TRISOMIA 21 : LA TERAPIA

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Sindrome di Down (Trisomia 21)

- **La più frequente causa costituzionale di disabilità intellettiva**

- **1/400 concepiti**
- **1/700 nati vivi**

Migliore qualità ed incremento speranza di vita nella SD

- **Aspettativa di vita media**
- 1929 : 9 anni
- 1947: 12-15 anni
- 1961: 18-19 anni
- ……..
- 2000: 45-46 anni (45-65 a = 13%)
- 2010: >60 anni

DATI EPIDEMIOLOGICI

- In Italia vivono circa 38.000 persone con SD di cui:

- ~ 10.000 tra 0 e 17 anni
- ~ 21.500 tra 18 e 44 anni
- ~ 6.500 > 44 anni

mod. Formica U. 2000

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

Survival among people with Down syndrome: a nationwide population-based study in Denmark

Jin Liang Zhu, PhD[1], Henrik Hasle, MD, PhD[2], Adolfo Correa, MD, PhD[3], Diana Schendel, PhD[3], J.M. Friedman, MD, PhD[4], Jørn Olsen, MD, PhD[1] and Sonja A. Rasmussen, MD, MS[3]

Purpose: Several studies have shown substantially longer survival among persons with Down syndrome in recent decades. We examined survival patterns among Danish persons with Down syndrome by karyotype.

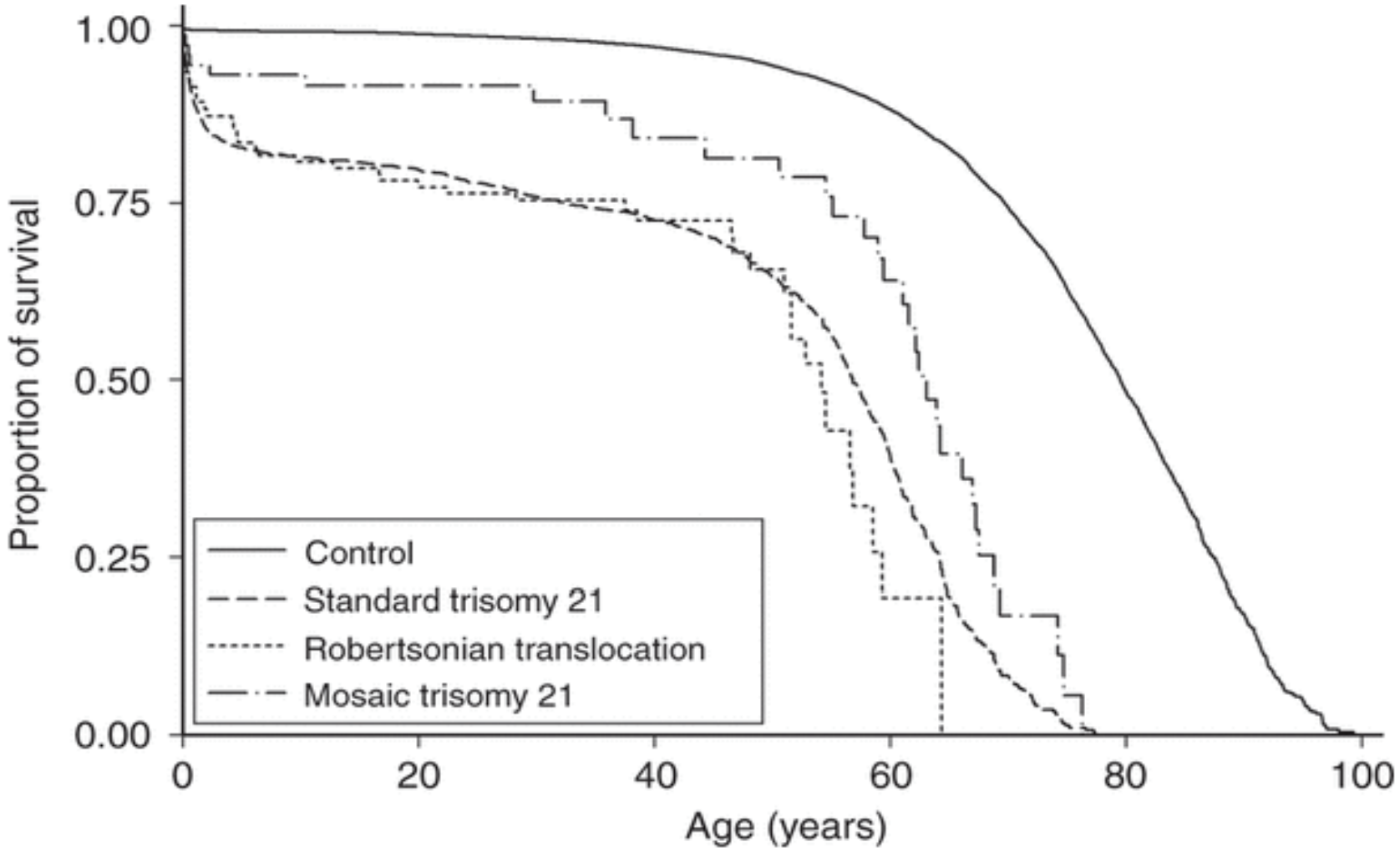
Methods: A national cohort of 3,530 persons with Down syndrome identified from the Danish Cytogenetic Register and a reference cohort of persons without Down syndrome randomly selected from the general population were followed from 1 April 1968 to 15 January 2009 by linkages to the Register of Causes of Death and the Civil Registration System.

Results: Overall, persons with Down syndrome had higher mortality than the reference cohort but to a lesser degree for persons with mosaic trisomy 21 than for persons with standard trisomy 21 or with Robertsonian translocations (hazard ratio 4.98 (95% confidence interval 3.51–7.08), 8.94 (8.32–9.60), and 10.23 (7.50–13.97), respectively). Among persons with Down syndrome born after April 1968, more recent birth cohorts had lower mortality rates than older birth cohorts, which was largely due to declining mortality among persons with Down syndrome who also had congenital heart defects.

Conclusion: Recent birth cohorts of persons with Down syndrome experienced declining mortality, likely due to treatment for congenital heart defects, and persons with mosaic trisomy 21 had better survival than persons with other Down syndrome karyotypes.

Genet Med 2013:15(1):64–69

Key Words: congenital heart defects; Down syndrome; mortality; mosaic trisomy 21; survival



Kaplan–Meier survival curves for three karyotypes of persons with Down syndrome and reference cohort, Denmark, 1968–2009. (Number of persons and deaths: 3,272 and 1,000, respectively, for persons with standard trisomy 21, 144 and 41, respectively, for persons with Robertsonian translocations, 114 and 32, respectively, for persons with mosaic trisomy 21, and 70,590 and 4,683, respectively, for the reference cohort)

Fattori che hanno portato ad un significativo aumento della sopravvivenza

1. ridotta mortalità infantile
2. miglioramento delle cure mediche e chirurgiche
3. programmazione di interventi di carattere sociale
4. programmi di precoce stimolazione motoria/intellettiva
5. disponibilità servizi territoriali
6. promozione dell'autonomia del soggetto

PRIORITA' NELL'ASSISTENZA DELLE PERSONE CON S.DOWN

1. CONTROLLI DI SALUTE

2. DEFINIZIONE DI PERCORSI ASSISTENZIALI INTEGRATI

Problematiche cliniche

PROBLEMI ORL
75%

PROBLEMI VISIVI
60%

CARDIOPATIE CONGENITE
40-50%

DISTURBI GASTROINTESTINALI
>12%

DISTIROIDISMI
12%

PROBLEMATICHE EMATOLOGICHE
≤10%

CELIACHIA
5%

American Academy of Pediatrics, 2011

Linee guida del follow-up

Linee Guida Multidisciplinari per l'Assistenza Integrata
alle Persone con Sindrome di Down e alle loro Famiglie

European Down Syndrome Association (EDSA)
www.edsa.info

The "EDSA essentials" n. 2
Documento pubblicato dalla EDSA nel Giugno 2005

Istituto Superiore di Sanità 2007

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS

Guidance for the Clinician in Rendering Pediatric Care

Clinical Report—Health Supervision for Children With Down Syndrome

American Academy of Pediatrics, 2011

SINDROME DI DOWN: 150 ANNI DI CAMMINO

Follow-up – Protocollo BOLOGNA

	N	3 m	6 m	9 m	12 m	18 m	24 m	36 m	Ann.
Anamnesi	•	•	•	•	•	•	•	•	•
Valutazione auxo	•	•	•	•	•	•	•	•	•
Valutazione neuromotoria	•	•	•	•	•	•	•	•	•
Prelievo venoso	S		•		•	•	•	•	•
ECO encefalo	•	•							
ECO addome	•								
Visita cardio	•				•				
Visita ORL + ABR	S	•	•		•			•	
Visita oculistico/ ortottica	S	•		•				•	
Visita odontoiatrica			•			•		•	

S= screening

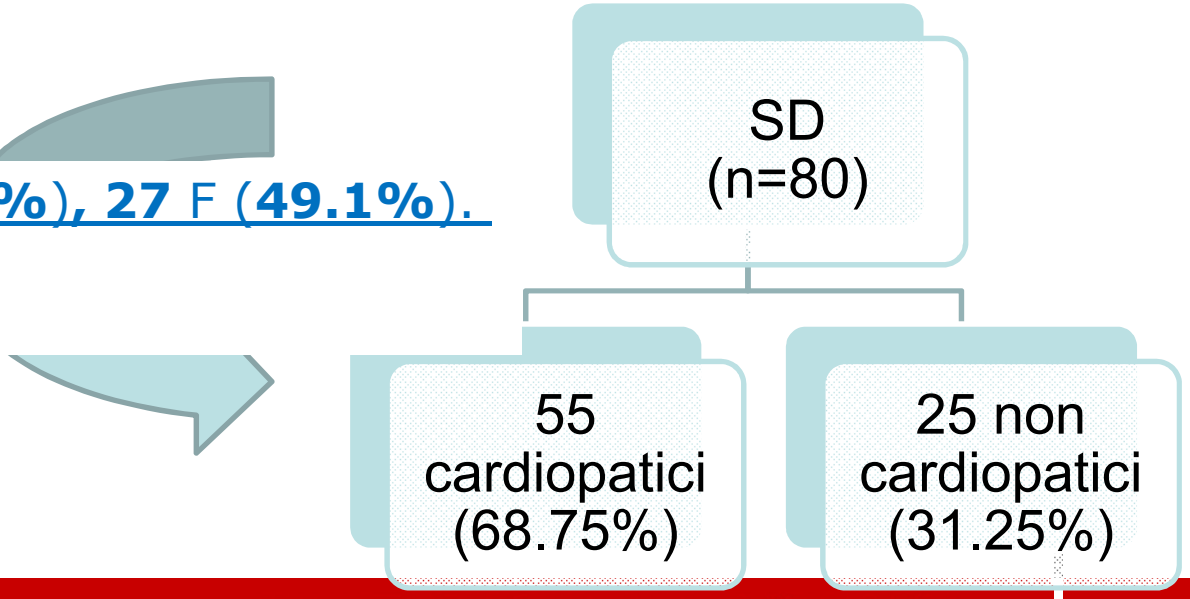
Rx rachide cervicale a 8 – 10 anni

CARDIOPATIA CONGENITA
ANNI 1998-2015
(AOUBO)

Nati tot: 65684
Nati SD: 80
Prev. nascita: 1.22 x 1000 nati (1/821)

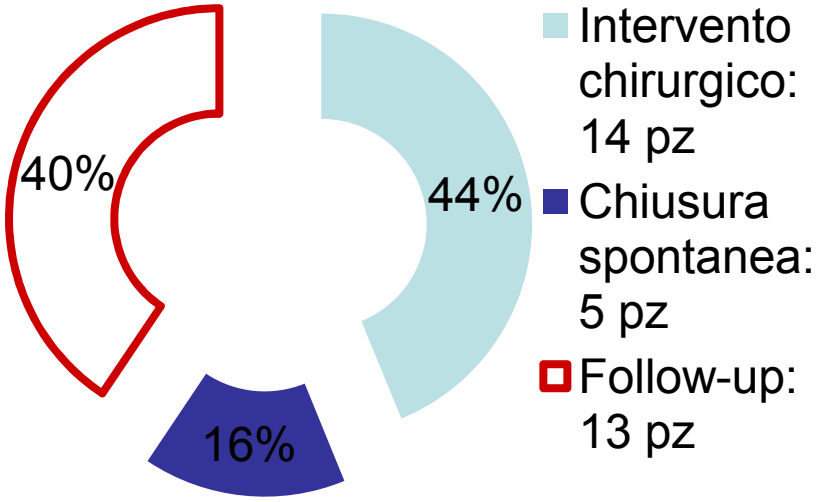
- **Genere:** 42 M (**52.5 %**), 38 F (**47.5%**).
- Sex-ratio M:F = 1.1
- **Età media: 7.5 anni** (6 mesi – 12.2 anni).

Genere: 28 M (**50.9%**), **27** F (**49.1%**).
Sex-ratio M:F = 1.03

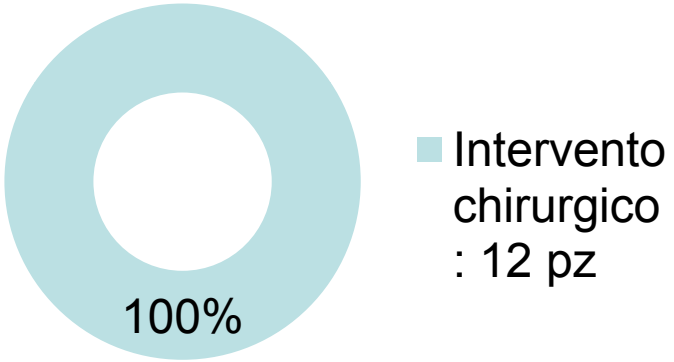


Trattamento delle CC e del CAV

- Pazienti cardiopatici



- **Pazienti con CAV**



Il timing chirurgico ottimale è compreso tra i 6 mesi e l'anno di vita per evitare l'insorgenza di complicanze soprattutto a carico del sistema vascolare polmonare (>R nella SD).

MALATTIA CELIACA (CD)

ANNI 1998-2017

(AOUBO)

Nati tot: 72.347
Nati SD: 92 (44 F , 48 M)
Prev. nascita: 1.3 ‰ x 1000 nati (1/786)

Genere: 48 M (**52.2 %**), **44** F (**47.8%**).
Sex-ratio M:F = 1.1
Età media: 8.8 anni (6 mesi – 14.1 anni).

- **Screening per MC ± biopsia/HLA → 4 CD**
- **Prevalenza CD → 4,4% (1/23)**

Malattia Celiaca (CD)

Oltre ai 4 pz (3 F, 1 M) nati al Sant'Orsola, sono stati identificati, presso l'Amb.Spec. MR dell'UO di Neonatologia dell'AOU di BO, altri 8 pz (5 F, 3 M) nati presso altri punti nascita e seguiti in FU

- Dei 12 pz in toto con CD:
  - 4 CD classica , 4 CD atipica , 4 CD silente
  - 5/7 presentavano HLA-DQ2 , 2/7 presentava HLA-DQ8
  - 6/12 patologie autoimmuni
  - 7/12 cardiopatia congenita

	Pz.1 (A.E.)	Pz.2 (D.M.)	Pz.3 (S.A.)	Pz.4 (D.R.U.)	Pz.5 (E.F.)	Pz.6 (B.C.)
Età Diagnosi	3 anni	14 anni	7anni + 8m	15 anni	2 anni + 5m	2 anni + 6m
Biopsia	SI	------	------	------	SI	SI
HLA	DQ2	DQ2	------	------	DQ2	DQ2
Forma	Atipica	Silente	Atipica	Silente	Silente	Silente
Patologia Associata	Ipotiroidismo DM tipo I	Ipertiroidismo	Dermatite Fungina Ric	Tiroidite Autoimm	--------	--------
Malformazione associata	--------	CAV completo	PDA	--------	Pielectasia Renale	CAV completo

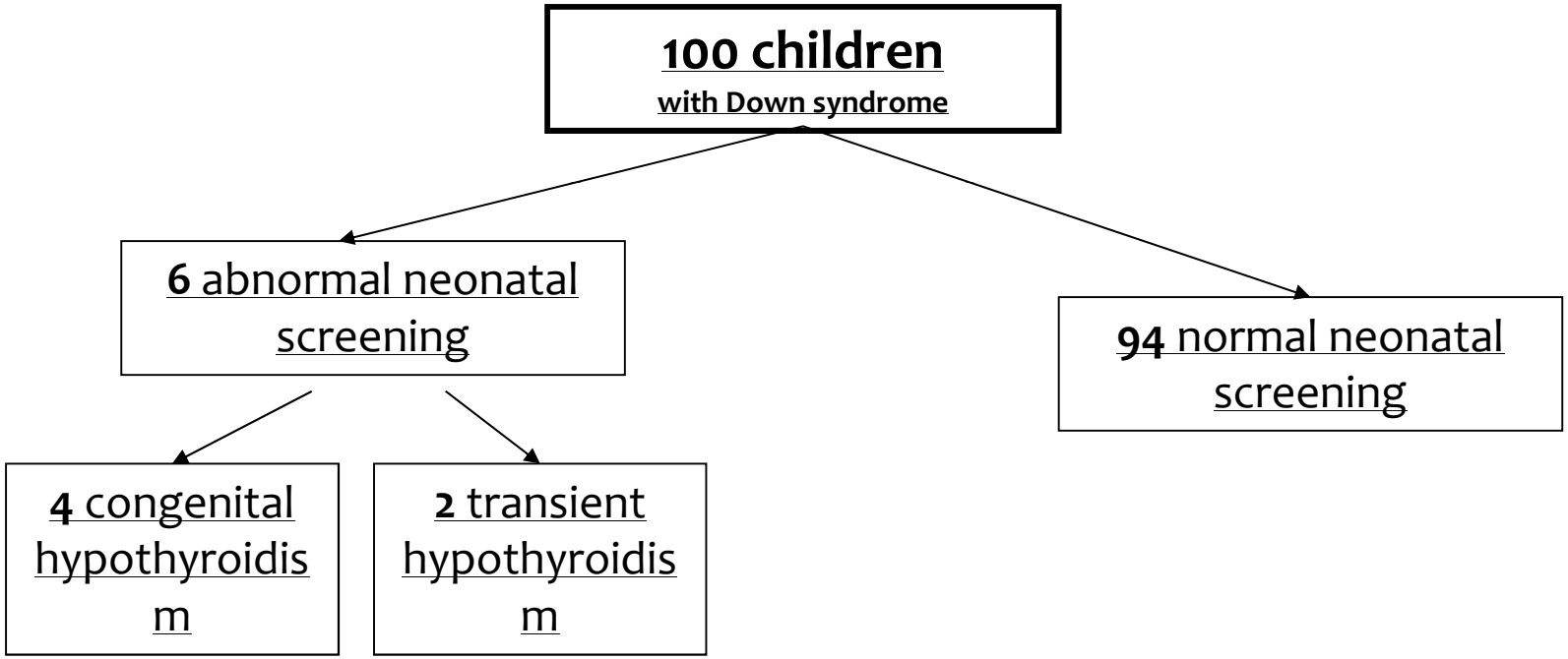
	Pz.7 (M.C.)	Pz.8 (B.M.)	Pz.9 (G.E.)	Pz10 (C.R.S.)	Pz11 (D.C.)	Pz12 (M.E.)
Età Diagnosi	7 anni + 6m	7 anni + 1m	1 anno + 6m	3 anni + 4m	4 anni	4 anni
Biopsia	--------	SI	SI	SI	SI	SI
HLA	DQ8	DQ2	---------	---------	---------	DQ8
Forma	Atipica	Silente	Classica	Classica	Classica	Classica
Patologia Associata	Alopecia	Ipotiroidismo	Ipotiroidismo	----------	----------	----------
Malformazione Associata	DIA	DIA II	DIV	---------	DIA DIV	----------

Role and modalities of thyroid function screening in children with Down syndrome: a prospective cohort study

G, Poletti, A. Rocca, G, D, Rana, A, Cassio, G. Cocchi

eurocat
european surveillance of congenital anomalies

13th EUROCAT Scientific Symposium – Milan, 16th-17th June 2016



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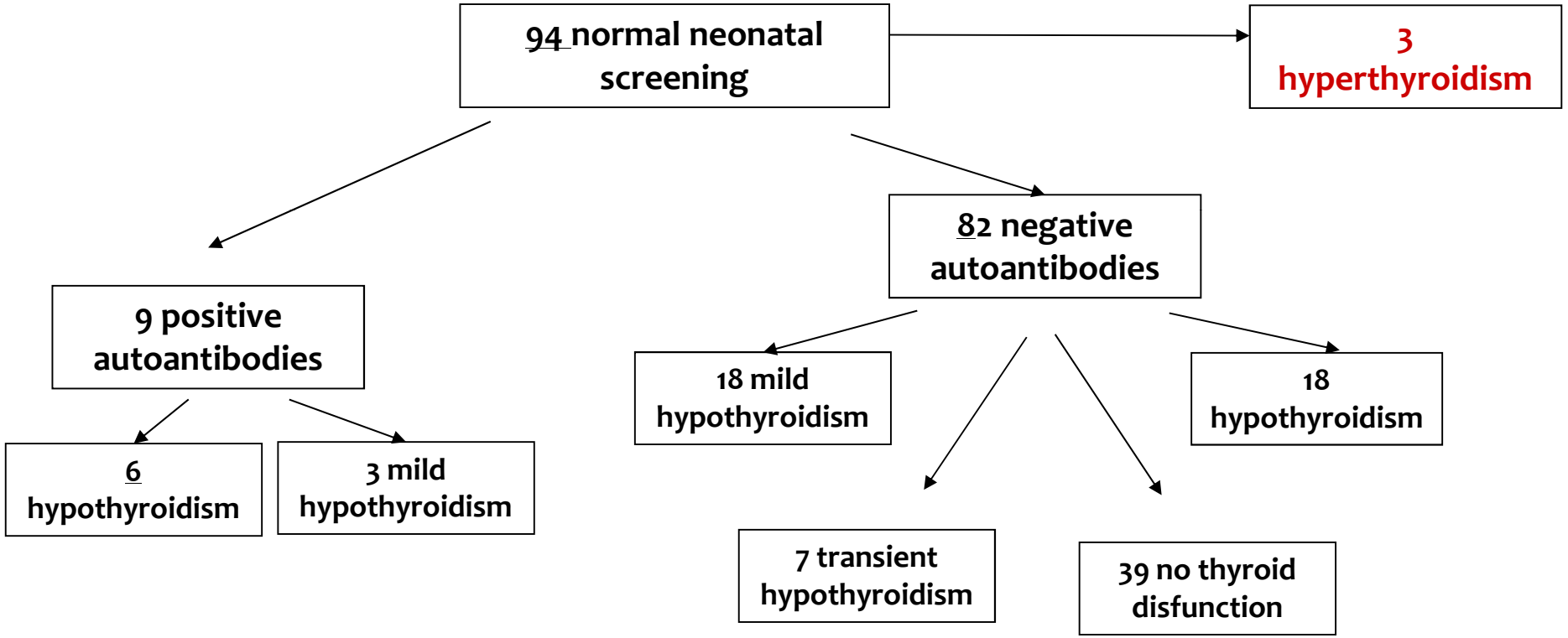

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Autoantibodies positivity is associated with a higher risk to develop **hypothyroidism**
(**p: 0.009 – OR: 0.14**)

Subclinical hypothyroidism in the first years of life in patients with Down syndrome

Cristina Claret[1,2], Albert Goday[1–3], David Benaiges[1,2], Juan J. Chillarón[1,2], Juana A. Flores[1,2], Elisa Hernandez[1,2], Josep M. Corretger[3] and Juan F. Cano[1,2]

Table 2. Factors associated with remission of subclinical hypothyroidism

	Remission	Persistence	*P*
Negative for antibodies to TPO/TGB, *n* (%)	35 (89.7%)	6 (42.9%)	<0.05

FT4, free thyroxine; TGB, thyroglobulin; TPO, thyroperoxidase; TSH, thyroid-stimulating hormone.

Ten-Year Longitudinal Study of Thyroid Function in Children with Down's Syndrome

Lorenzo Iughetti[a] Barbara Predieri[a] Patrizia Bruzzi[a] Flavia Predieri[a] Giulia Vellani[a] Simona Filomena Madeo[a] Livia Garavelli[b] Ornella Biagioni[c] Giorgio Bedogni[d] Mauro Bozzola[e]

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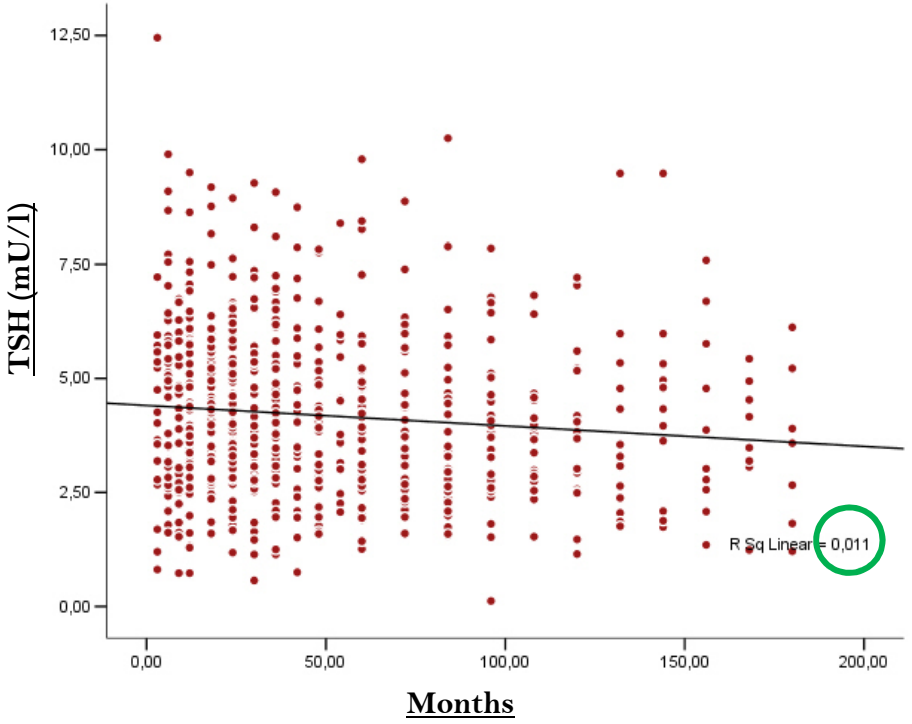
In children with Down syndrome **subclinical hypothyroidism** is a **self-limiting** condition



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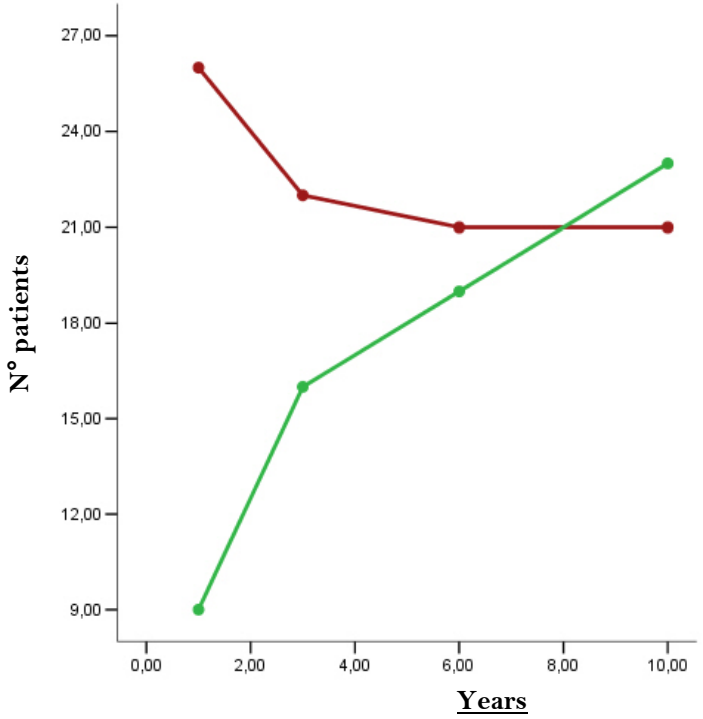


Red line: TSH between **5-10 mU/l** **[no therapy]**

Green line: TSH up to **10 mU/l** **[therapy]**

Median age: 2,8 years

4 children started therapy **at 3 months** of age

We suggest to screen thyroid function **every 3 months during the first year of life** and **then annually.**

Thyroid function should be monitored **dosing TSH, thyroid hormone and autoantibodies.**

If TSH is up to 10 UI/L, it is reasonable to treat the patient initially but it's important to re-evaluate off treatment at a later date, to see if the subclinical hypothyroidism has resolved.

IMPORTANZA DEL FOLLOW UP

	N	3 m	6 m	9 m	12 m	18 m	24 m	36 m	Ann.
Anamnesi	•	•	•	•	•	•	•	•	•
Valutazione auxo	•	•	•	•	•	•	•	•	•
Valutazione neuromotoria	•	•	•	•	•	•	•	•	•
Prelievo venoso	S		•		•	•	•	•	•
ECO encefalo	•	•							
ECO addome	•								
Visita cardio	•				•				
Visita ORL + ABR	S	•	•		•			•	
Visita oculistico/ ortottica	S	•		•				•	
Visita odontoiatrica			•			•		•	

S = Screening

Rx rachide cervicale a 8 – 10 anni

Sindrome di Down

Ricerca di una terapia specifica per la disabilità cognitiva

Attualmente non esistono trattamenti farmacologici riconosciuti efficaci ed in grado di migliorare in modo significativo i <u>disturbi cognitivi</u> associati alla Sindrome di Down

Front Behav Neurosci. 2015; 9: 265.
Published online 2015 Oct 6. doi: 10.3389/fnbeh.2015.00265
PMCID: PMC4594009
PMID: 26500515

Timing of therapies for Down syndrome: the sooner, the better

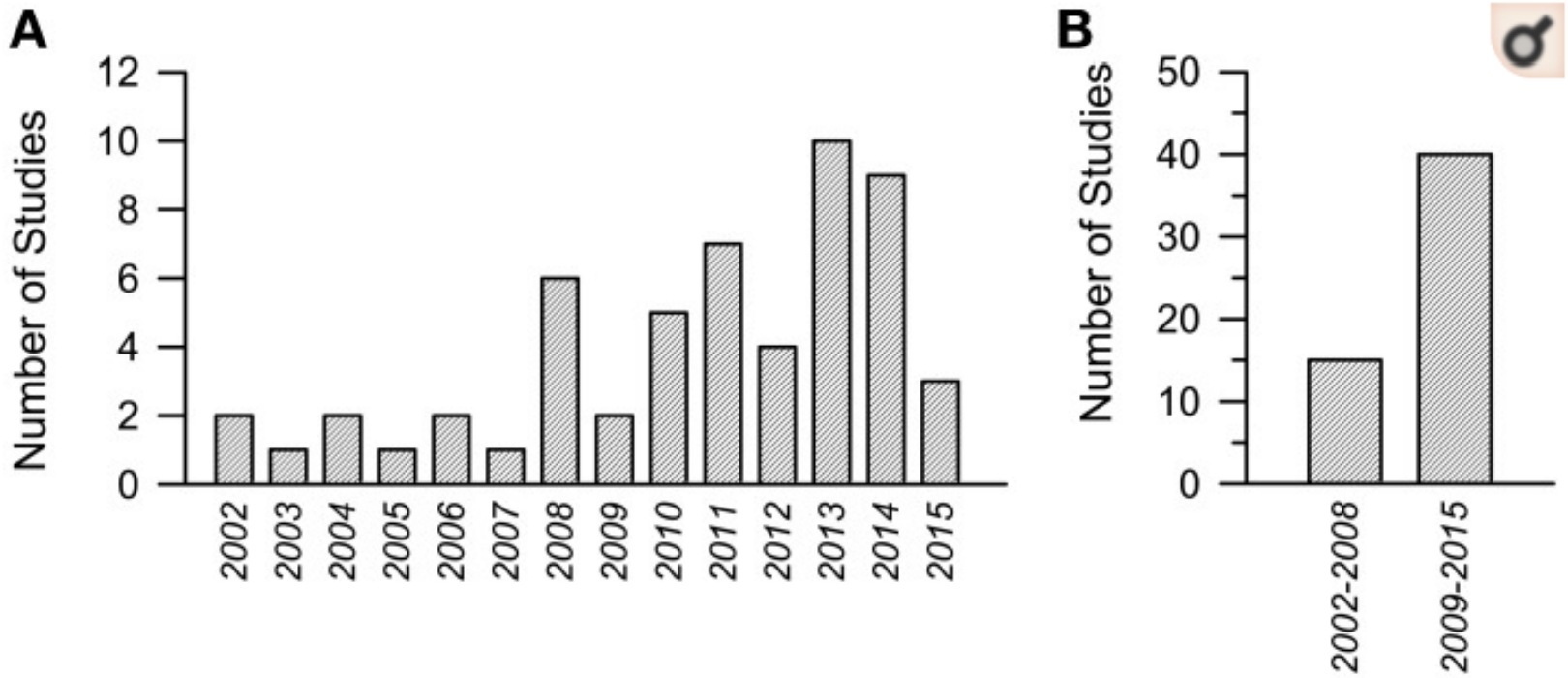
Fiorenza Stagni, Andrea Giacomini, Sandra Guidi, Elisabetta Ciani, and Renata Bartesaghi*

Abstract

Go to:

Intellectual disability (ID) is the unavoidable hallmark of Down syndrome (DS), with a heavy impact on public health. Accumulating evidence shows that DS is characterized by numerous neurodevelopmental alterations among which the reduction of neurogenesis, dendritic hypotrophy and connectivity alterations appear to play a particularly prominent role. Although the mechanisms whereby gene triplication impairs brain development in DS have not been fully clarified, it is theoretically possible to correct trisomy-dependent defects with targeted pharmacotherapies. This review summarizes what we know about the effects of pharmacotherapies during different life stages in mouse models of DS. Since brain alterations in DS start to be present prenatally, the prenatal period represents an optimum window of opportunity for therapeutic interventions. Importantly, recent studies clearly show that treatment during the prenatal period can rescue overall brain development and behavior and that this effect outlasts treatment cessation. Although late therapies are unlikely to exert drastic changes in the brain, they may have an impact on the hippocampus, a brain region where neurogenesis continues throughout life. Indeed, treatment at adult life stages improves or even rescues hippocampal neurogenesis and connectivity and hippocampal-dependent learning and memory, although the duration of these effects still remains, in the majority of cases, a matter of investigation. The exciting discovery that trisomy-linked brain abnormalities can be prevented with early interventions gives us reason to believe that treatments during pregnancy may rescue brain development in fetuses with DS. For this reason we deem it extremely important to expedite the discovery of additional therapies practicable in humans in order to identify the best treatment/s in terms of efficacy and paucity of side effects. Prompt achievement of this goal is the big challenge for the scientific community of researchers interested in DS.

Keywords: Down syndrome, intellectual disability, mouse models, adult therapies, perinatal therapies


A
Number of Studies
0
2
4
6
8
10
12
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
B
Number of Studies
0
10
20
30
40
50
2002-2008
2009-2015

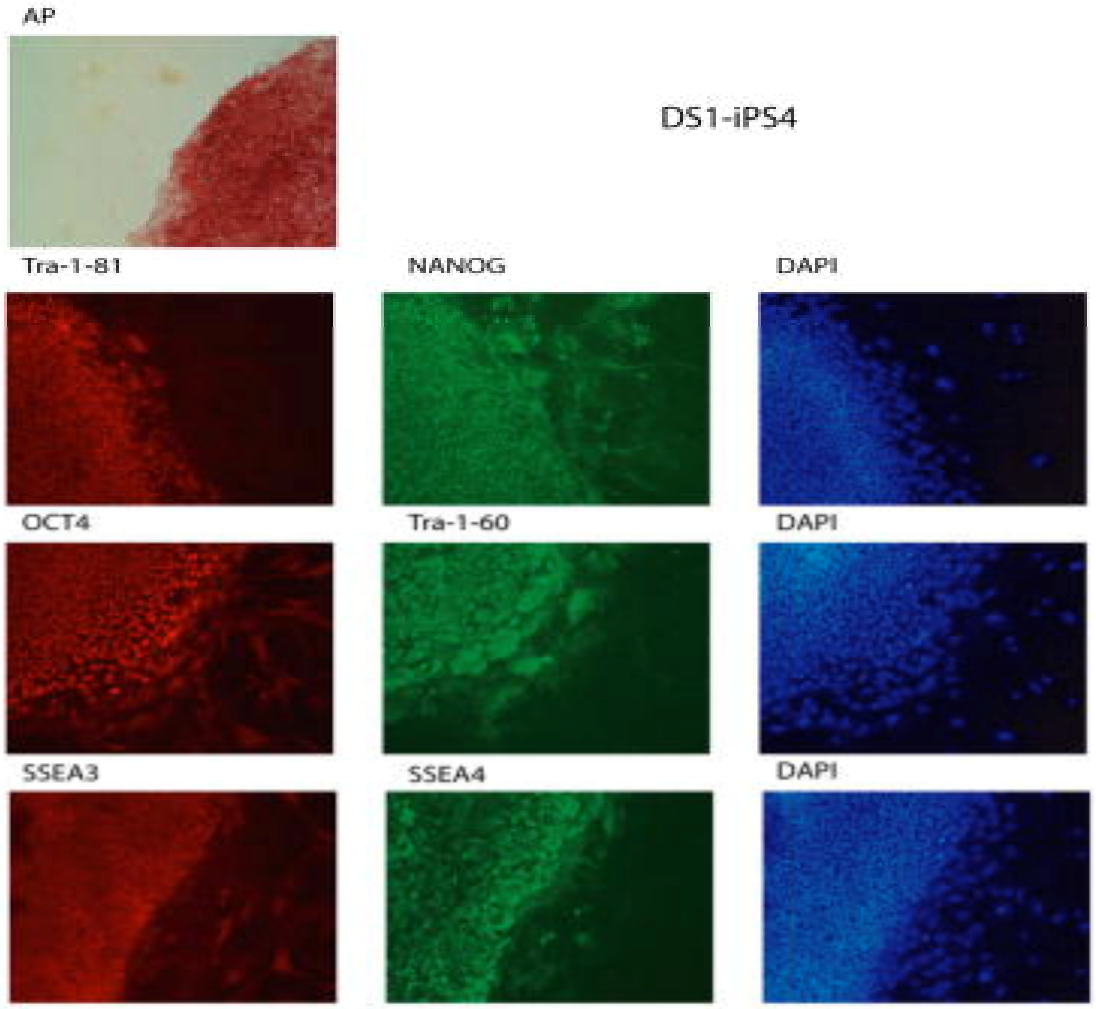
Sindrome di Down (Trisomia 21)
Modelli di studio

1990-1995 - Modello murino

Ts65Dn

Sindrome di Down (Trisomia 21)
Modelli di studio

2008 - Cellule staminali pluripotenti indotte trisomiche



M. Dierssen and R. de la Torre (Eds.)
Progress in Brain Research, Vol. 197
ISSN: 0079-6123

CHAPTER 1

Therapeutic approaches in the improvement of cognitive performance in Down syndrome: past, present, and future

Rafael de la Torre[†,*] and Mara Dierssen[‡]

Sindrome di Down
Ricerca di una terapia

1. **Neurogenesi / Neuroprotezione**
2. Integratori /Antiossidanti
3. Modulazione dei neurotrasmettitori
4. Terapia basata su meccanismi patogenetici

1. Neurogenesi - Neuroprotezione

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., et al., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805–809.

J Neurosci. 2010 Jun 30;30(26):8769-79. doi: 10.1523/JNEUROSCI.0534-10.2010.

Early pharmacotherapy restores neurogenesis and cognitive performance in the Ts65Dn mouse model for Down syndrome.

Bianchi P, Ciani E, Guidi S, Trazzi S, Felice D, Grossi G, Fernandez M, Giuliani A, Calzà L, Bartesaghi R.

Department of Human and General Physiology, University of Bologna, I-40126 Bologna, Italy.

PLoS One. 2012;7(11):e50724. doi: 10.1371/journal.pone.0050724. Epub 2012 Nov 29.

Prenatal treatment prevents learning deficit in Down syndrome model.

Incerti M, Horowitz K, Roberson R, Abebe D, Toso L, Caballero M, Spong CY.

Unit on Perinatal and Developmental Neurobiology, National Institute of Child and Human Development, Bethesda, Maryland,

1.Neurogenesi - Neuroprotezione

2. Neurogenesis stimulation		
2.1 Antidepressants		
2.1.1 Fluoxetine	Ts65Dn Mouse	Clark et al. 2006, Bianchi et al. 2010b, Heinen et al. 2012, Guidi et al. 2013
2.1.2 Lithium	Ts65Dn Mouse	Bianchi et al. 2010a, Contestabile et al. 2013
2.2 Peptide 6 (CNTF)	Ts65Dn Mouse	Blanchard et al. 2011
2.3 Sonic Hedgehog (SHH)	Ts65Dn Mouse	Roper et al. 2006, Das et al. 2013

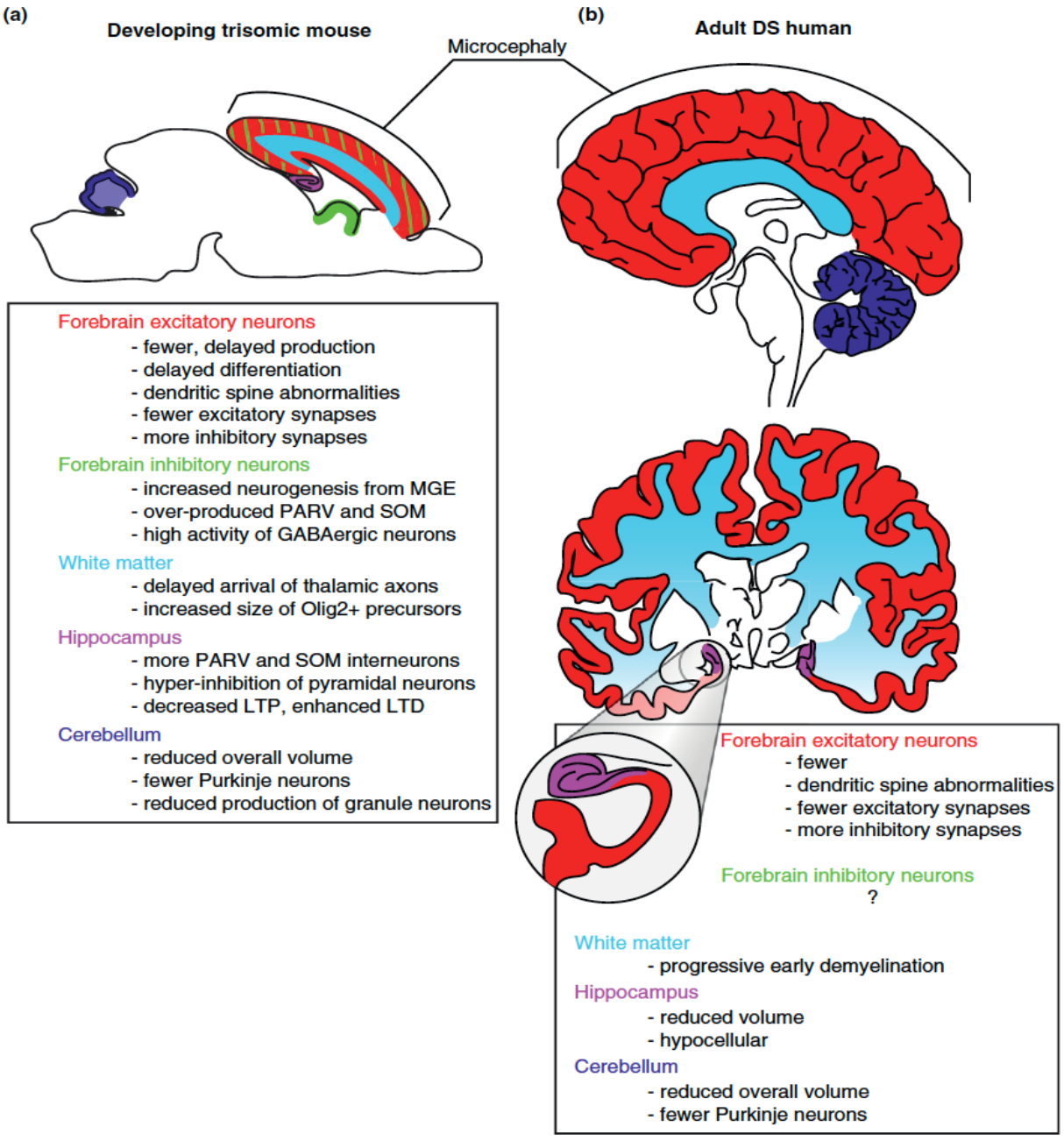
Neurobiology of Disease

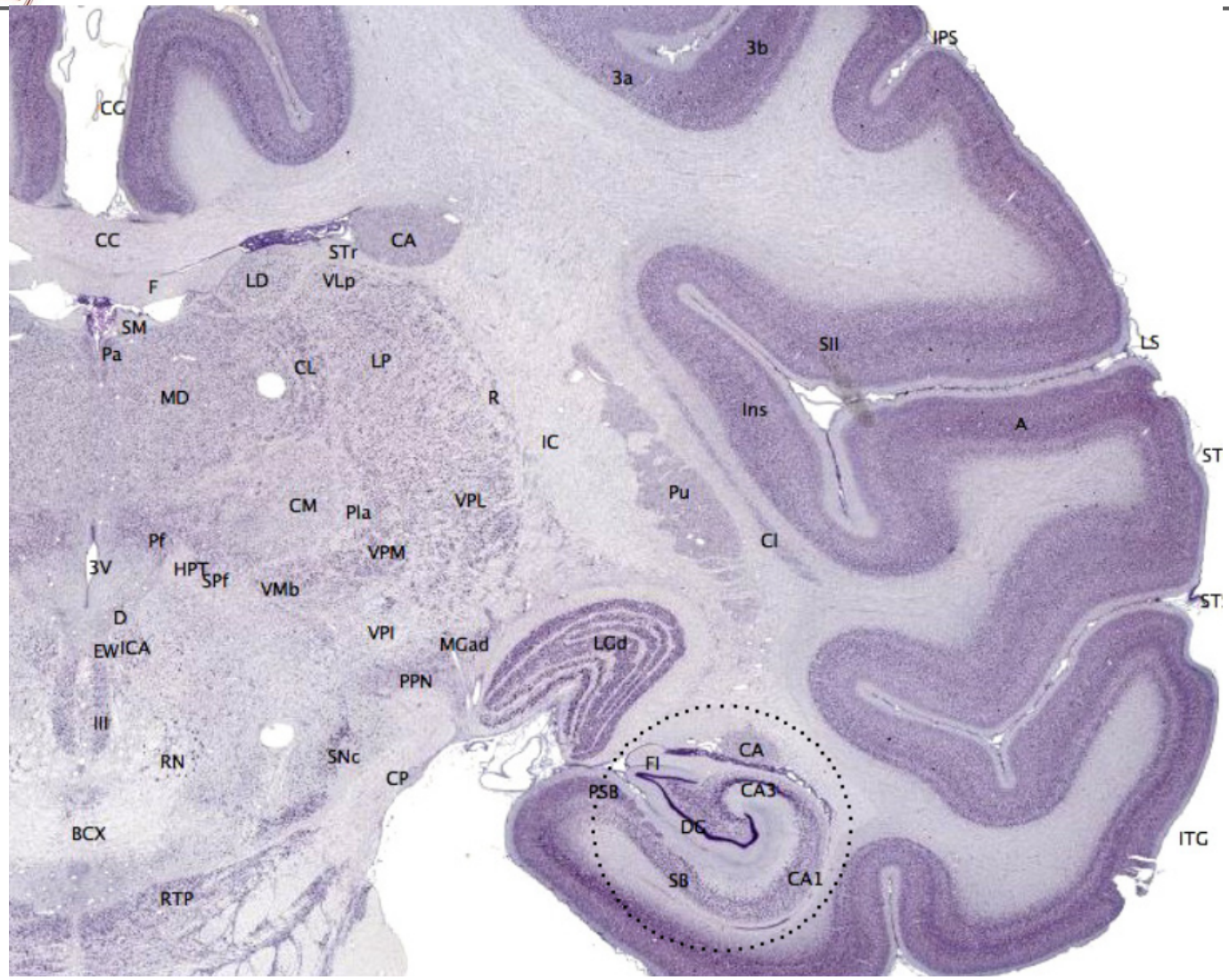
Early Pharmacotherapy Restores Neurogenesis and Cognitive Performance in the Ts65Dn Mouse Model for Down Syndrome

Patrizia Bianchi,[1] Elisabetta Ciani,[1] Sandra Guidi,[1] Stefania Trazzi,[1] Daniela Felice,[1] Gabriele Grossi,[2] Mercedes Fernandez,[3] Alessandro Giuliani,[3] Laura Calzà,[3] and Renata Bartesaghi[1]

[1]Department of Human and General Physiology, University of Bologna, I-40126 Bologna, Italy, [2]Center for Applied Biomedical Research, S. Orsola-Malpighi University Hospital, I-40138 Bologna, Italy, and [3]BioPharmaNet-Department of Veterinary Morphophysiology and Animal Production, University of Bologna, I-40064 Bologna, Italy

Down syndrome (DS) is a genetic pathology characterized by intellectual disability and brain hypotrophy. Widespread neurogenesis impairment characterizes the fetal and neonatal DS brain, strongly suggesting that this defect may be a major determinant of mental retardation. Our goal was to establish, in a mouse model for DS, whether early pharmacotherapy improves neurogenesis and cognitive behavior. Neonate Ts65Dn mice were treated from postnatal day (P) 3 to P15 with fluoxetine, an antidepressant that inhibits serotonin (5-HT) reuptake and increases proliferation in the adult Ts65Dn mouse (Clark et al., 2006). On P15, they received a BrdU injection and were killed after either 2 h or 1 month. Results showed that P15 Ts65Dn mice had notably defective proliferation in the hippocampal dentate gyrus, subventricular zone, striatum, and neocortex and that proliferation was completely rescued by fluoxetine. In the hippocampus of untreated P15 Ts65Dn mice, we found normal 5-HT levels but a lower expression of 5-HT1A receptors and brain-derived neurotrophic factor (BDNF). In Ts65Dn mice, fluoxetine treatment restored the expression of 5-HT1A receptors and BDNF. One month after cessation of treatment, there were more surviving cells in the dentate gyrus of Ts65Dn mice, more cells with a neuronal phenotype, more proliferating precursors, and more granule cells. These animals were tested for contextual fear conditioning, a hippocampus-dependent memory task, and exhibited a complete recovery of memory performance. Results show that early pharmacotherapy with a drug usable by humans can correct neurogenesis and behavioral impairment in a model for DS.


(a)
Developing trisomic mouse
Microcephaly
(b)
Adult DS human
Forebrain excitatory neurons
- fewer, delayed production
- delayed differentiation
- dendritic spine abnormalities
- fewer excitatory synapses
- more inhibitory synapses
Forebrain inhibitory neurons
- increased neurogenesis from MGE
- over-produced PARV and SOM
- high activity of GABAergic neurons
White matter
- delayed arrival of thalamic axons
- increased size of Olig2+ precursors
Hippocampus
- more PARV and SOM interneurons
- hyper-inhibition of pyramidal neurons
- decreased LTP, enhanced LTD
Cerebellum
- reduced overall volume
- fewer Purkinje neurons
- reduced production of granule neurons
Forebrain excitatory neurons
- fewer
- dendritic spine abnormalities
- fewer excitatory synapses
- more inhibitory synapses
Forebrain inhibitory neurons
?
White matter
- progressive early demyelination
Hippocampus
- reduced volume
- hypocellular
Cerebellum
- reduced overall volume
- fewer Purkinje neurons
TRENDS in Neurosciences


3b
IPS
3a
CG
CC
CA
STr
F
LD
VLp
SM
Pa
SII
LS
CL
LP
MD
R
Ins
A
IC
ST
Pu
CM
Pla
VPL
Pf
Cl
VPM
3V
HPT
SPf
VMb
ST
D
VPl
EW
ICA
MGad
LGd
PPN
III
RN
SNc
CP
FI
CA
PSB
CA3
DG
BCX
ITG
SB
CA1
RTP

Prozac contro sindrome di Down, al via la sperimentazione negli Usa e in Italia

Il test nasce da un'idea di ricercatori italiani. Buoni risultati sui topi. "Non è detto che nell'uomo l'effetto sia lo stesso effetto"

Lo leggo dopo | 16 gennaio 2016

POTREBBE essere possibile che il Prozac, uno degli antidepressivi più famosi, possa avere un effetto positivo sulla sindrome di Down. Il primo test del farmaco in questo ambito, riferisce la rivista del Mit Technology Review, prenderà il via questo mese all'University of Texas Southwestern Medical Center in Dallas, ma anche in Italia si proverà a percorrere questa strada, anche se in condizioni

Sindrome di Down
Ricerca di una terapia

1. Neurogenesi / Neuroprotezione

2. **Integratori – Antiossidanti**

3. Modulazione dei neurotrasmettitori

5. Terapia basata su meccanismi patogenetici

Resveratrolo

Resveratrolo, molecola naturale che rigenera i neuroni in sindrome di Down

13/07/2016

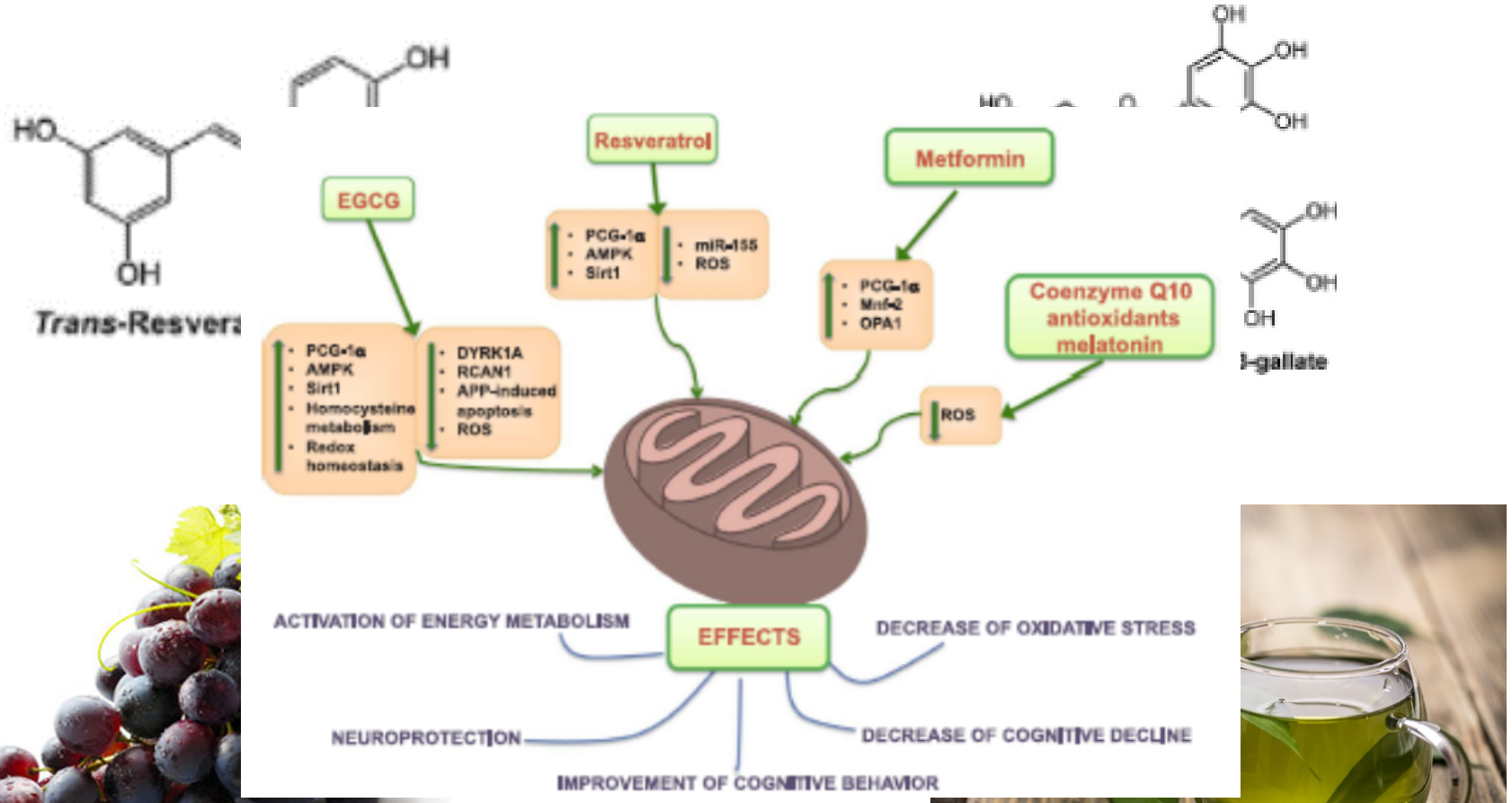
La disabilità intellettiva è tra le conseguenze più evidenti dell'alterazione cromosomica che caratterizza i soggetti con sindrome di Down. La presenza di una terza copia del cromosoma 21 riduce, in particolare, la capacità di generare nuove cellule nervose nell'area del cervello denominata ippocampo. Una ricerca attesta ora che utilizzando il resveratrolo, un polifenolo presente in un'ampia varietà di piante e frutti, tra cui l'uva rossa e quindi il vino, è possibile stimolare la formazione di nuovi neuroni. Lo studio, condotto dall'Istituto di biomembrane e bioenergetica del Consiglio nazionale delle ricerche (Ibbe-Cnr) di Bari, in collaborazione con il Dipartimento di scienze mediche di base, neuroscienze e organi di senso dell'Università di Bari, Dipartimento di neuroscienze e tecnologie del cervello dell'Iit di Genova e l'Inserm di Parigi, è pubblicato sulla rivista *Biochimica et Biophysica Acta-Molecular Basis of Disease.*

"Con questo lavoro, eseguito su linee cellulari di un modello animale con sindrome di Down, dimostriamo che il resveratrolo è in grado di ripristinare la neurogenesi agendo a livello dei mitocondri", spiega Rosa Anna Vacca, ricercatrice dell'Ibbe-Cnr e coordinatrice del lavoro. "In condizioni normali, i mitocondri forniscono l'energia necessaria per alimentare i diversi processi cellulari, tra cui la proliferazione e la corretta funzionalità dei neuroni, che risultano alterati nelle persone con sindrome di Down e vengono invece riportati a valori normali dal resveratrolo. Esistono migliaia di studi sugli effetti protettivi del resveratrolo in diverse malattie, da quelle metaboliche e neurodegenerative a quelle dell'apparato cardio-vascolare e nell'invecchiamento: è però la prima volta che questa molecola viene testata in sindrome di Down, attraverso un meccanismo che inoltre correla il deficit della funzionalità dei neuroni alla ridotta funzionalità mitocondriale".

Plant polyphenols as natural drugs for the management of Down syndrome and related disorders

Rosa Anna Vacca[a,*], Daniela Valenti[a], Salvatore Caccamese[b], Maria Daglia[c], Nady Braidy[d], Seyed Mohammad Nabavi[e,f,**]

Neuroscience and Biobehavioral Reviews 71 (2016) 865–877

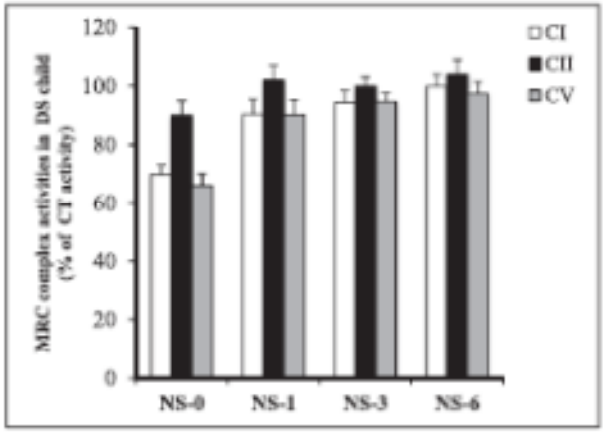


Clinical Nutrition 34 (2015) 783–784

Letter to the Editor

Green tea EGCG plus fish oil omega-3 dietary supplements rescue mitochondrial dysfunctions and are safe in a Down's syndrome child

Rosa Anna Vacca*, Daniela Valenti
Institute of Biomembranes and Bioenergetics, National Council of Research, Bari, Italy



Laboratory analysis				
		EGCG/fish oil diet supplementation		
	Basal	1 month	3 months	6 months
Creatinine (ref 0.6–1.3 mg/dL)	0.69	0.66	0.69	0.65
GOT/AST (ref. 0–35 U/L)	23	27	26	30
GPT/ALT (ref. 0–45 U/L)	21	21	26	35
Total Cholesterol (ref. < 200 mg/dL)	166	162	172	165
HDL Cholesterol (ref. 30–75 mg/dL)	64	65	62	70
LDL Cholesterol (ref. < 150 mg/dL)	87	83	92	79
Triglycerides (ref. 40–160 mg/dL)	74	72	91	80
Folic acid (ref 3–20 ng/mL)	3.01	1.90	18.40*	6.20**
FT3 (eu. 2.75–7.80 nmol/L)	5.36	5.46	6.25	7.90
FT4 (eu. 10.2–22.7 pmol/L)	13.9	14.3	13.8	16.1
TSH (eu. 0.40–4.00 uU/mL)	6.26	6.63	5.82	3.57
Thyroglobulin (ref 0–78 ng/mL)	112.70	44.8	37	57
Ab anti-Thyroglobulin (Neg. < 18.00 UI/mL)	19.00	17.1	9.4	5.9
Ab anti-TPO (Neg. < 28.0 UI/mL)	18.6	25	20.7	16

*supplementation of 1 cp (0.4 mg folic acid)/die
** supplementation of 1 cp (0.4 mg folic acid)/2 die

Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): a double-blind, randomised, placebo-controlled, phase 2 trial

Rafael de la Torre, Susana de Sola, Gimena Hernandez, Magí Farré, Jesus Pujol, Joan Rodriguez, Josep María Espadaler, Klaus Langohr, Aida Cuenca-Royo, Alessandro Principe, Laura Xicota, Nathalie Janel, Silvina Catuara-Solarz, Gonzalo Sanchez-Benavides, Henri Bléhaut, Iván Dueñas-Espín, Laura del Hoyo, Bessy Benejam, Laura Blanco-Hinojo, Sebastiá Videla, Montserrat Fitó, Jean Maurice Delabar, Mara Dierssen for the TESDAD study group

Summary

Background Early cognitive intervention is the only routine therapeutic approach used for amelioration of intellectual deficits in individuals with Down's syndrome, but its effects are limited. We hypothesised that administration of a green tea extract containing epigallocatechin-3-gallate (EGCG) would improve the effects of non-pharmacological cognitive rehabilitation in young adults with Down's syndrome.

Methods We enrolled adults (aged 16–34 years) with Down's syndrome from outpatient settings in Catalonia, Spain, with any of the Down's syndrome genetic variations (trisomy 21, partial trisomy, mosaic, or translocation) in a double-blind, placebo-controlled, phase 2, single centre trial (TESDAD). Participants were randomly assigned at the IMIM-Hospital del Mar Medical Research Institute to receive EGCG (9 mg/kg per day) or placebo and cognitive training for 12 months. We followed up participants for 6 months after treatment discontinuation. We randomly assigned participants using random-number tables and balanced allocation by sex and intellectual quotient. Participants, families, and researchers assessing

Lancet Neurol 2016; 15: 801–10

See Comment page 776

IMIM-Hospital del Mar Medical Research Institute and CIBER of Physiopathology of Obesity and Nutrition (CIBEROBN), University Pompeu Fabra (CEXS-UPF), Barcelona, Spain (R de la Torre PharmD, S de Sola PhD, M Farré MD, J Rodriguez MSc, A Cuenca-Royo PhD, L Xicota MSc, G Hernandez MD,

Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): a double-blind, randomised, placebo-controlled, phase 2 trial

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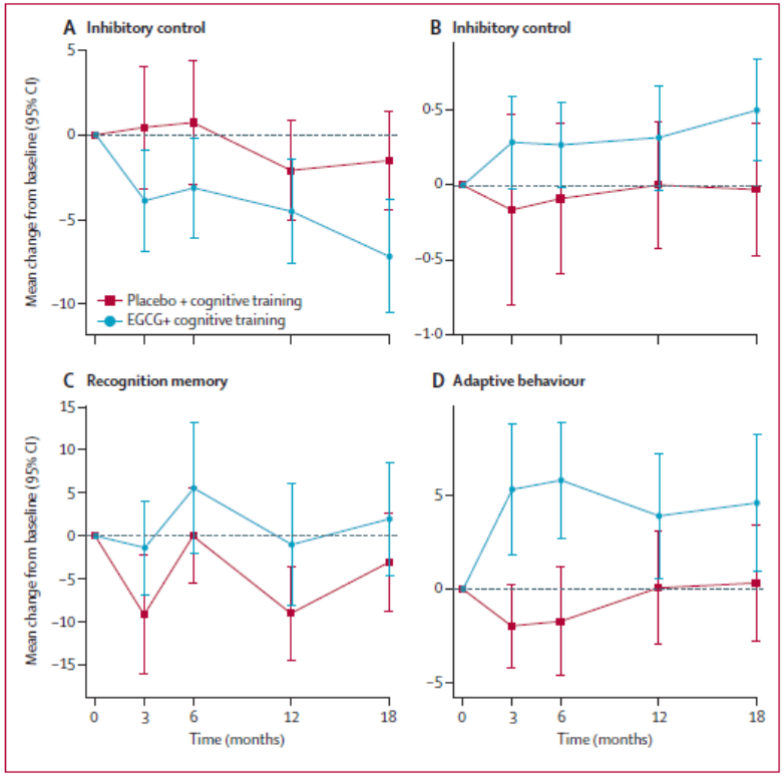


Figure 2: Effects of EGCG and cognitive training or placebo and cognitive training on neurocognitive performance and adaptive behaviour

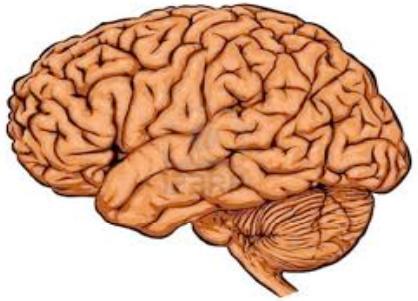
Sindrome di Down
Ricerca di una terapia

1. Neurogenesi / Neuroprotezione
2. Integratori – Antiossidanti
3. **Modulazione dei neurotrasmettitori**
4. Terapia basata su meccanismi patogenetici

3. Neurotrasmissione

Morbo di Alzheimer nella sindrome di Down:

10%	30-39 anni
55%	50-59 anni



1. **Trasmissione colinergica**
   Inibitori delle acetilcolinesterasi
   (Donepezil – Rivastigmina)

2. **Trasmissione glutammatergica**
   Antagonisti dei recettori NMDA (*Memantina*)

3. **Trasmissione GABAergica**
   Antagonisti dei recettori $GABA_A$ (basso IT)

3. Neurotransmission modulation		
3.1 Choline supplement	Ts65Dn Mouse	Moon et al. 2010
3.2 Melatonin	Ts65Dn Mouse	Corrales et al. 2013
3.3 Acetyl L-Carnitine	Clinical Trial	Pueschel 2006
3.4 Adrenergic agonists		
3.4.1 Formoterol (b2)	Ts65Dn Mouse	Dang et al. 2013
3.4.2 Xamoterol (b1)	Ts65Dn Mouse	Salehi et al. 2009, Faizi et al. 2011

3.6 Glutamatergic neurotransmission		
3.6.1 Memantine	Ts65Dn Mouse	Costa et al. 2008, Rueda et al. 2010, Lockrow et al. 2011, Scott-McKean and Costa 2011
	Clinical Trial (age >40 yrs)	Hanney et al. 2012
	Clinical Trial (age 18-32 yrs)	Boada et al. 2012
3.7 GABA Receptor antagonists		
3.7.1 Picrotoxin	Ts65Dn Mouse	Kleschevnikov et al. 2004, Costa and Grybko 2005, Fernandez et al. 2007, Kleschevnikov et al. 2012b3.7.2 α5IA Ts65Dn Mouse Braudeau et al. 2011a, b
3.7.2 α5IA	Ts65Dn Mouse	Braudeau et al. 2011a, b
3.7.3 Bumetanide	Ts65Dn Mouse	Deidda et al. 2015

Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOWS): a randomised, double-blind, placebo-controlled trial

*Marisa Hanney, Vee Prasher, Nicola Williams, Emma L Jones, Dag Aarsland, Anne Corbett, Dale Lawrence, Ly-Mee Yu, Stephen Tyrer, Paul T Francis, Tony Johnson, Roger Bullock, Clive Ballard, on behalf of the MEADOWS trial researchers**

Lancet 2012; 379: 528–36

Published Online
January 10, 2012
DOI:10.1016/S0140-6736(11)61676-0

See Comment page 498

*Members listed at end of paper

Wolfson Centre for Age-Related Diseases, King's College London, London, UK (M Hanney PhD, E L Jones DPhil, Prof P T Francis PhD, Prof C Ballard MD); Birmingham Community Healthcare National Health Service Trust, Birmingham, UK (V Prasher MD, D Lawrence MRCPsych); Centre for Statistics in Medicine, Oxford, UK (N Williams MSc, L-M Yu PhD); University Hospital Stavanger, Stavanger,

Summary

Background Prevalence of Alzheimer's disease in people with Down's syndrome is very high, and many such individuals who are older than 40 years have pathological changes characteristic of Alzheimer's disease. Evidence to support treatment with Alzheimer's drugs is inadequate, although memantine is beneficial in transgenic mice. We aimed to assess safety and efficacy of memantine on cognition and function in individuals with Down's syndrome.

Methods In our prospective randomised double-blind trial, we enrolled adults (>40 years) with karyotypic or clinically diagnosed Down's syndrome, with and without dementia, at four learning disability centres in the UK and Norway. We randomly allocated participants (1:1) to receive memantine or placebo for 52 weeks by use of a computer-generated sequence and a minimisation algorithm to ensure balanced allocation for five prognostic factors (sex, dementia, age group, total Down's syndrome attention, memory, and executive function scales [DAMES] score, and centre). The primary outcome was change in cognition and function, measured with DAMES scores and the adaptive behaviour scale (ABS) parts I and II. We analysed differences in DAMES and ABS scores between groups with analyses of covariance or quantile regression in all patients who completed the 52 week assessment and had available follow-up data. This study is registered, number ISRCTN47562898.

Findings We randomly allocated 88 patients to receive memantine (72 [82%] had DAMES data and 75 [85%] had ABS data at 52 weeks) and 85 to receive placebo (74 [87%] and 73 [86%]). Both groups declined in cognition and function but rates did not differ between groups for any outcomes. After adjustment for baseline score, there were non-

Lancet 2012; 379: 528–36

Published Online
January 10, 2012

Citation: Transl Psychiatry (2012) 2, e141, doi:10.1038/tp.2012.66

www.nature.com/tp

Antagonism of NMDA receptors as a potential treatment for Down syndrome: a pilot randomized controlled trial

R Boada[1,2], C Hutaff-Lee[2], A Schrader[2], D Weitzenkamp[3], TA Benke[1,2,4,5,6,7], EJ Goldson[1,2] and ACS Costa[6,7,8]

Down syndrome (DS) is the most common genetic cause of intellectual disability. The *N*-methyl-D-aspartate (NMDA) receptor uncompetitive antagonist memantine hydrochloride (memantine), has been shown to improve learning/memory and rescue one form of hippocampus synaptic plasticity dysfunction in the best-studied mouse model of DS available, the Ts65Dn mouse. Given the status of memantine as a treatment for Alzheimer's disease (AD) approved by the Food and Drug Administration, the preclinical evidence of potential efficacy in Ts65Dn mice, and the favorable safety profile of memantine, we designed a study to investigate whether the findings in the mouse model could be translated to individuals with DS. In this pilot, proof-of-principle study we hypothesized that memantine therapy would improve test scores of young adults with DS on measures of episodic and spatial memory, which are generally considered to be hippocampus dependent. Accordingly, in this randomized, double-blind, placebo-controlled trial, we compared the effect of 16-week treatment with either memantine or placebo on cognitive and adaptive functions of 40 young adults with DS using a carefully selected set of neuropsychological outcome measures. Safety and tolerability were also monitored. Although no significant differences were observed between the memantine and placebo groups on the two primary outcome measures, we found a significant improvement in the memantine group in one of the secondary measures associated with the primary hypothesis. Only infrequent and mild adverse events were noted.

Translational Psychiatry (2012) **2**, e141; doi:10.1038/tp.2012.66; published online 17 July 2012

3.6 Glutamatergic neurotransmission		
3.6.1 Memantine	Ts65Dn Mouse	Costa et al. 2008, Rueda et al. 2010, Lockrow et al. 2011, Scott-McKean and Costa 2011
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3.7.2 α5IA	Ts65Dn Mouse	Braudeau et al. 2011a, b
3.7.3 Bumetanide	Ts65Dn Mouse	Deidda et al. 2015

Il corretto scambio di informazioni tra i diversi gruppi di neuroni del nostro cervello dipende dal perfetto bilanciamento tra l'azione di neurotrasmettitori eccitatori ed inibitori" spiega Andrea Contestabile, uno dei coordinatori del lavoro e ricercatore nel dipartimento di Neuroscienze di IIT, "Nella Sindrome di Down, l'azione inibitoria del GABA si trasforma in eccitatoria ed il flusso di informazioni tra neuroni diventa eccessivo e sregolato. Questa inversione dell'azione del GABA è dovuta allo squilibrio di un elettrolita, lo ione cloruro. Tuttavia l'azione inibitoria del GABA può essere completamene ristabilita riducendo la concentrazione di ione cloruro tramite l'azione del diuretico Bumetanide".

nature medicine

Nat Med. 2015 Apr;21(4):318-26

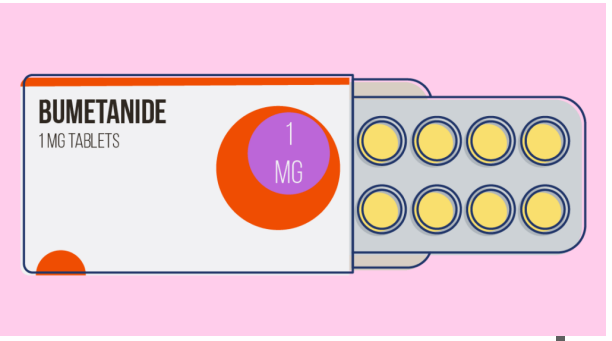
Reversing excitatory $GABA_AR$ signaling restores synaptic plasticity and memory in a mouse model of Down syndrome

Gabriele Deidda[1,2], Martina Parrini[1,2], Shovan Naskar[1,2], Ignacio F Bozarth[1], Andrea Contestabile[1,3] & Laura Cancedda[1,3]

- **GABAAR signaling was found to be excitatory rather than inhibitory, and the reversal potential for GABAAR-driven Cl− currents (*E*Cl) was shifted toward more positive potentials in the hippocampi of adult DS mice.**

- **Hippocampal expression of the cation Cl− cotransporter NKCC1 was increased in both trisomic mice and individuals with DS.**

- **NKCC1 inhibition by BUMETANIDE restored *E*Cl, synaptic plasticity and hippocampus-dependent memory in adult DS mice.**



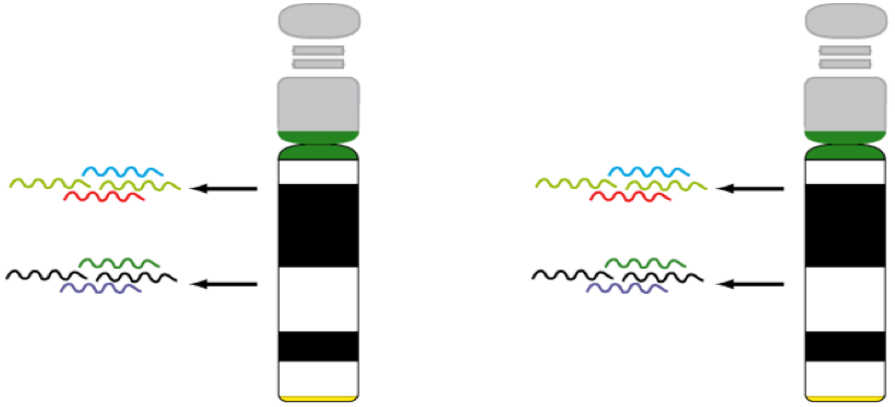
Sindrome di Down
Ricerca di una terapia

1. Neurogenesi / Neuroprotezione
2. Integratori – Antiossidanti
3. Modulazione dei neurotrasmettitori
4. **Terapia basata su meccanismi patogenetici**

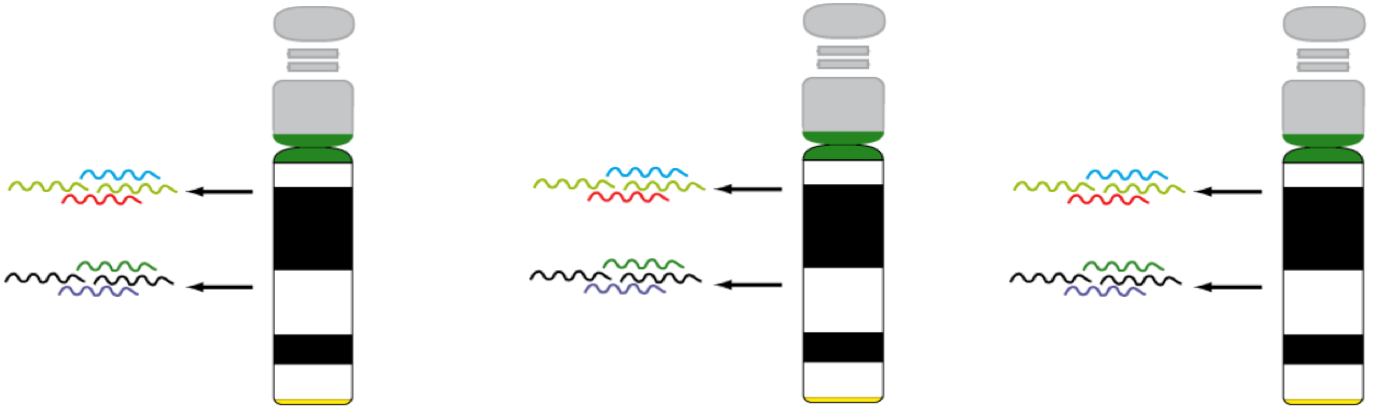
Sindrome di Down (Trisomia 21)

4. Ricerca di una terapia basata sui meccanismi patogenetici

2 copie del cromosoma 21

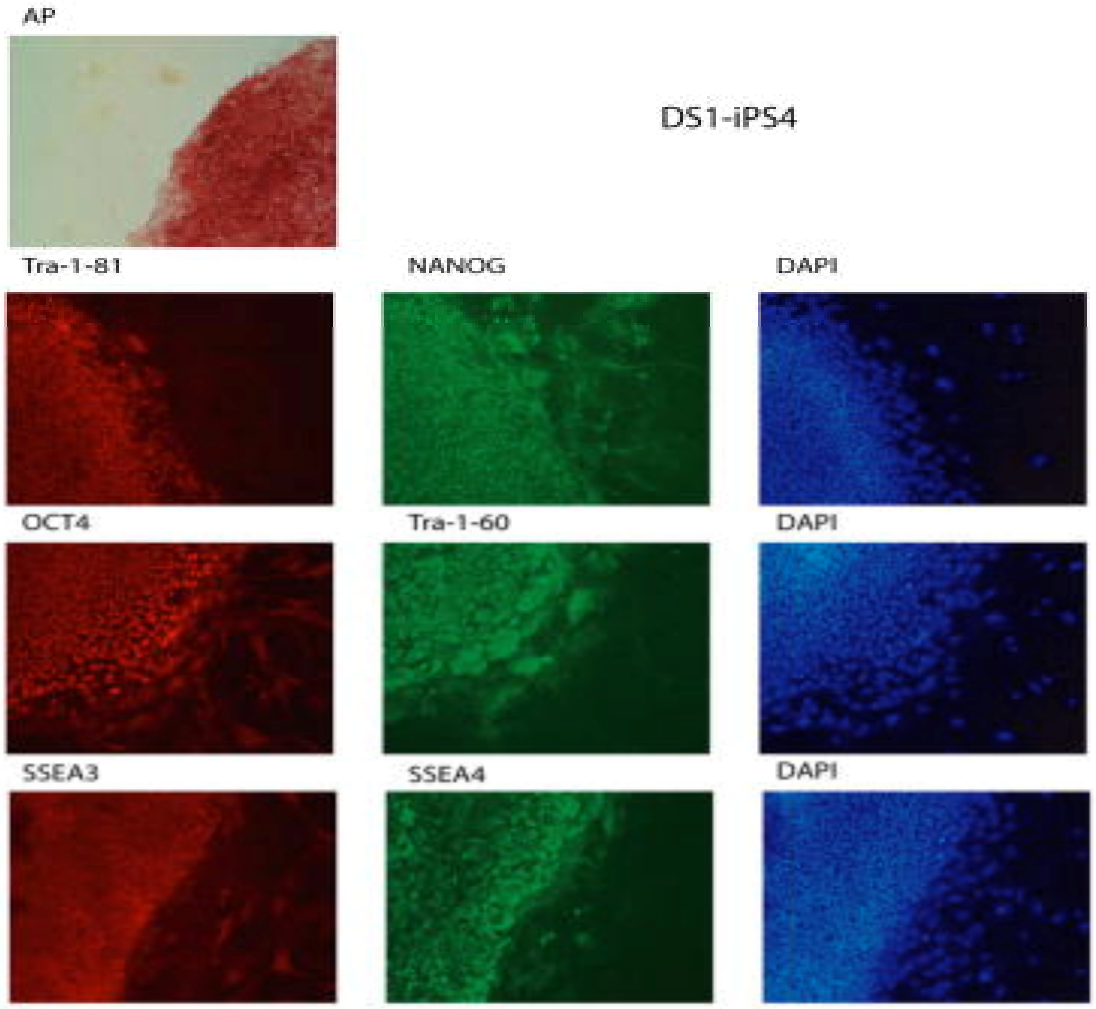


3 copie del cromosoma 21

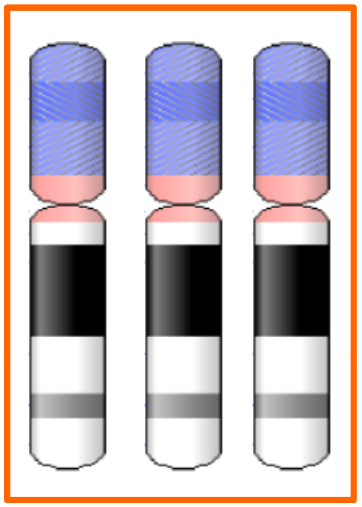


Sindrome di Down (Trisomia 21)
Modelli di studio

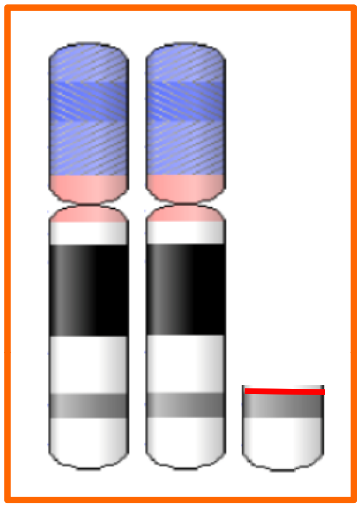
2008 - Cellule staminali pluripotenti indotte trisomiche



7. Pathogenesis investigation		
7.1 Down Syndrome Candidate Regions (DSCR)	Cytogenetics in partial trisomy	Lyle et al. 2009, Korbel et al. 2009, others
7.2 Cellular biology, molecular biology and molecular genetics of trisomy 21		
7.2.1 Epigallocatechine gallate	Ts65Dn Mouse	Xie et al. 2008
	tgYAC152F7 Mouse	Guedj et al. 2009
	Tg152F7, Tg189N3, Ts65Dn Mice	Noll et al. 2009
	Ts65Dn Mouse	Mazur-Kolecka et al. 2012
	Cell culture from DS subjects	Valenti et al. 2013 ⇦
	Clinical Trial (age 14-29 yrs)	de la Torre et al. 2013
7.2.2 DYRK1A inhibitors	Structure-based Screening	Wang D et al. 2012
7.2.3 Beta-amyloid	Ts65Dn Mouse	Netzer et al. 2010
7.3 Mouse models of DS	DS Mouse Models	Rueda et al. 2012, others
7.4 General ID models	Computational Biology	Sturgeon et al. 2012, Wang W et al. 2012
7.5 NRIP1	DS foetal fibroblasts	Izzo et al. 2017 ⇦



Trisomia 21 completa



Trisomia 21 parziale

Schema sperimentale

Ricerca bibliografica

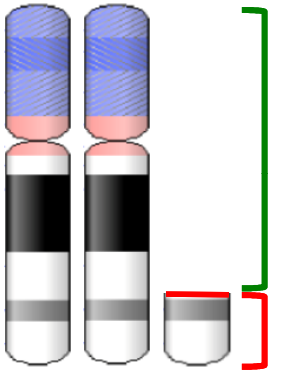
1,322 articoli

Selezione dei casi

125 casi

Costruzione della mappa comparativa

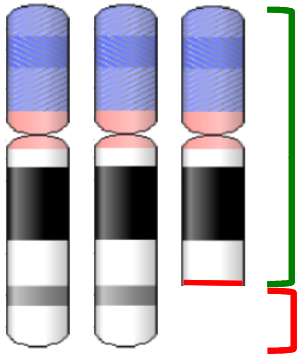
Trisomie 21 parziali e regione critica per la sindrome di Down (DSCR)



Regione esclusa

Regione candidata

Trisomia 21 parziale con sindrome di Down



Regione esclusa

Regione candidata (non esclusa)

Trisomia 21 parziale senza sindrome di Down

OXFORD JOURNALS

Human Molecular Genetics

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRENT ISSUE

Systematic reanalysis of partial trisomy 21 cases with or without Down syndrome suggests a small region on 21q22.13 as critical to the phenotype

Maria Chiara Pelleri[1], Elena Cicchini[1], Chiara Locatelli[2], Lorenza Vitale[1,†], Maria Caracausi[1,†], Allison Piovesan[1,†], Alessandro Rocca[2], Giulia Poletti[2], Marco Seri[3], Pierluigi Strippoli[1,*] and Guido Cocchi[4]

+ Author Affiliations

*To whom correspondence should be addressed. Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Unit of Histology, Embryology and Applied Biology, University of Bologna, Via Belmeloro 8, 40126, Bologna (BO), Italy. Tel: +39-0512094117, Fax: +39-0512094110, e-mail: pierluigi.strippoli@unibo.it

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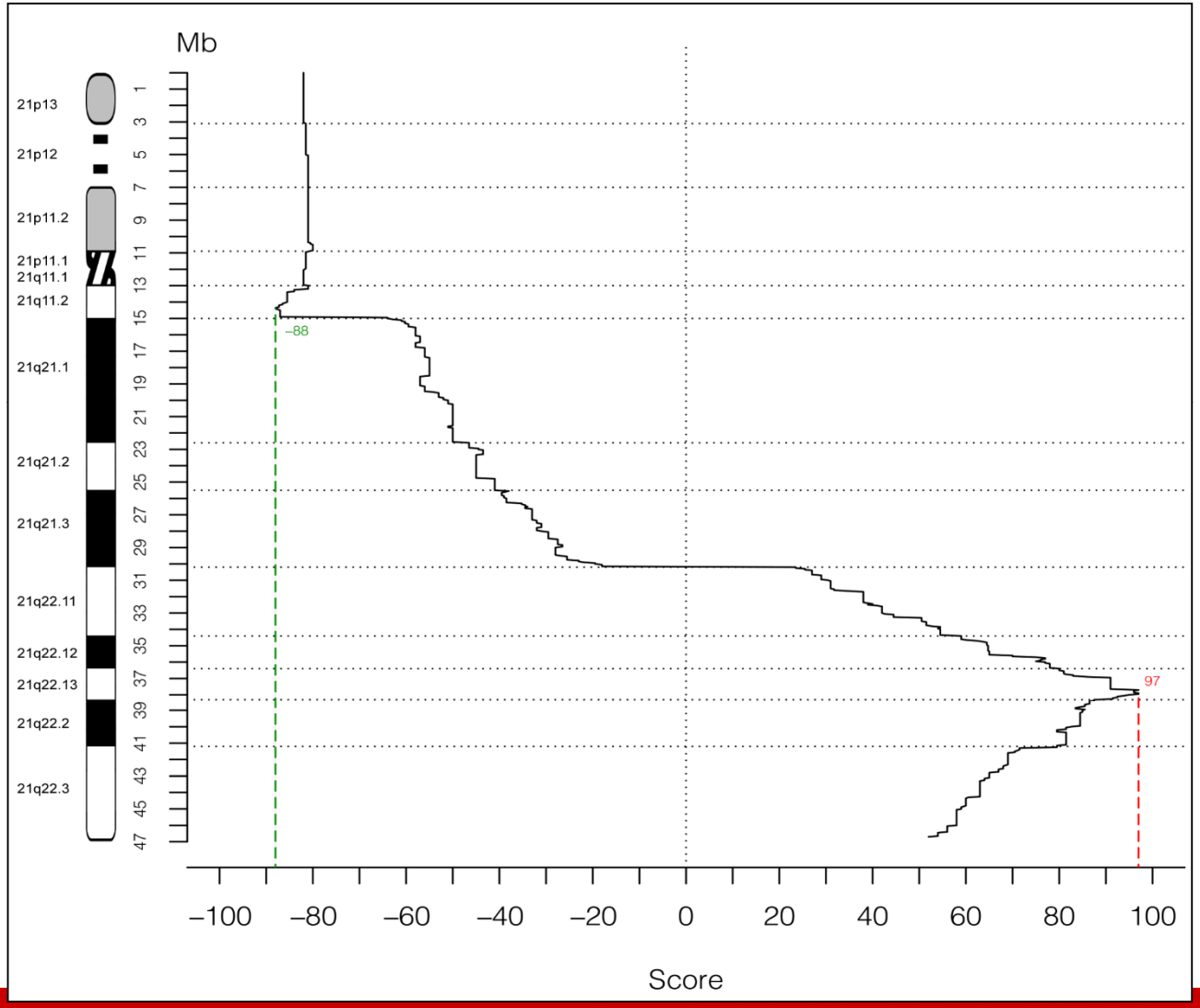
Accepted April 12, 2016.

Identificazione della DSCR altamente ristretta



Identificazione della DSCR altamente ristretta

Gene or sequence interval [in red: known markers of special interest]	Start Coordinate End Coordinate NC_000021.9 Genome Version: GRCh38/hg38 [not in scale: rows may represent intervals of different size]	059 1994* Korenberg DUP21SOL DS	113 2009 Korbel DUP21HAD DS

Alcuni studi hanno suggerito che la **regione critica** per la **sindrome di Down** si trovi sulla **regione 21q22.1-q22.3** del cromosoma, un'area che include i geni che codificano per la proteina precorritrice della **beta-amiloide**, dell'**enzima superossido dismutasi** e probabilmente del **proto-oncogene ETS2**.

HR-DSCR 46 kb

RP11-95G19 Start	37,785,634			
RP11-1012D8 Start	*37,838,167*			
D21S233	*37,850,895*	37,851,007		
KCNJ6 End		37,919,731		
PT21 #113 (Korbel)	37,929,228	37,929,228		aCGH
PT21 #113 (Korbel)	37,929,229	37,929,229		aCGH
PT21 #119 (Melis)	37,937,642	37,937,642		
HR-DSCR Boundary	37,963,130	37,963,130		
nsv1060057 Start	37,963,131			
nsv1058886 Start	*37,969,257*			
RP11-95G19 End		37,971,033		
D21S407	37,973,282	37,973,493		
PT21 #059 (Korenberg)	37,975,580	37,975,580	aCGH	
PT21 #059 (Korenberg)	37,975,581	37,975,581	aCGH	
esv3646996 Start	37,975,815			
nsv1060057 End		37,992,022		
DSCR4 Start	38,006,553			
RP11-1012D8 End		38,024,835		
esv3646996 End		38,051,566		
D21S259	38,076,863	38,077,136		
DSCR4 End		38,121,360		

Il CROMOSOMA 21 presenta una regione che è la principale responsabile delle caratteristiche che si osservano nella S.D. e viene definita **REGIONE CRITICA.**

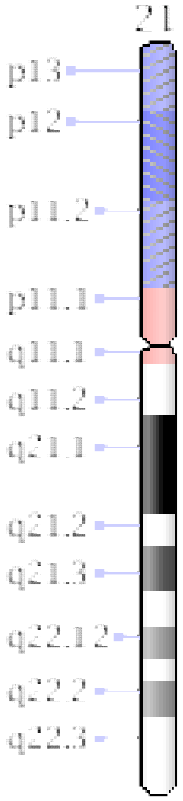
Si tratta della banda q22.1-q22.3 delle dimensioni di 46 kB **(<millesimo del cr.21).**

All'interno di questa "REGIONE CRITICA" vi sono
dei geni in parte noti quali quelli che hanno un ruolo in alcune patologie:

1. **CARDIOPATIE CONGENITE**
2. Lesioni oculari pricipalmente **CATARATTA**

ma molti altri non sono completamente noti

Down Syndrome Critical Region



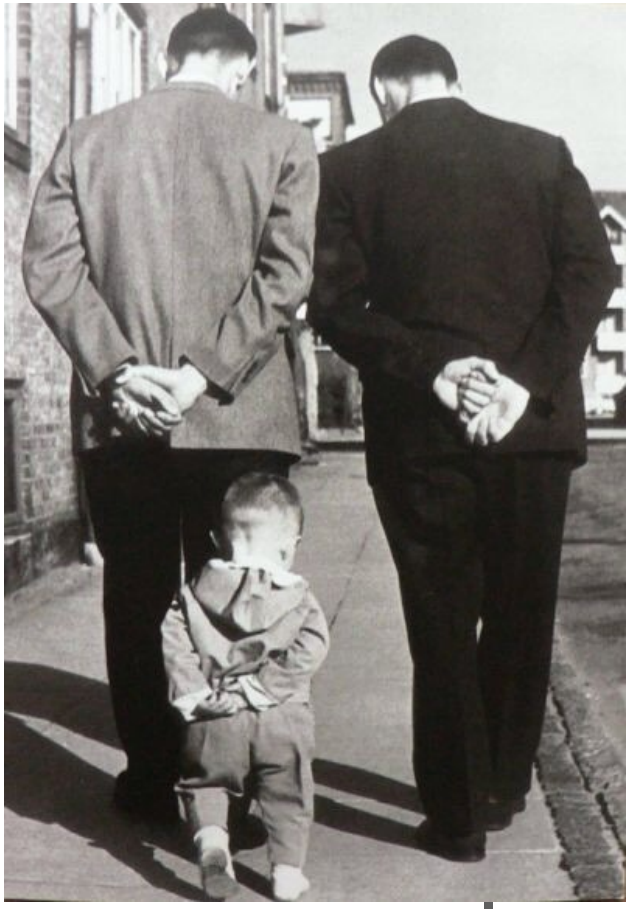
"Responsible for all aspects of the phenotype"

"Responsible for all or most severe DS features"

"Sufficient to cause the full DS phenotype"

"Suffices to induce the main phenotypic symptoms of the classic syndrome of trisomy 21"

La ricerca passo dopo passo…



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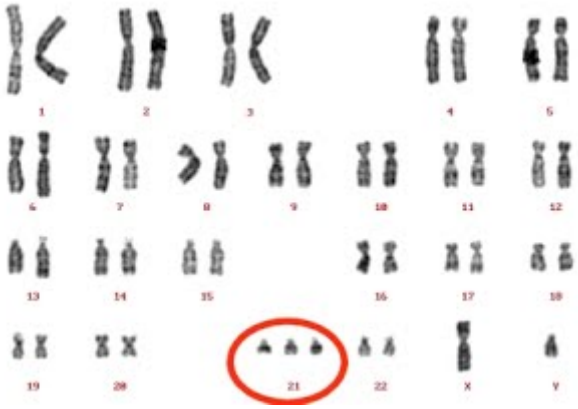
Ipotesi di Jérome Lejeune (1980)



MALATTIA METABOLICA

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Plasma and urinary metabolomic profiles of Down syndrome correlate with alteration of mitochondrial metabolism

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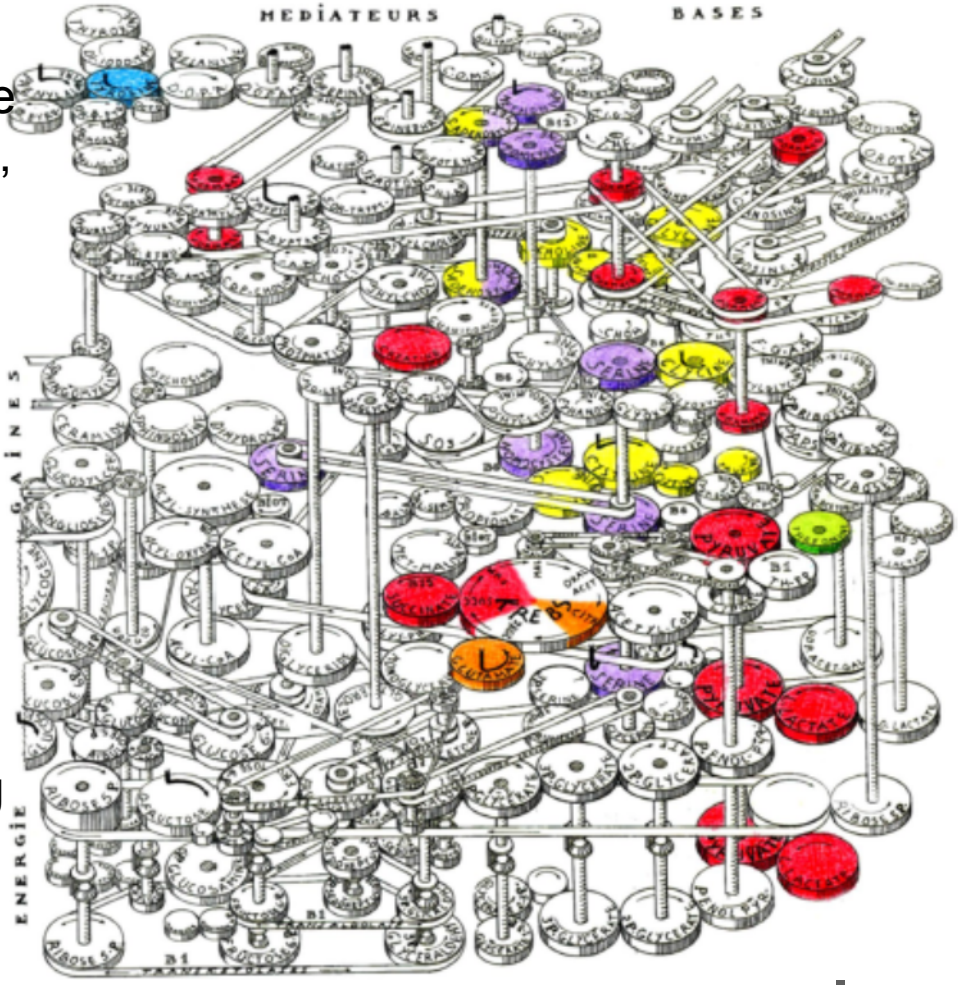
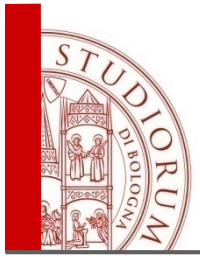
- "Even if the network is correct and the insulating system properly developed, genetic mistakes can prevent the function. Generally speaking, one gets the feeling that the machine is running but cannot develop its full power. Exactly like a motor to which the fuel is not provided in correct amount."
- "One would believe that either the brain does not dispose of enough energy or that some toxic is impairing its ignition process"

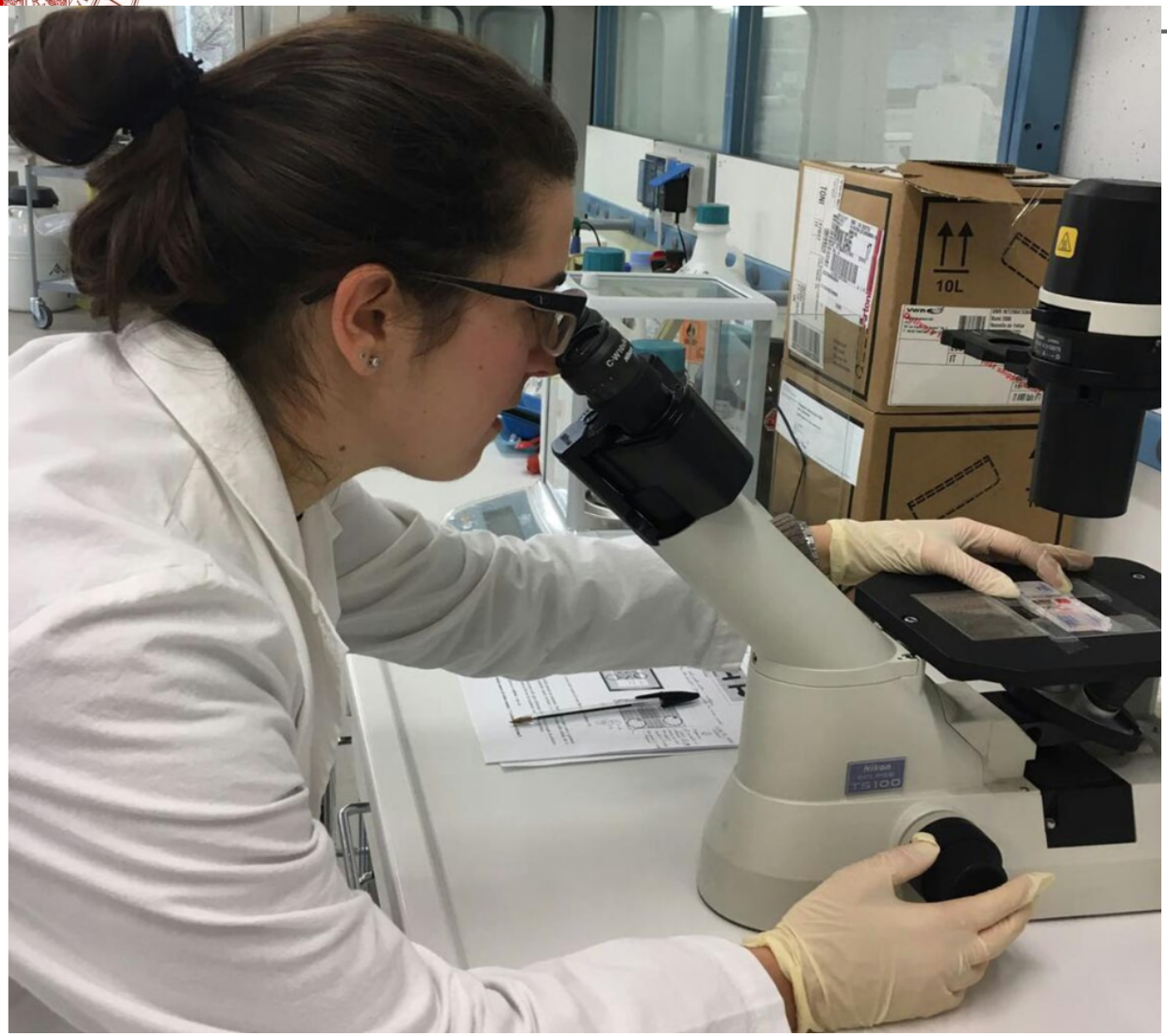
"Phenylketonuria, galactosemia, vitamine B6 dependant homocystinuria, to take few examples, can be properly handled and the children protected against mental deficiency. Who could believe that during the coming years no new progress will be achieved?"



Grazie per l'attenzione

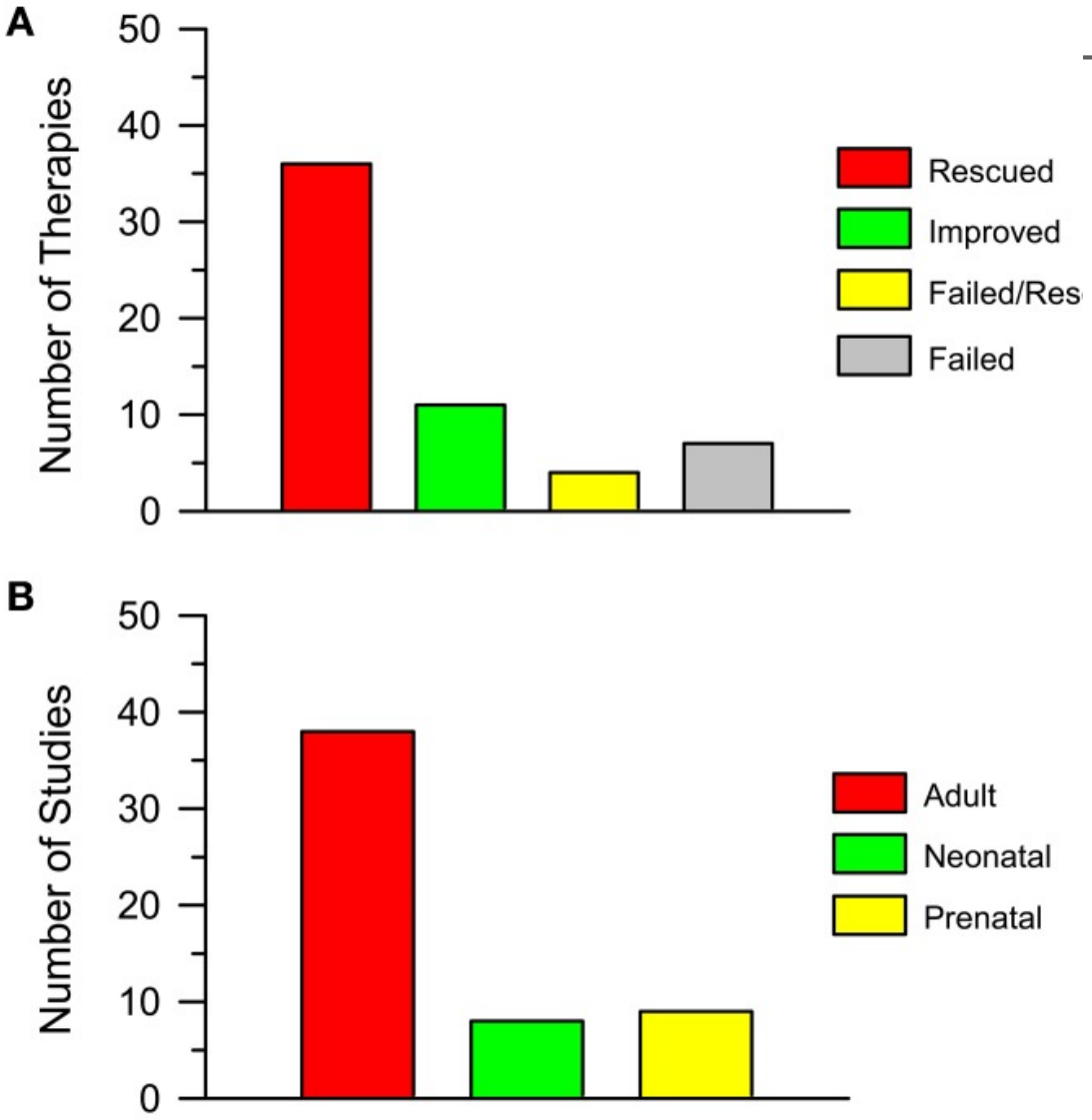


TRASCRITTOMA


10L
Nikon
TS100

386	21q22.11	21q22.11 End					34,400,000	4,200,000
387	21q22.12	21q22.12 Start				34,400,001		2,000,000
388	21q22.12	C21orf140	protein coding	VALIDATED	Official	34,400,112	34,401,072	961
389	21q22.12	KCNE1	protein coding	REVIEWED	Official	34,418,715	34,512,275	93,561
390	21q22.12	LOC101928182	ncRNA	MODEL		*34,419,638*	*34,425,353*	5,716
391	21q22.12	RCAN1 Start	protein coding	REVIEWED	Official	34,516,442		98,701
392	21q22.12	RP11-79A12 End			BAC Clone		34,525,627	159,138
393	21q22.12	D21S323			Probe	34,597,075	34,597,398	324
394	21q22.12	RCAN1 End	protein coding	REVIEWED	Official		34,615,142	98,701
395	21q22.12	CLIC6	protein coding	REVIEWED	Official	34,669,292	34,718,227	48,936
396	21q22.12	D21S65			Probe	*34,716,787*	*34,716,978*	192
397	21q22.12	LINC00160	ncRNA	VALIDATED	Official	34,723,807	34,737,182	13,376
398	21q22.12	LINC01426	ncRNA	VALIDATED	Official	34,745,825	34,784,886	39,062
399	21q22.12	RUNX1	protein coding	REVIEWED	Official	34,787,801	35,049,310	261,510
400	21q22.12	D21S393			Probe	*34,889,366*	*34,889,448*	83
401	21q22.12	RUNX1-IT1	ncRNA	VALIDATED	Official	35,037,925	35,039,426	1,502
402	21q22.12	LOC100506403	ncRNA	VALIDATED		35,372,507	35,580,764	208,258
403	21q22.12	D21S1221			Probe	*35,507,078*	*35,507,313*	236
404	21q22.12	D21S17			Probe	35,598,157	35,598,368	212
405	21q22.12	RP11-957K9 Start			BAC Clone	35,617,664		181,527
406	21q22.12	D21S211			Probe	*35,654,159*	35,654,254	96
407	21q22.12	D21S1283			Probe	35,708,230	35,708,414	185
408	21q22.12	MIR802	ncRNA	PROVISIONAL	Official	35,720,715	35,720,808	94
409	21q22.12	RP11-957K9 End			BAC Clone		35,799,190	181,527
410	21q22.12	PT21 #056 (Korenberg)			Array CGH	35,865,924	35,865,924	1
411	21q22.12	PT21 #056 (Korenberg)			Array CGH	35,865,925	35,865,925	1

3. Neurotransmission modulation		
3.7.3 CGP55845	Ts65Dn Mouse	Kleschevnikov et al. 2012a, b
3.7.4 Ethosuximide, Gabapentin	Ts65Dn Mouse	Vidal et al. 2012
3.7.5 RO4938581	Ts65Dn Mouse	Martínez-Cué et al. 2013
3.8 GABA derivative (Piracetam)	Ts65Dn Mouse	Moran et al. 2002
	Clinical trial (age 6.5-13 yrs)	Lobaugh et al. 2001


A
Number of Therapies
50
40
30
20
10
0
Rescued
Improved
Failed/Res
Failed
B
Number of Studies
50
40
30
20
10
0
Adult
Neonatal
Prenatal