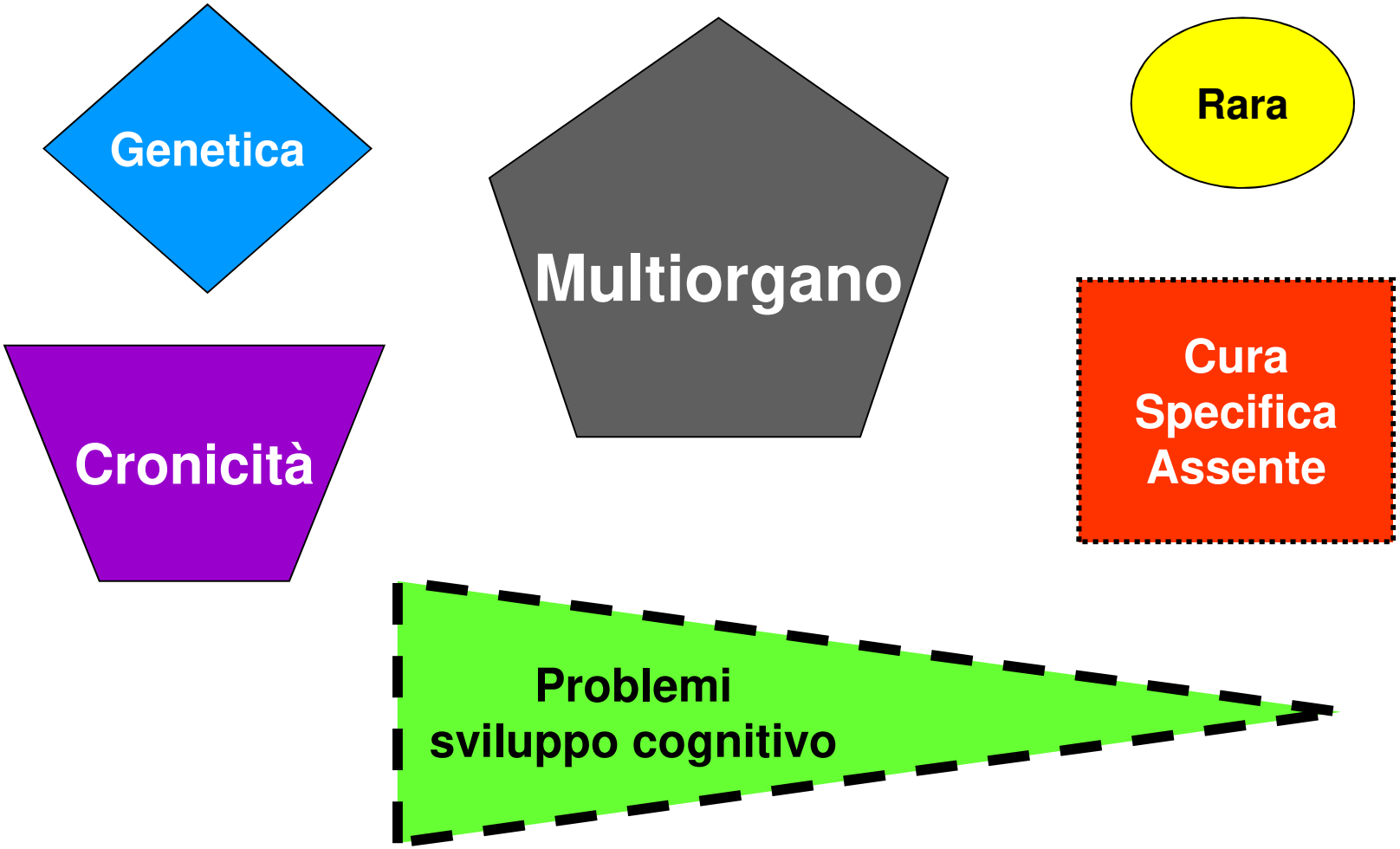
«Abbiamo promesso ogni giorno al nostro bimbo che lo avremmo riportato indietro», ha detto la madre, Connie Yates, in un video straziante girato in ospedale e fatto pervenire al *Mail online*. «Volevamo fargli il bagnetto — ha aggiunto il padre Chris — metterlo nella culla in cui non ha mai potuto dormire, ma ce lo hanno negato. Sappiamo che nostro figlio morirà ma non

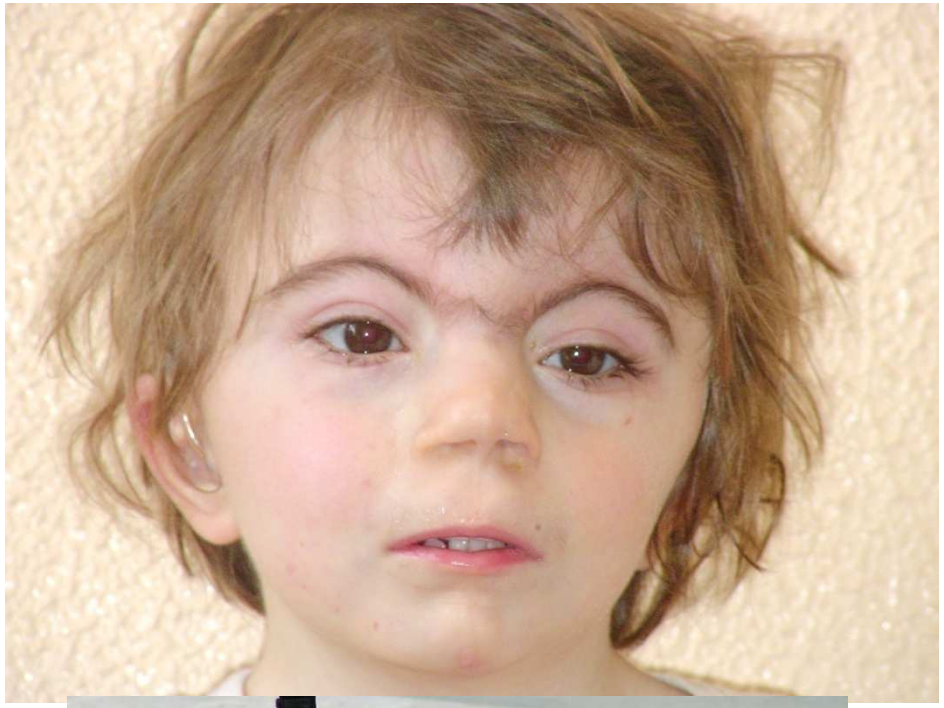
Insieme
A sinistra, Chris Gard e Connie Yates — genitori di Charlie, 10 mesi, a cui oggi sarà staccata la spina — hanno scritto su Facebook un post contro i diversi giudici che non hanno consentito di far curare il loro bambino negli Stati Uniti (Ansa)

Terapia ?

MUSICA
la rubrica multitasking
CITAZIONI
CURIOSITA'
LIBRO DELLA SETTIMANA
FILM
COSA BOLLE IN PENTOLA ?
PERSONE

Malattie genetiche





NIPBL (65%)

SMC1A (5%)

HDAC8 (5 %)

RAD21 <1 %

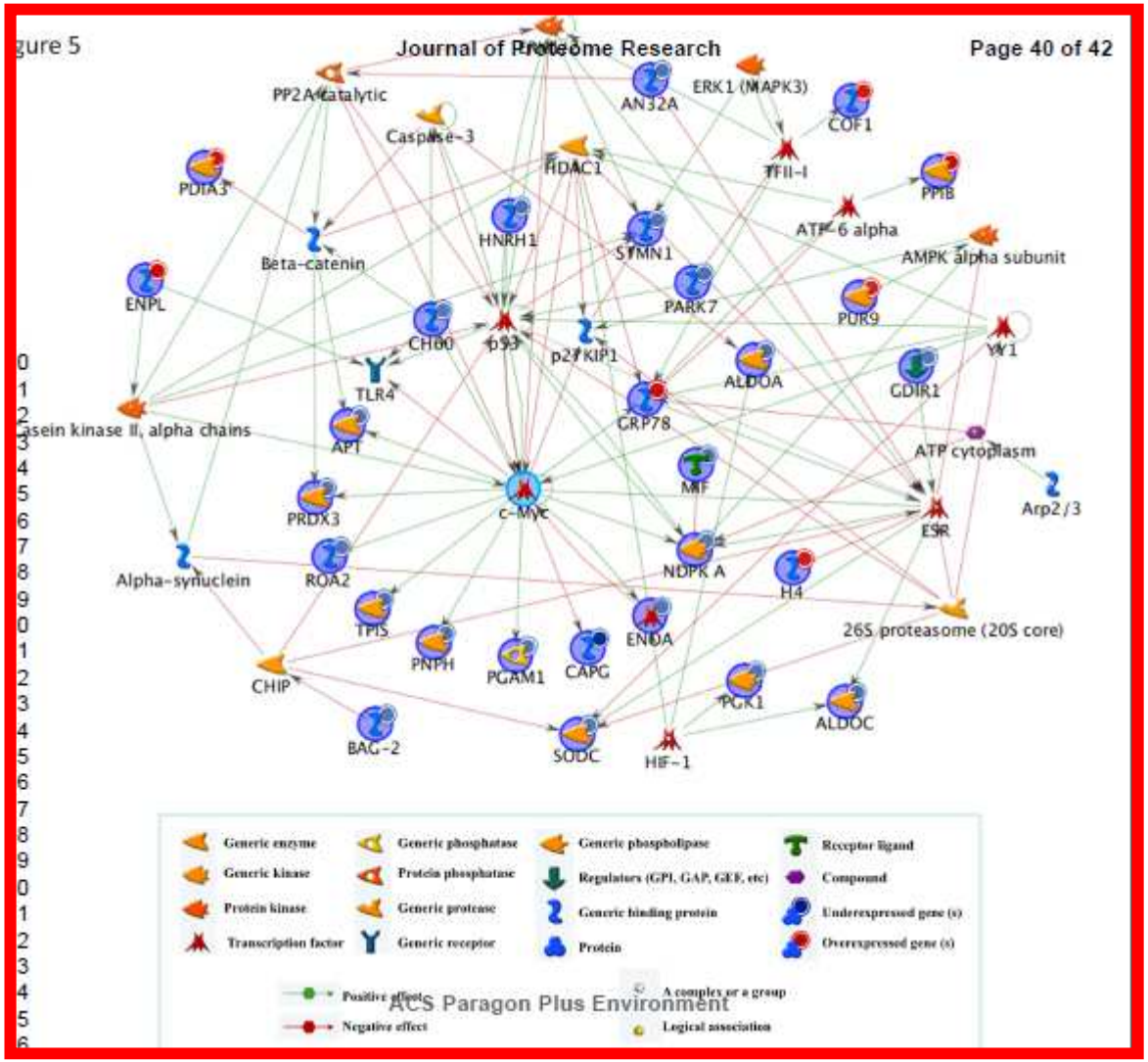
SMC3 <1 %

Subscriber access provided by UNIV DI MILANO

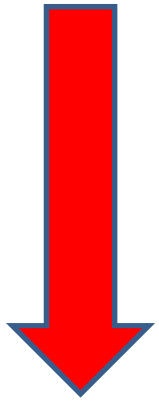
Article

Proteomic Profile Identifies Dysregulated Pathways in Cornelia de Lange Syndrome Cells With Distinct Mutations in SMC1A and SMC3 Genes

Anna Gimigliano, Linda Mannini, Laura Bianchi, Michele Puglia, Matthew A Deardorff, Stefania Menga, Ian D Krantz, Antonio Musio, and Luca Bini



Elemento fondamentale per arrivare ad un trattamento



Conoscenza delle basi fisiopatologiche e biologico cellulari/biochimiche della condizione

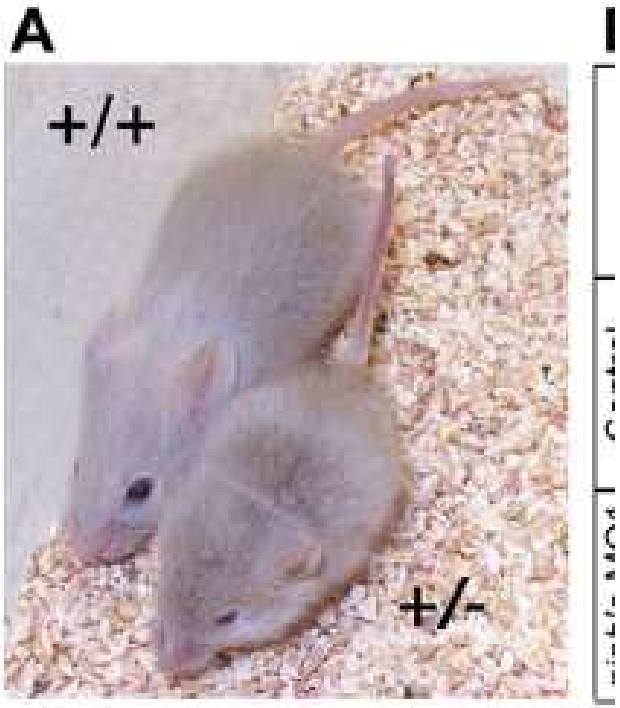
Modelli murini => topi transgenici

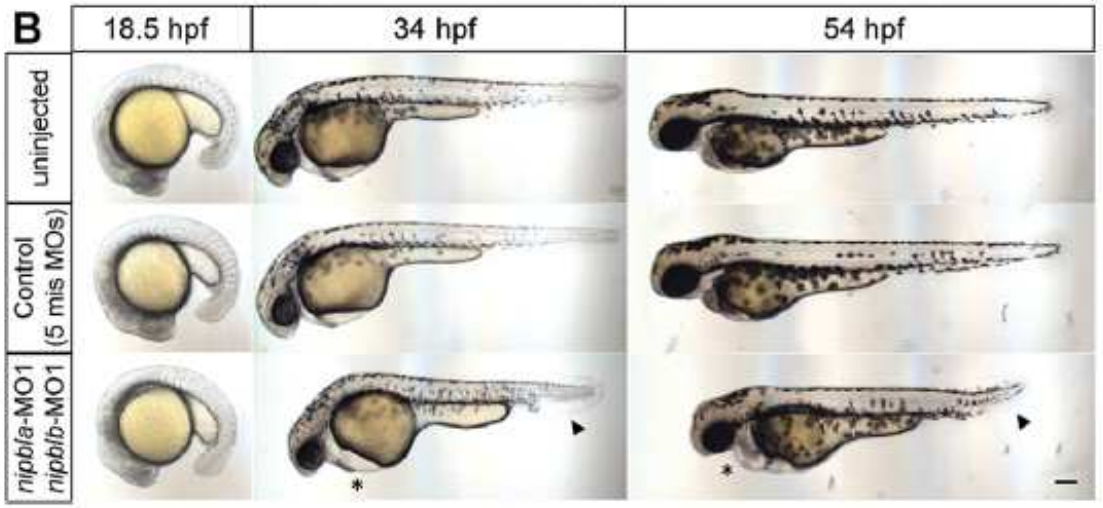
American Journal of Medical Genetics Part C (Seminars in Medical Genetics)

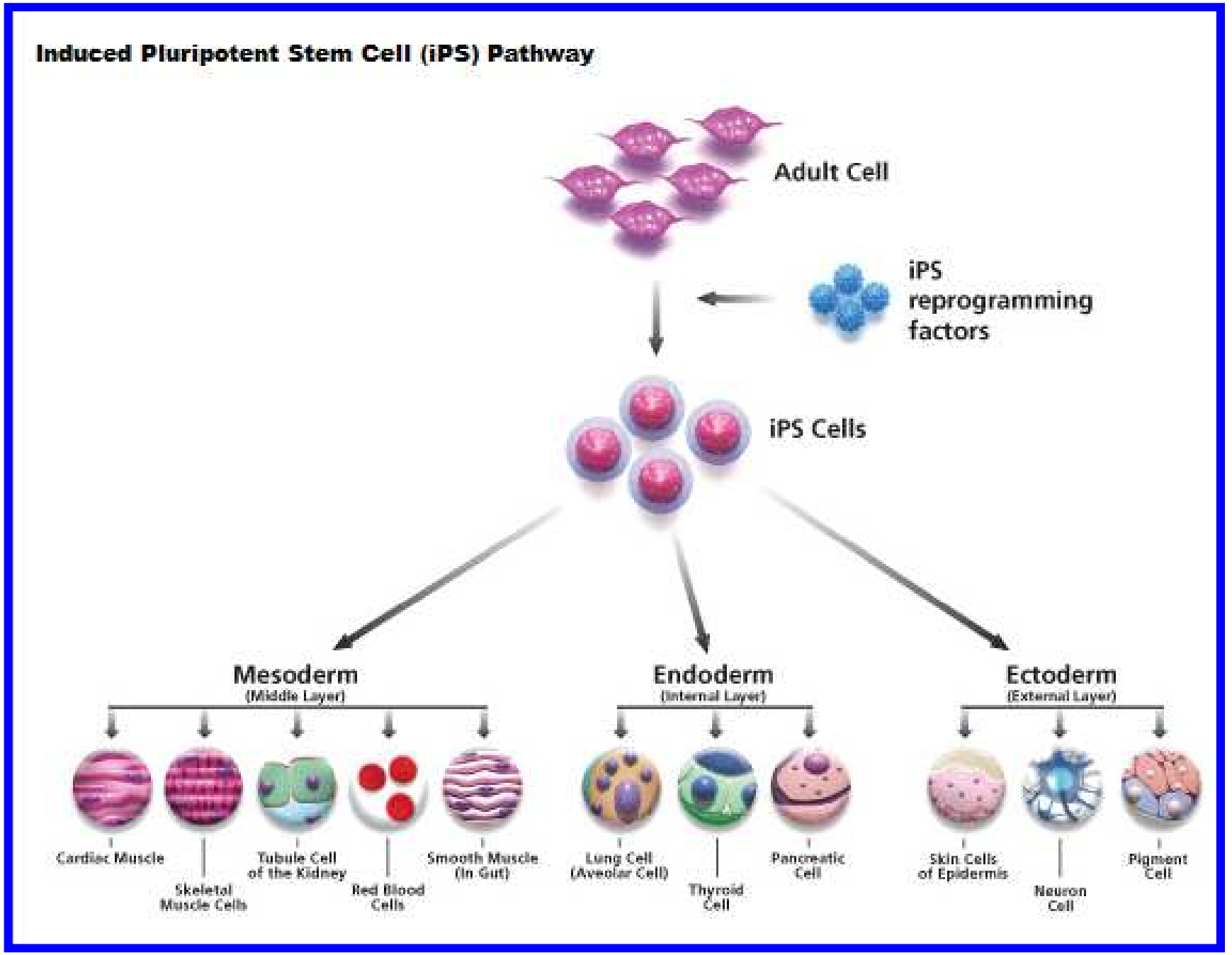
ARTICLE

Using Mouse and Zebrafish Models to Understand the Etiology of Developmental Defects in Cornelia de Lange Syndrome

SHIMAKO KAWAUCHI, ROSAYSELA SANTOS, AKIHIKO MUTO, MARTHA E. LOPEZ-BURKS, THOMAS F. SCHILLING, ARTHUR D. LANDER, AND ANNE L. CALOF*






Induced Pluripotent Stem Cell (iPS) Pathway
Adult Cell
iPS
reprogramming
factors
iPS Cells
Mesoderm
(Middle Layer)
Endoderm
(Internal Layer)
Ectoderm
(External Layer)
Cardiac Muscle
Skeletal
Muscle Cells
Tubule Cell
of the Kidney
Red Blood
Cells
Smooth Muscle
(In Gut)
Lung Cell
(Aveolar Cell)
Thyroid
Cell
Pancreatic
Cell
Skin Cells
of Epidermis
Neuron
Cell
Pigment
Cell

Studio attraverso iPS

- Identificare le differenze biologiche metaboliche delle cellule con il difetto genetico rispetto alle cellule normali
- Ipotizzare e testare in vitro sostanze in grado di permettere alle cellule di recuperare la normale fisiologia
- Verificare l'applicabilità e la sicurezza dell'uso di queste sostanze come trattamenti farmacologici

Drug repositioning strategy

BRIEFINGS IN BIOINFORMATICS. VOL 12. NO 4. 346–356
Advance Access published on 18 April 2011
doi:10.1093/bib/bbr021

Drug repositioning for orphan diseases

Divya Sardana, Cheng Zhu, Minlu Zhang, Ranga C. Gudivada, Lun Yang and Anil G. Jegga

Submitted: 12th December 2010; Received (in revised form): 18th February 2011

Hay Mele *et al. Orphanet Journal of Rare Diseases* (2015) 10:55
DOI 10.1186/s13023-015-0273-2

OJRD ORPHANET JOURNAL OF RARE DISEASES

LETTER TO THE EDITOR **Open Access**

Drug repositioning can accelerate discovery of pharmacological chaperones

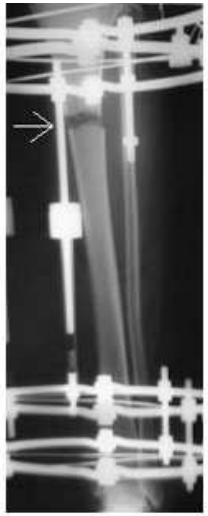
Bruno Hay Mele[1], Valentina Citro[2], Giuseppina Andreotti[3*] and Maria Vittoria Cubellis[2*]

Drug repositioning strategy

- Strategia alternative ed efficente => trovare nuove connessioni tra principi attivi noti e malattie rare

- In pratica: identificazione e sviluppo di nuovi usi per principi attivi abbandonati o già in uso

Edoardo

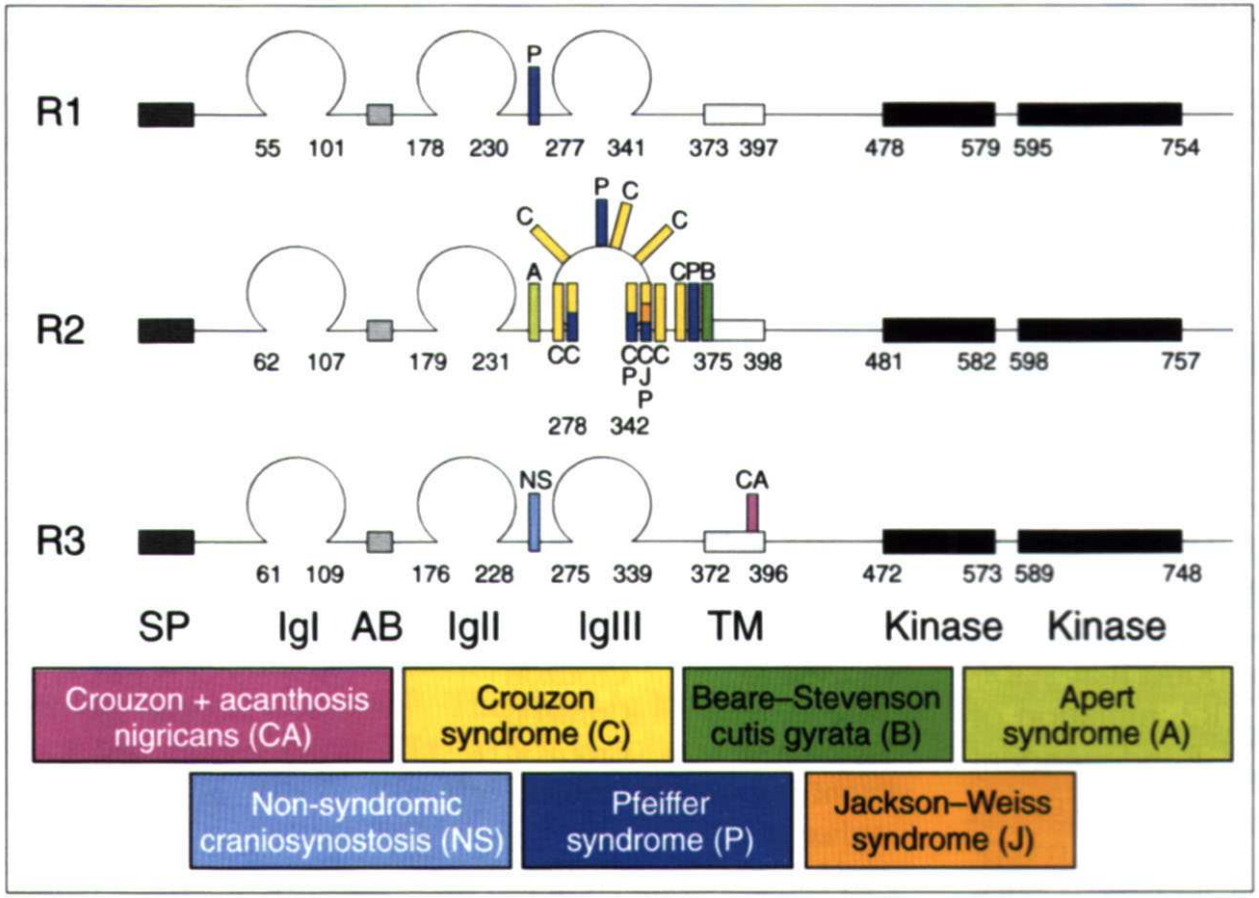


Allungamento di gamba:
è possibile vedere il punto
d'interruzione dell'osso (freccia),
e l'apparato per la distrazione

Fine dell'allungamento ed
inizio della guarigione con
formazione di callo osseo
(freccia)

Guarigione completa dell'arto,
fissatore rimosso, sito di
allungamento completamente
saldato (freccia)

FGFR3



Mutazioni diverse di FGFR3 responsabili anche

Ipocondroplasia

Displasia Tanatofora

Drug repositioning strategy

Meclozina cloridrato

- somministrazione in embrioni di topi eterozigoti *knock-out* per FGFR3, incrementa la lunghezza totale dell'abbozzo embrionale delle tibie dei topi KO.

- crescita ossea di topi KO e topi *wild-type*, trattati o meno con meclozina a dosi nel *range* utilizzato per disturbi da chinetosi. => incremento significativo della lunghezza dopo 2 settimane di terapia nei topo KO

Drug repositioning strategy

Statine

- significativo miglioramento del processo di condrogenesi delle cellule iPSC derivate dai pazienti.

- efficacia notevole nel correggere lo sviluppo scheletrico dei topi *knock-out* per acondroplasia

Mini Review

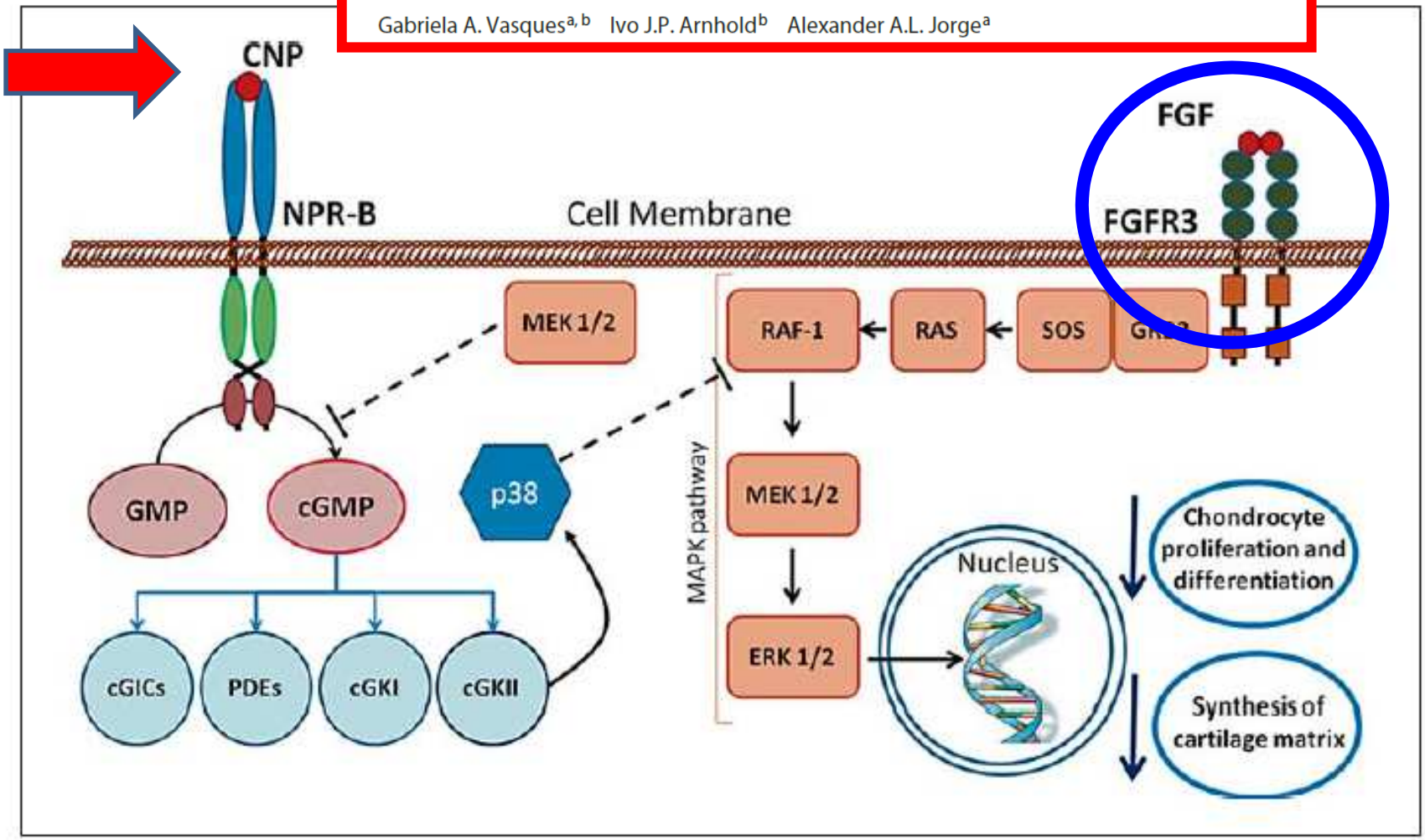
HORMONE
RESEARCH IN
PÆDIATRICS

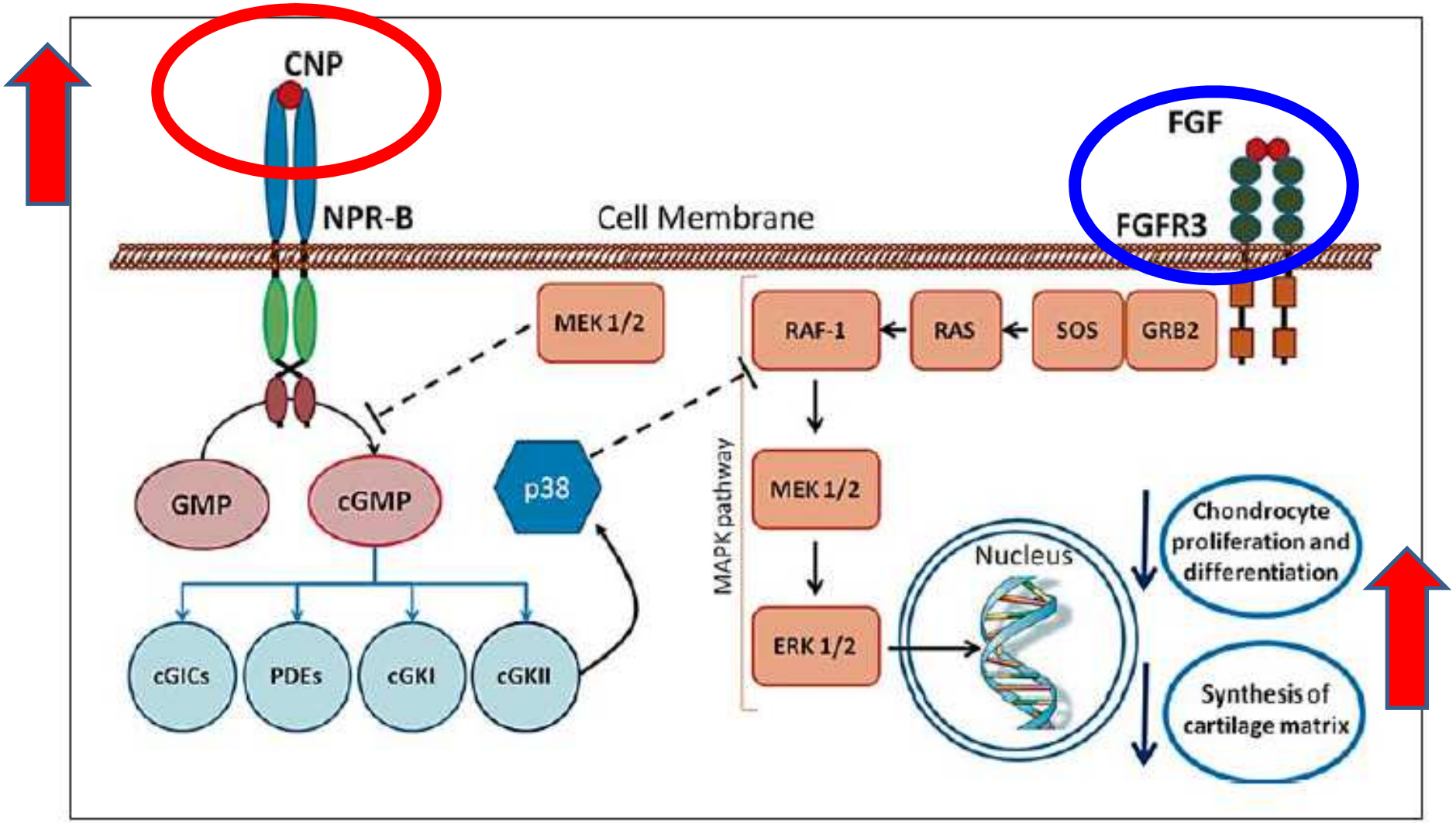
Horm Res Paediatr
DOI: 10.1159/000365049

Received: March 17, 2014
Accepted: June 3, 2014
Published online: September 3, 2014

Role of the Natriuretic Peptide System in Normal Growth and Growth Disorders

Gabriela A. Vasques[a, b] Ivo J.P. Arnhold[b] Alexander A.L. Jorge[a]




CNP
NPR-B
Cell Membrane
FGF
FGFR3
MEK 1/2
RAF-1
RAS
SOS
GRB2
GMP
cGMP
p38
MAPK pathway
MEK 1/2
ERK 1/2
Nucleus
cGICs
PDEs
cGKI
cGKII
Chondrocyte proliferation and differentiation
Synthesis of cartilage matrix

REPORT

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,*]

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Products/ Pipeline

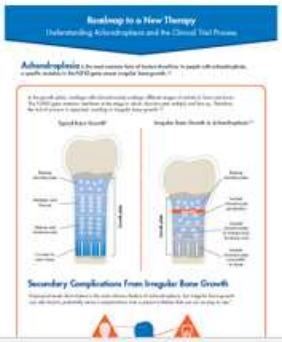
- Overview
- **Pipeline**
  - Pegvaliase (BMN 165) for PKU
  - **Vosoritide (BMN 111) for Achondroplasia**
  - BMN 270 for Hemophilia A
  - BMN 250 for MPS

Vosoritide (BMN 111) for Achondroplasia

Vosoritide is designed for the treatment of achondroplasia, the most common form of dwarfism.

Achondroplasia is the most common form of human dwarfism and is characterized by failure of normal conversion of cartilage into bone, which results in disproportionate short stature. This condition is caused by a mutation in the fibroblast growth factor receptor 3 gene (FGFR3), a negative regulator of bone growth. Disproportionate growth between endochondral bone and underlying organs leads to a number of orthopedic, neurological,

ROADMAP TO A NEW THERAPY



Clinical Trial 2

- A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia
- This study is collecting serial growth measurements for pediatric patients with Achondroplasia who may also be considered for enrollment in a subsequent study involving treatment with study drug. Participation in this study is a pre-requisite for enrollment in the drug treatment study.

Mini-Review • DOI: 10.1515/tnsci-2017-0001 • Translational Neuroscience • 8 • 2017 • 1-6

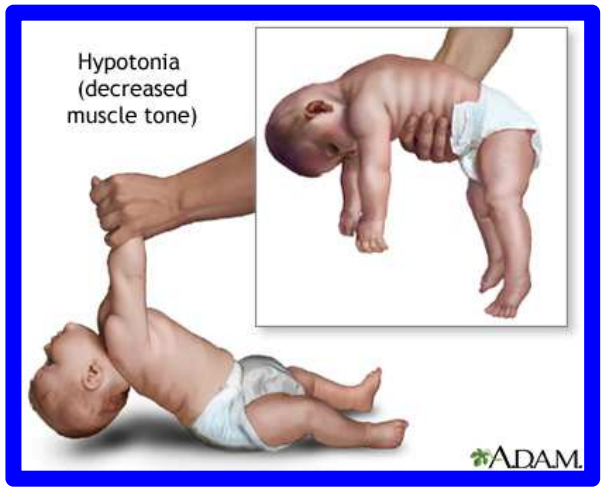
Translational Neuroscience

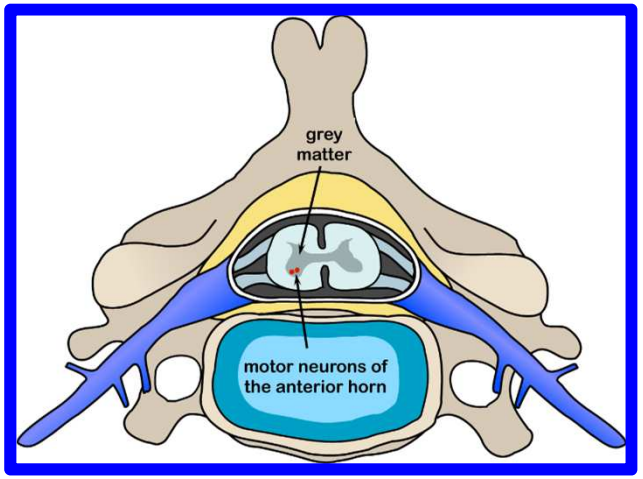
DE GRUYTER OPEN

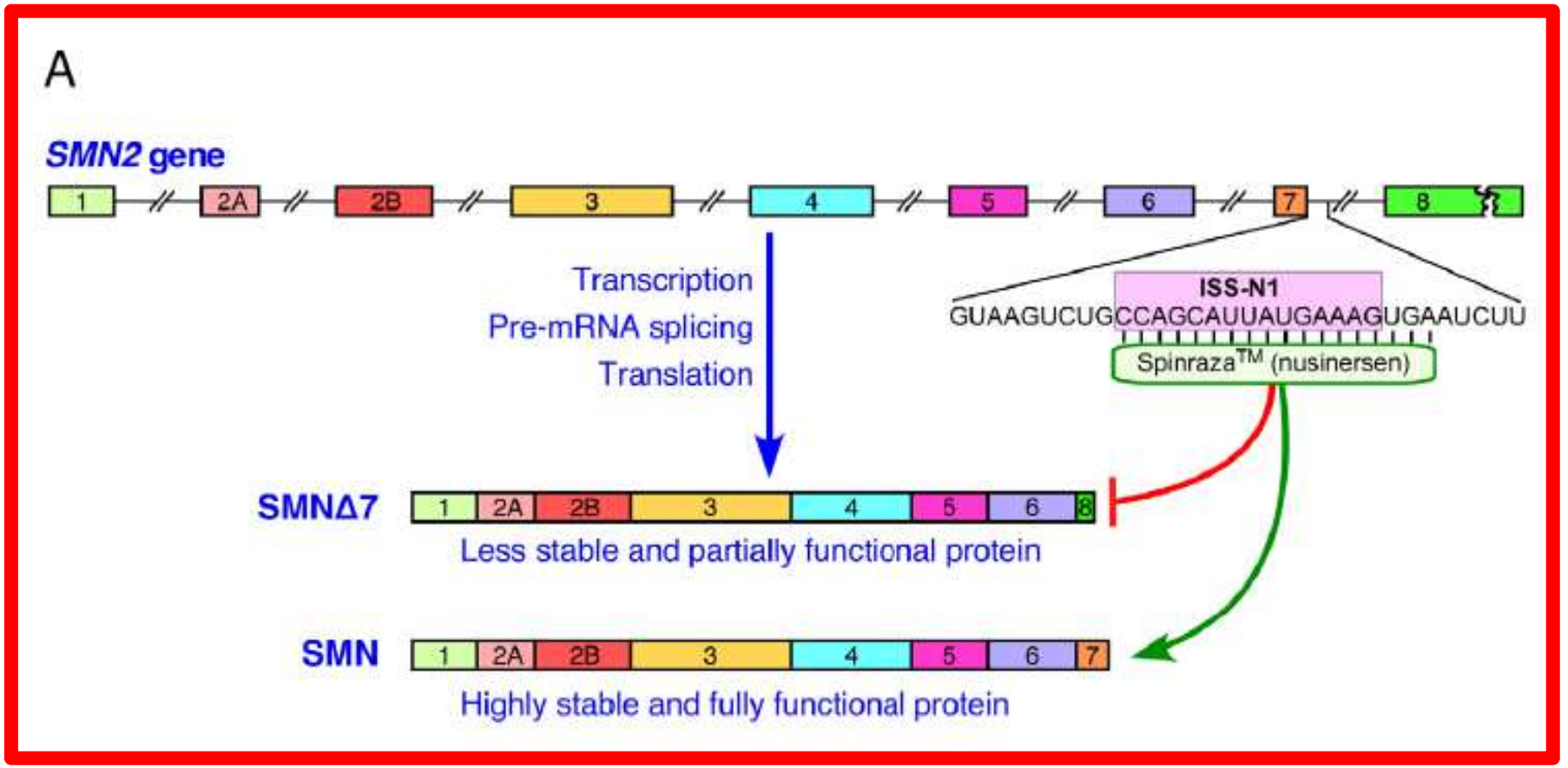
ISS-N1 MAKES THE FIRST FDA-APPROVED DRUG FOR SPINAL MUSCULAR ATROPHY

Eric W. Ottesen*

respiratory insufficiency [1,2]. SMA is caused by low levels of Survival Motor Neuron (SMN) protein due to homozygous deletion or mutation of the *SMN1* gene [3,4]. SMN is






A
SMN2 gene
1
2A
2B
3
4
5
6
7
8
Transcription
Pre-mRNA splicing
Translation
ISS-N1
GUAAGUCUGCCAGCAUUAUGAAAGUGAAUCUU
Spinraza™ (nusinersen)
SMNΔ7
Less stable and partially functional protein
SMN
Highly stable and fully functional protein

the AJMG
SEQUENCE
Decoding news and trends for the medical genetics community
By Deborah Levenson

TREATMENT UPDATE

FIRST DRUG TO TREAT SPINAL MUSCULAR ATROPHY GETS FDA APPROVAL

Costly injectable shown to stall debilitating muscle-wasting effects of rare genetic disorder

The drug's approval is based on the interim findings that 40% of patients treated with Spinraza achieved improvement in the motor milestones but none of the control patients did.

Results of additional open label uncontrolled clinical studies in symptomatic patients—ages 30 days to 15 years at the time of first dose—and in presymptomatic patients—ages 8 days to 42 days at the time of first dose—generally support the clinical efficacy demonstrated in the controlled clinical trial in infantile-onset patients

Spinraza (nusinersen) is an injection administered into the fluid surrounding the spinal cord.

It is given in six doses during the first year of life and three times annually after age 1.

"To help type 1 [infancy-onset] patients, you have to get them as early as possible," says Thomas W. Prior, ……..
"Now that we've got a therapy, we have to think of NBS [newborn screening] for the disease.".

the AJMG
SEQUENCE
Decoding news and trends for the medical genetics community
By Deborah Levenson

TREATMENT UPDATE

FIRST DRUG TO TREAT SPINAL MUSCULAR ATROPHY GETS FDA APPROVAL

Costly injectable shown to stall debilitating muscle-wasting effects of rare genetic disorder

Cost

Meanwhile, the cost of the drug is "obscene," says Dr. Swoboda. The list price of one dose is $125,000, so the drug will cost $750,000 for the six doses needed in the first year and about $375,000 for the subsequent three doses annually, presumably for the rest of patients' lives.

Costi diretti del solo farmaco per 3 anni di terapia / pz

1.125.000 dollari

=

986669.0054 euro

NEWSFOCUS

Science giugno 2014

Can Down Syndrome Be Treated?

People with Down syndrome are signing up for trials of several drugs aimed at helping their cognitive impairment, even as researchers explore more radical ideas to "cure" the genetic disorder

"I think this current generation of **parents** is looking for the next step **beyond acceptance** and inclusion." —Robert Schoen, Research Down Syndrome

Although the prospect of treating Down syndrome at an early age, or even in the womb, is still far off, one geneticist now calls it **"an achievable goal."**

Spegnimento di un cromosoma 21

Modello iPS

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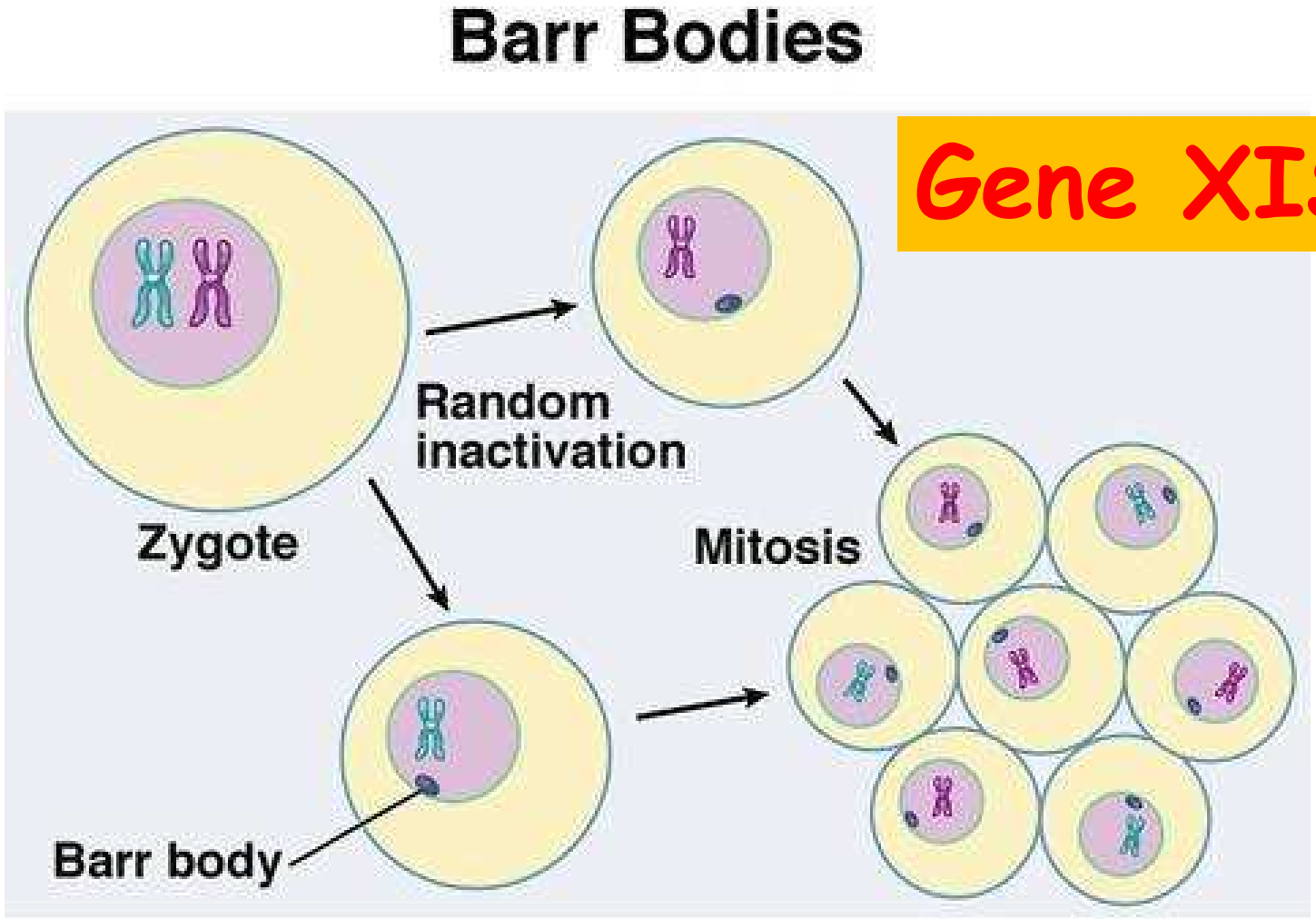
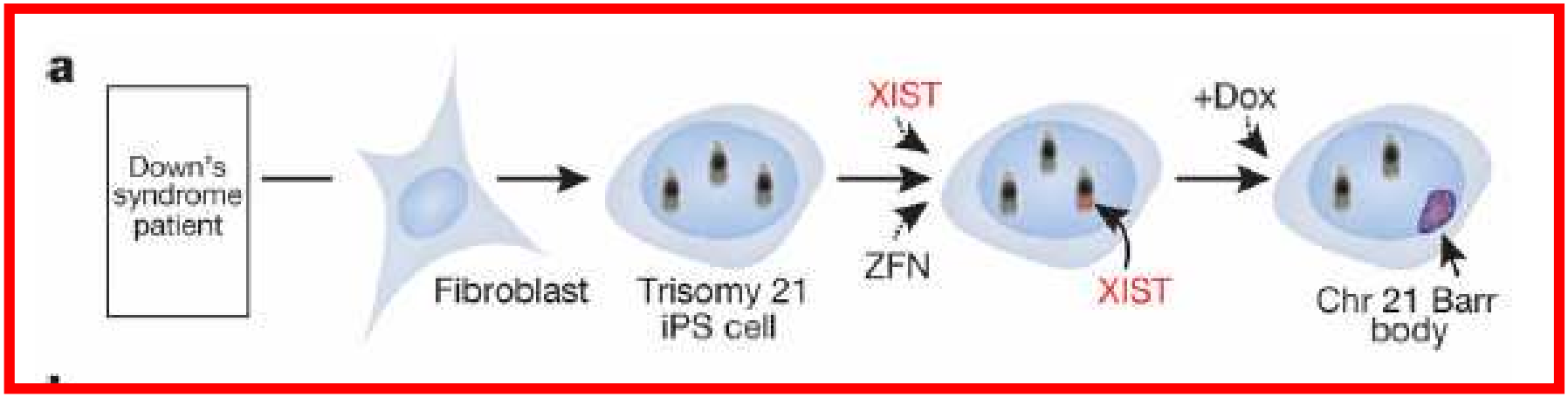


Published in final edited form as:
Nature. 2013 August 15; 500(7462): . doi:10.1038/nature12394.

Translating Dosage Compensation to Trisomy 21

Jun Jiang[1], **Yuanchun Jing**[1], **Gregory J. Cost**[2], **Jen-Chieh Chiang**[1], **Heather J. Kolpa**[1], **Allison M. Cotton**[3], **Dawn M. Carone**[1], **Benjamin R. Carone**[1], **David A. Shivak**[2], **Dmitry Y. Guschin**[2], **Jocelynn R. Pearl**[2], **Edward J. Rebar**[2], **Meg Byron**[1], **Philip D. Gregory**[2], **Carolyn J. Brown**[3], **Fyodor D. Urnov**[2], **Lisa L. Hall**[1], and **Jeanne B. Lawrence**[1,*]

[1]Department of Cell and Developmental Biology, University of Massachusetts Medical School, 5 Lake Avenue North, Worcester, MA 01655



Basi bio-anatomiche della ID nella S di Down

- Riduzione del numero di neuroni (spt nel cervelletto , ippocampo e corteccia frontale)
- Alterazione della maturazione neuronale (ridotta ramificazione dendritica, riduzione della densità delle spine dendritiche)
- Cambiamenti più subdoli a livello cellulare che interferiscono con i processi di signalling

Table 1. Candidate dosage sensitive genes on chromosome 21causing DS phenotype (11, 23, 24)

Gene Symbol	Full Name	Location
APP	amyloid beta (A4) precursor protein	21q21.2|21q21.3
OLIG1	oligodendrocyte transcription factor 1	21q22.11
OLIG2	oligodendrocyte lineage transcription factor 2	21q22.11
DYRK1A	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	21q22.13
DSCAM	Down syndrome cell adhesion molecule	21q22.2
SYNJ1	synaptojanin 1	21q22.2
JAM2	junctional adhesion molecule 2	21q21.2
SIM2	single-minded homolog 2 (Drosophila)	21q22.2|21q22.13
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	21q22.3
PTTG1IP	pituitary tumor-transforming 1 interacting protein	21q22.3
ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif 1	21q21.3
ITSN1	intersectin 1	21q22.1-q22.2
SYNJ11	synaptojanin 1	21q22.2
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	21q22.3
ETS2	ETS proto-oncogene 2, transcription factor	21q22.3
SLC19A1	solute carrier family 19 member 1	21q22.3
COL6A1	collagen type VI alpha 1	21q22.3

Inhibition of DYRK1A activity has a positive impact in Dyrk1A transgenic models

All this evidence obtained in Dyrk1A transgenic mice suggests that treatment with EGCG may be exploited in DS to improve brain functional alterations due to triplication of DYRK1A

278 DOI 10.1002/mnfr.201300325 Mol. Nutr. Food Res. 2014, 58, 278–288

RESEARCH ARTICLE

Epigallocatechin-3-gallate, a DYRK1A inhibitor, rescues cognitive deficits in Down syndrome mouse models and in humans

Rafael De la Torre[1,2,3], Susana De Sola[1], Meritxell Pons[3,4], Arnaud Duchon[5], María Martínez de Lagran[3,4], Magí Farré[1,6], Montserrat Fitó[2], Bessy Benejam[7], Klaus Langohr[1,8], Joan Rodriguez[1], Mitona Pujadas[1,2], Jean Charles Bizot[9], Aída Cuenca[1,10], Nathalie Janel[11], Silvina Catuara[4], Maria Isabel Covas[2], Henri Blehaut[12], Yann Herault[5], Jean Marie Delabar[10] and Mara Dierssen[3,4]

L'epigallocatechina gallato (o EGCG) è un tipo di catechina ed è la più abbondante catechina nel tè, e in particolare nel tè verde. Ha azione un antiossidante

Neurogenesis ›
Volume 4, 2017 - Issue 1

Journal homepage

Commentary

Epigallocatechin gallate: A useful therapy for cognitive disability in Down syndrome?

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Article: e1270383 | Received 30 Sep 2016, Accepted 02 Dec 2016, Published online: 02 Feb 2017

Download citation http://dx.doi.org/10.1080/23262133.2016.1270383 Check for updates

In conclusion, the available data in mouse models of DS show that EGCG may partially improve trisomy-due brain and behavioral defects, but does not rescue them. Data in individuals with DS show that three months of treatment with green tea extracts containing EGCG exert some benefits on cognitive performance but that these effects disappear with time.[17] This fits in with the disappearance of the effects of EGCG in the Ts65Dn mouse model.[20] However, it is important to note that in individuals with DS treatment with EGCG plus cognitive training for 12 months leads to effects that are partially retained after

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2014
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Published by John Wiley & Sons Ltd

CLINICAL GENETICS

doi: 10.1111/cge.12364

Social and Behavioural Research in Clinical Genetics

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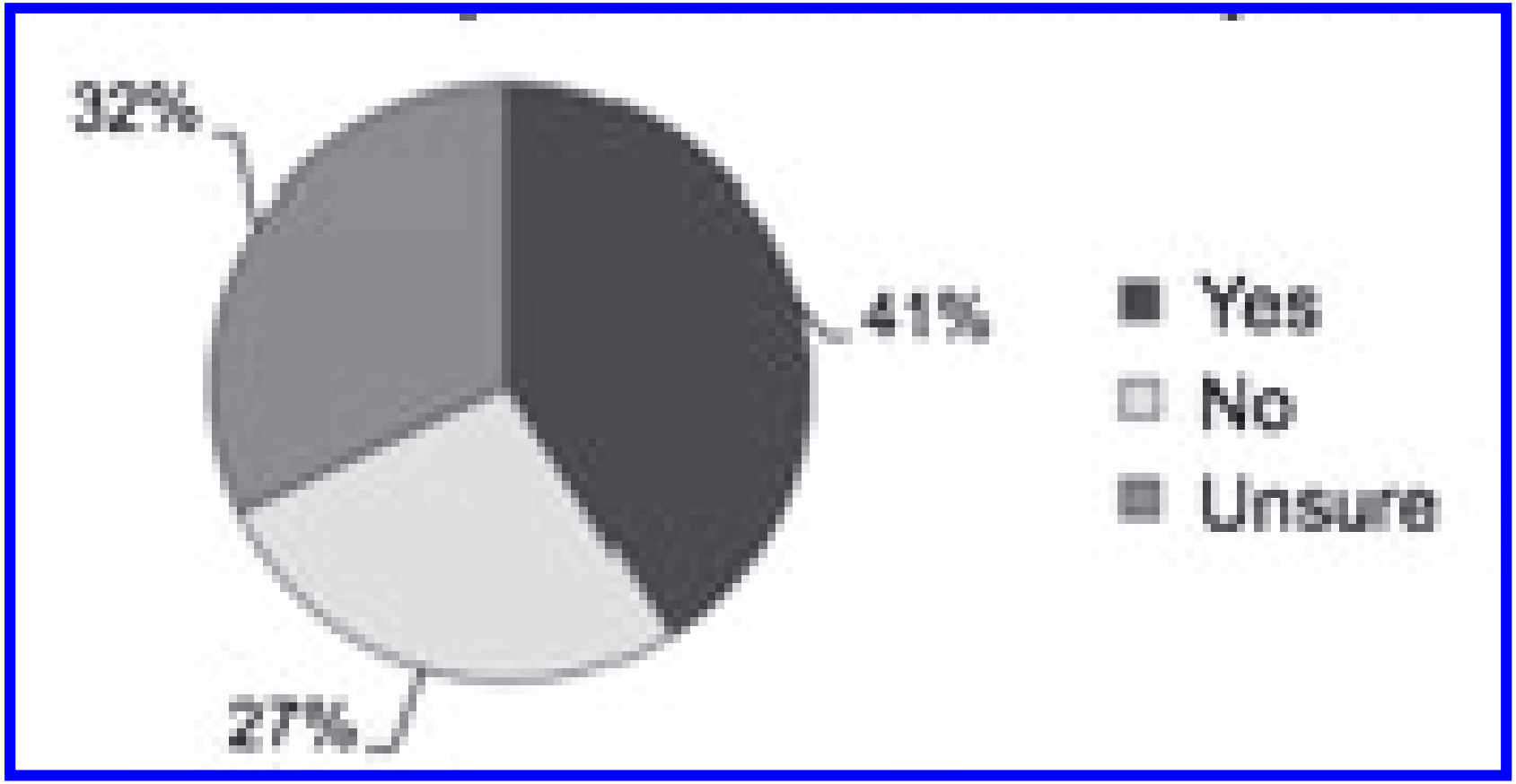
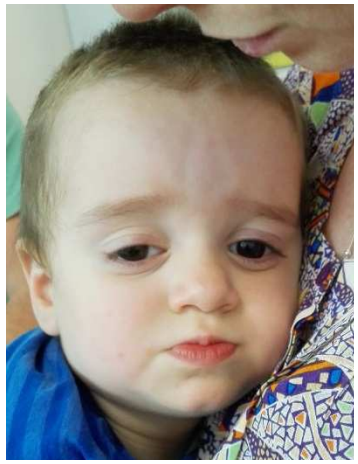
A 'cure' for Down syndrome: what do parents want?

Questionario promosso da
Lower Mainland Down Syndrome Society
British Columbia Canada

101 risposte su 246 inviti (41%)

Se fosse possibile «curare» tuo figlio con SD lo vorresti fare ?





Martino
24 mesi

- Accrescimento staturo-ponderale ai limiti di norma
- Ritardo psicomotorio
- Quadro comportamentale nell'ambito dello spettro autistico
- Assenza di malformazioni maggiori
- Non deficit visivi ed uditivi

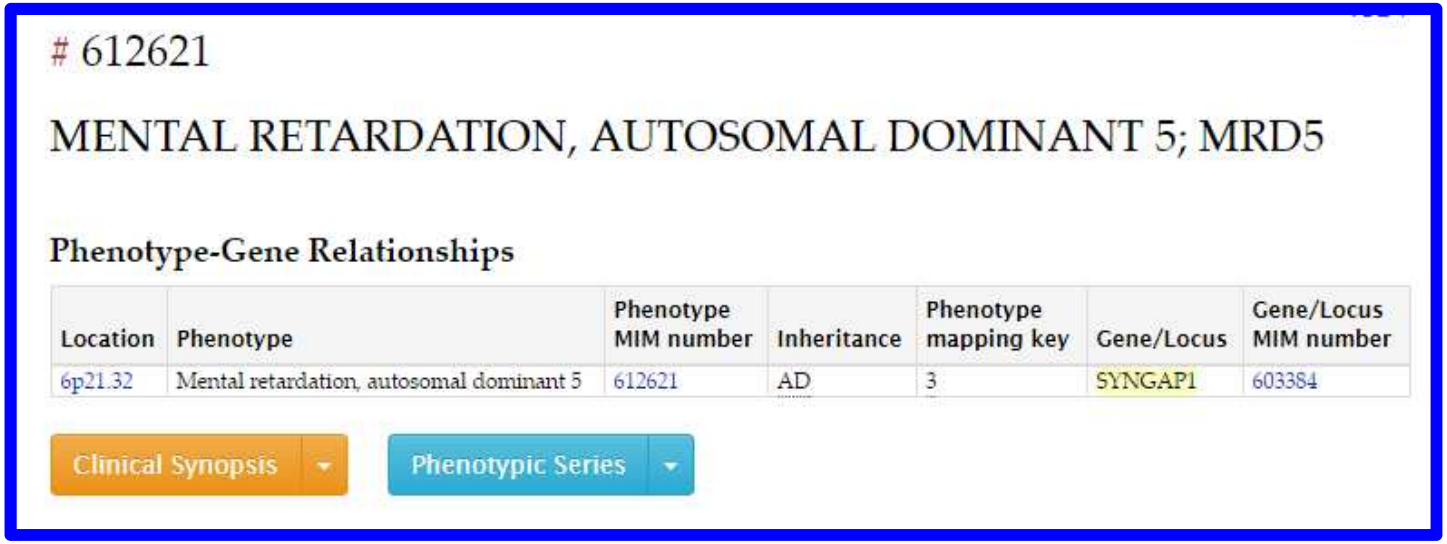
Accertamenti eseguiti
arrayCGH nella norma

Tecniche: Analisi mediante sequenziamento di nuova generazione (NGS) dei geni MECP2, CDKL5, FOXG1, MEF2C associati alla sindrome di Rett e dei geni di patologie in diagnosi differenziale SCN1A, PCDH19 (Dravet), STXBP1, UBE3A (Angelman), SYNGAP1.

CONCLUSIONI DIAGNOSTICHE:

Il sequenziamento dei geni analizzati non ha evidenziato la presenza di varianti patogenetiche nei geni MECP2, CDKL5, FOXG1, MEF2C, TCF4, UBE3A, STXBP1, SCN1A, PCDH19.

E' stata identificata nel gene SYNGAP1 (NM__006772), la presenza della variazione nucleotidica c.2059C>T che secondo le predizioni porta alla proteina tronca p.(Arg687*).Tale variante non è mai stata riportata in letteratura e nei database genomici (HGMD, 1000 Genomes ed ExAC), non è presente nel campione dei genitori ed è quindi "de novo". Mutazioni trasmesse con modalità dominante in questo gene sono associate a quadri clinici eterogenei di disabilità intellettiva e/o autismo e/o epilessia idiopatica generalizzata (Parker et al, 2015; von Stülpnagel C et al, 2015; Tan C et al, 2016).



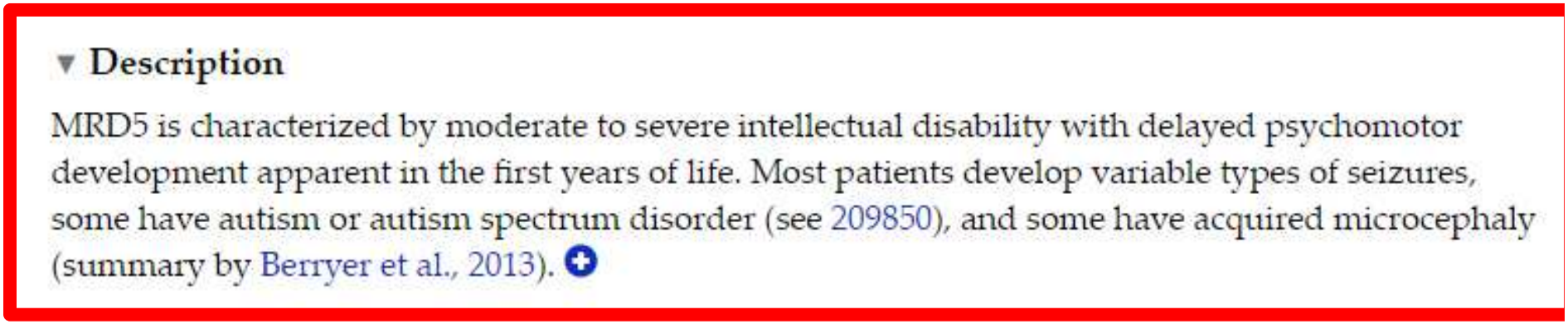
612621

MENTAL RETARDATION, AUTOSOMAL DOMINANT 5; MRD5

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
6p21.32	Mental retardation, autosomal dominant 5	612621	AD	3	SYNGAP1	603384

Clinical Synopsis | Phenotypic Series



Description

MRD5 is characterized by moderate to severe intellectual disability with delayed psychomotor development apparent in the first years of life. Most patients develop variable types of seizures, some have autism or autism spectrum disorder (see 209850), and some have acquired microcephaly (summary by Berryer et al., 2013).

Condizioni ultra rare

* noti i problemi
* noto il difetto di base
* ignota la storia naturale
* ignota la terapia

Il vero farmaco orfano…….

è la riabilitazione !!

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Pediatria della disabilità

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Risultati concreti della pediatria della disabilità

- OGGI => Garantire a tutti i pazienti il miglior stato di salute possibile e a tutte le famiglie la miglior qualità di vita possibile

- IN PROSPETTIVA => Permettere a quei malati rari per i quali la ricerca sta per offrire nuove prospettive terapeutiche di giovarsene essendo nelle condizioni ottimali per essere arruolati in trials

Grazie per l'attenzione