E.O. Ospedali Galliera
di Genova

LE PROGERIE: FOCUS SULLA SINDROME DI DOWN

DALLA GENETICA ALLA CLINICA

Dott. Alessandro Cocchella

CENTRO PER LA CURA DELLA SINDROME DI DOWN

Dip.to di Geriatria, Gerontologia e Scienze Motorie

Direttore: Dott. Ernesto Palummeri

E.O. OSPEDALI GALLIERA - GENOVA

QUESTIONI FONDAMENTALI

- Esiste una correlazione tra assetto genetico e processo di invecchiamento?
- La Sindrome di Down (SD) può essere effettivamente considerata una sindrome progeroide?
- Quali sono le principali problematiche cliniche della persona con SD?

PROGERIA: DEFINIZIONE

RARA CONDIZIONE GENETICA CHE CAUSA

INVECCHIAMENTO PRECOCE IN ETÀ PEDIATRICA

Sindromi progeroidi
(Invecchiamento biologico accelerato)

Sindrome di Down

Sindrome di Werner

Sindrome di Cockayne

Atassia - telangiectasia

Sindrome di Seip

Laminopatie (Hutchinson-Gilford)

Sindrome di Klinefelter

Sindrome di Turner

Distrofia Miotonica

John Tacket, 15 anni
1988-2004

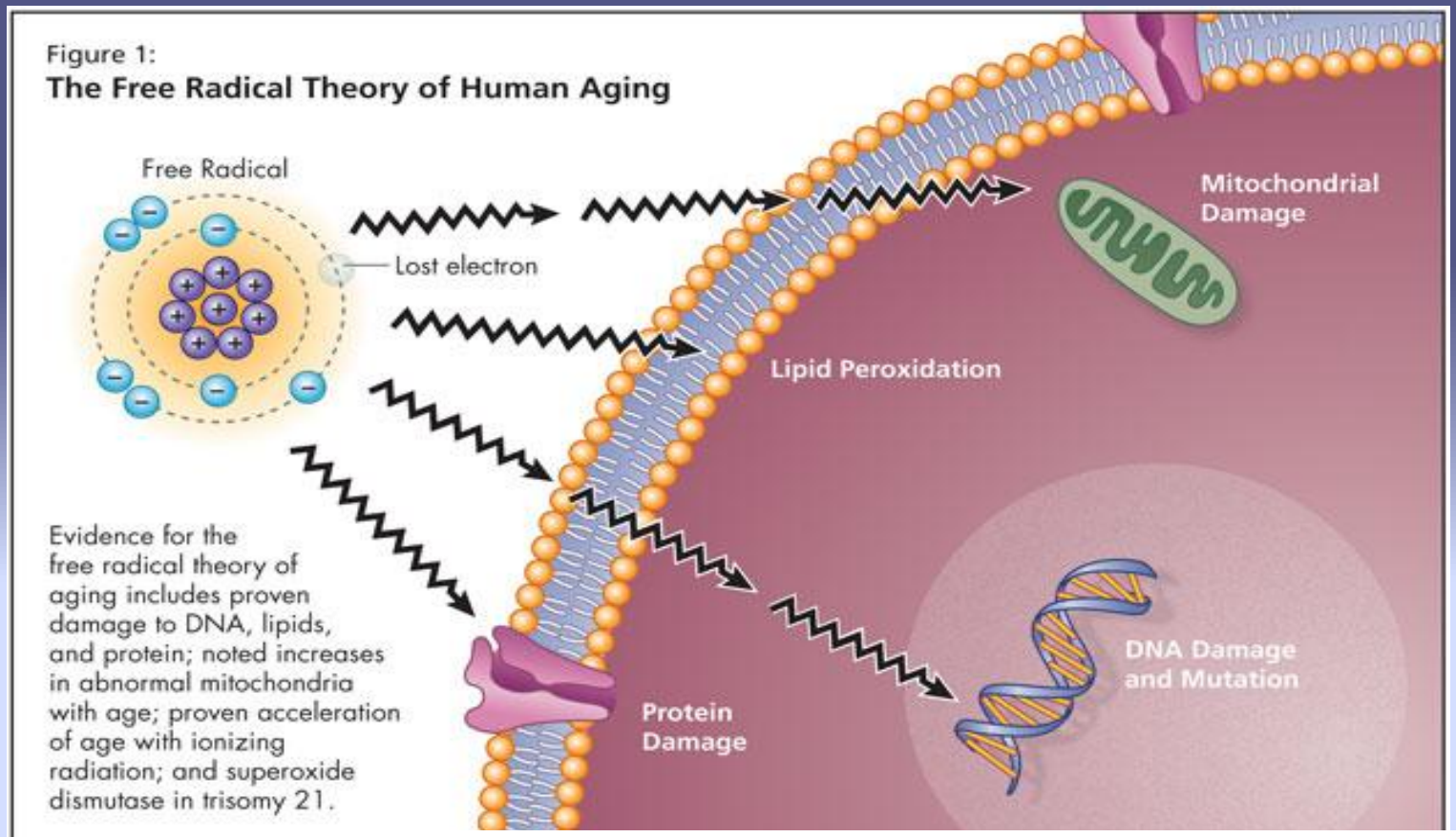
HUTCHINSON- GILFORD PROGERIA

SYNDROME DI COCKAYNE

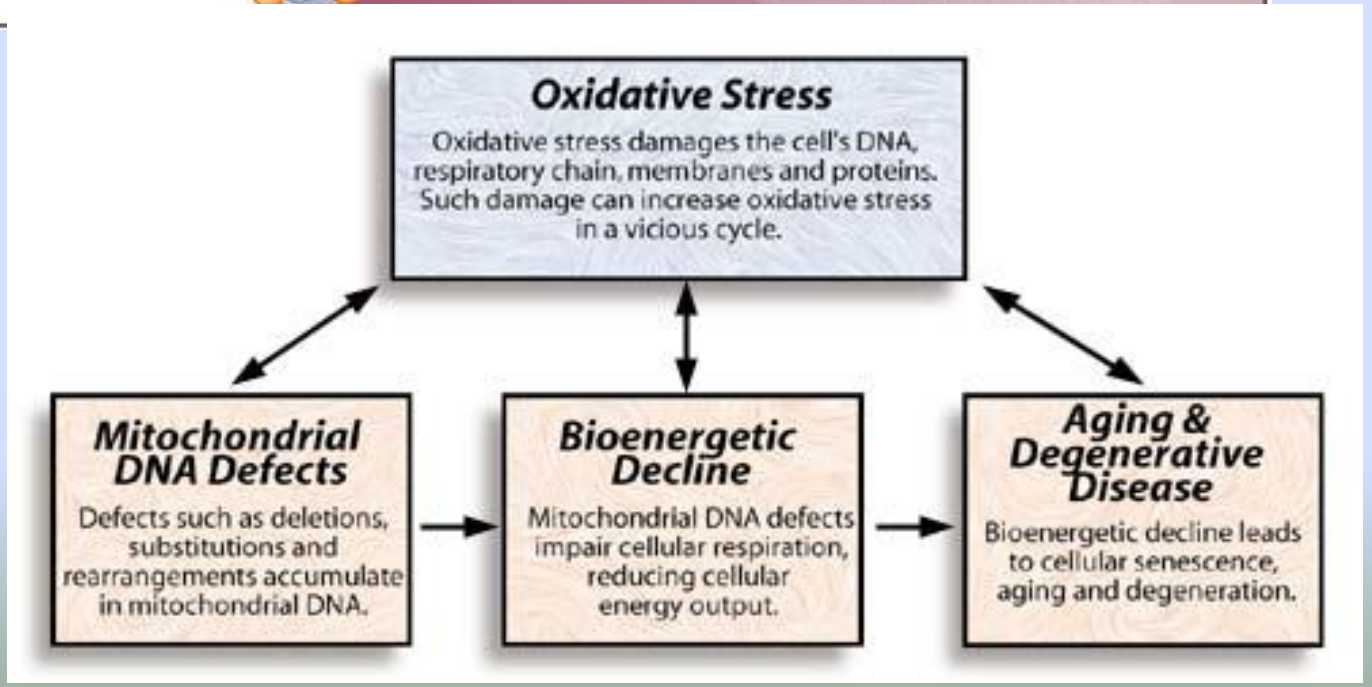
GENETICA E INVECCHIAMENTO

- TELOMERI
- MECCANISMI DI RIPARAZIONE DNA
- NEUTRALIZZAZIONE RADICALI LIBERI
- INFLUENZA DI ALCUNI POLIMORISMI SU COMORBIDITA' DELL'ANZIANO (es. ApoE)

Figure 1:
The Free Radical Theory of Human Aging



Evidence for the free radical theory of aging includes proven damage to DNA, lipids, and protein; noted increases in abnormal mitochondria with age; proven acceleration of age with ionizing radiation; and superoxide dismutase in trisomy 21.



LA SINDROME DI DOWN

DALLA GENETICA...

ANEUPLOIDIA

- Presenza di cromosomi in più o in meno rispetto al corredo diploide (2n+1, 2n-1…)

- Le più frequenti sono le trisomie e le monosomie

DALLA GENETICA...

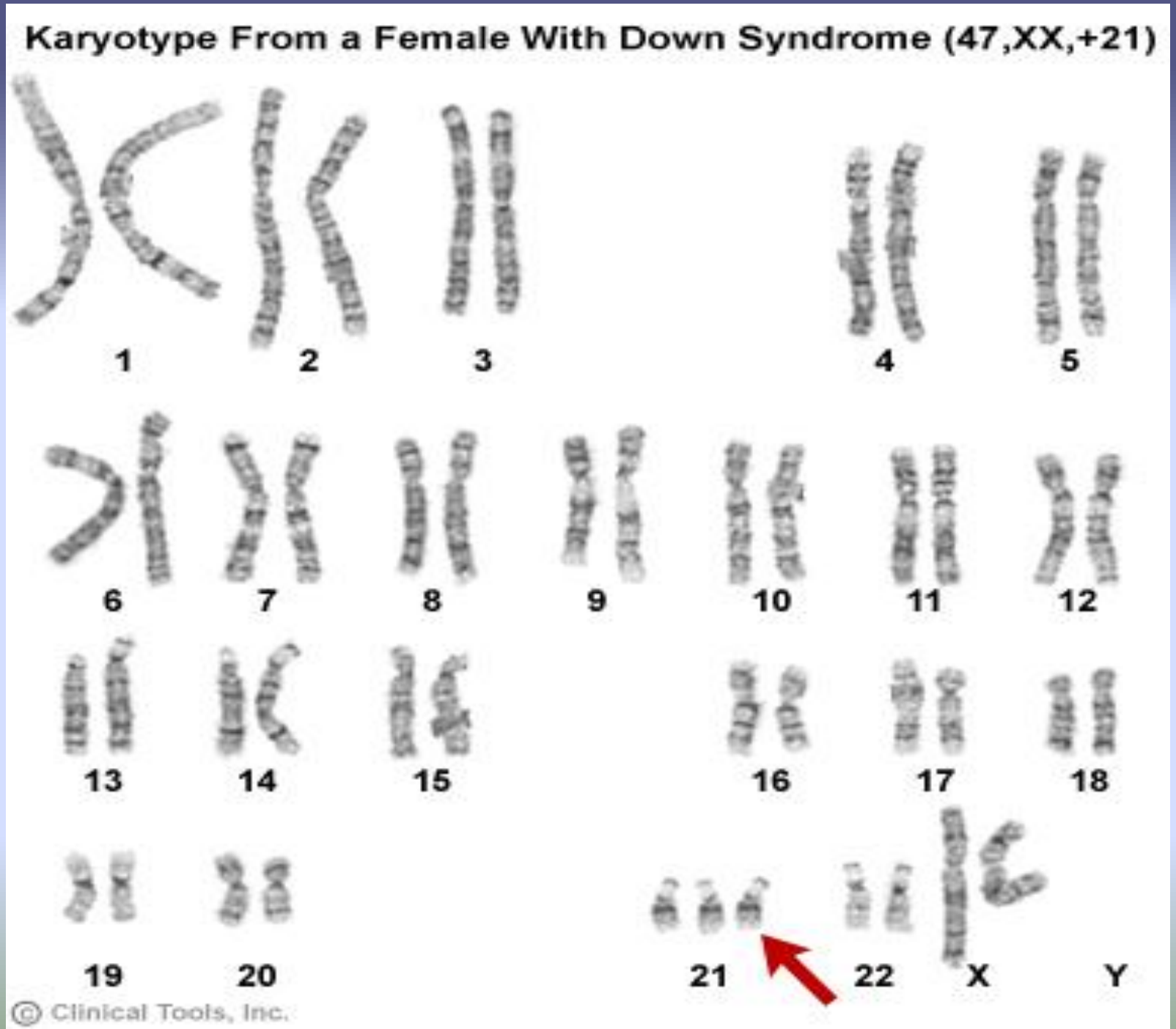
SINDROME DI DOWN = TRISOMIA 21

MA QUANTE FORME DI TRISOMIA 21 ESISTONO?

- TRISOMIA 21 LIBERA (~ 95%)
- TRISOMIA 21 DA TRASLOCAZIONE (~ 4%)
- TRISOMIA 21 A MOSAICO (~ 1%)
- DUPLICAZIONE DI PORZIONI DEL CROMOSOMA 21 (RARO)

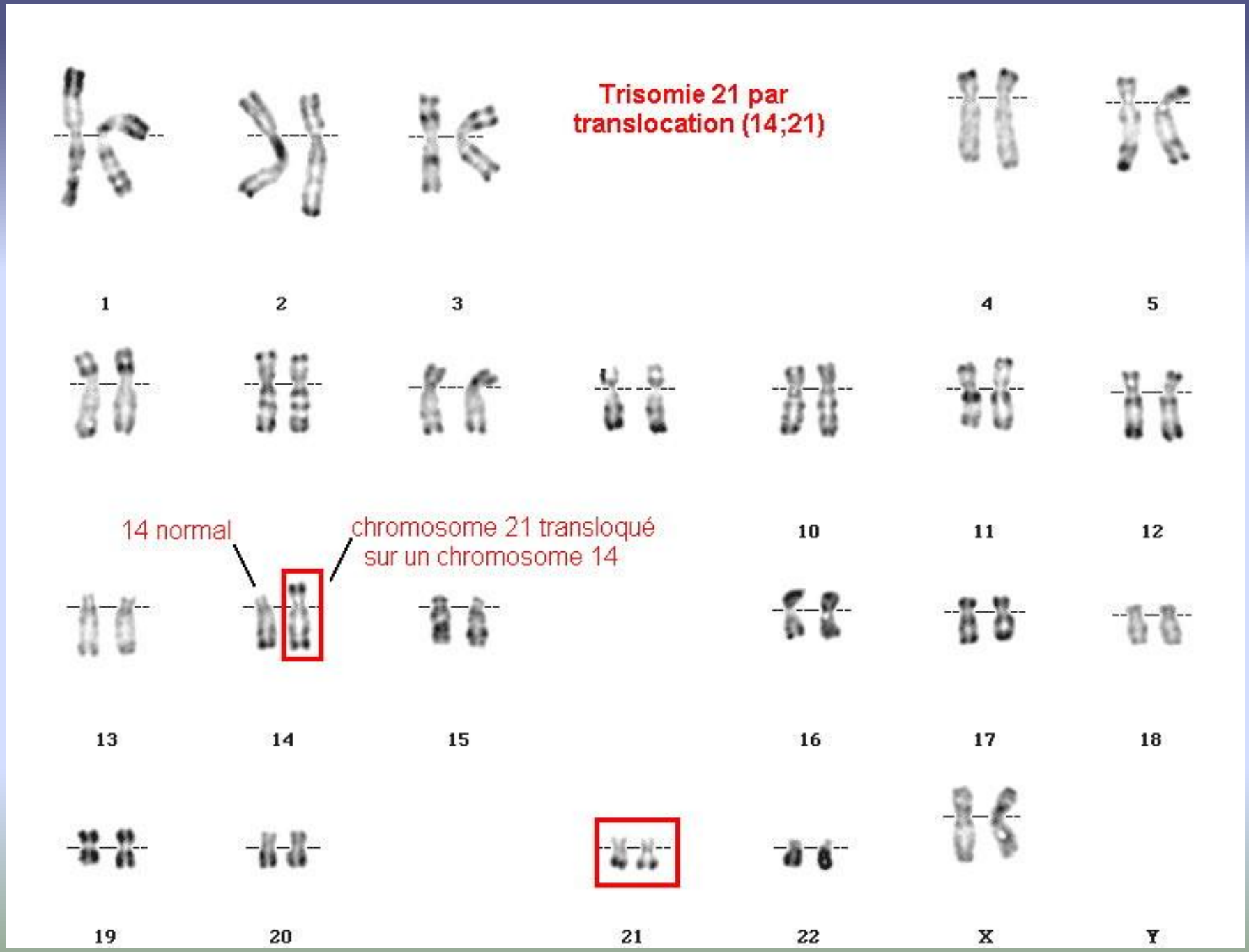
DALLA GENETICA...

TRISOMIA 21 LIBERA



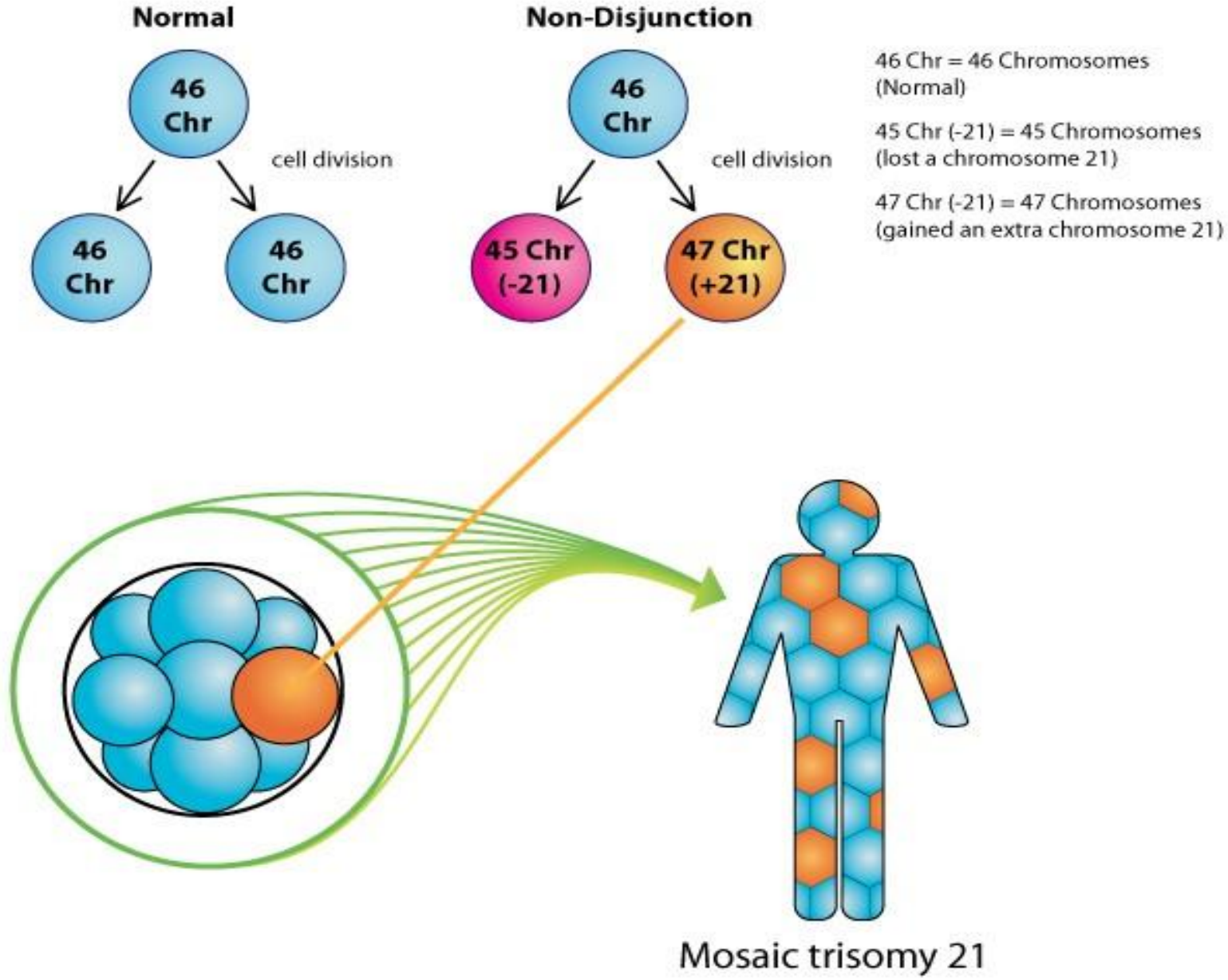
DALLA GENETICA...

TRISOMIA DA TRASLOCAZIONE



DALLA GENETICA...

TRISOMIA 21 "A MOSAICO"



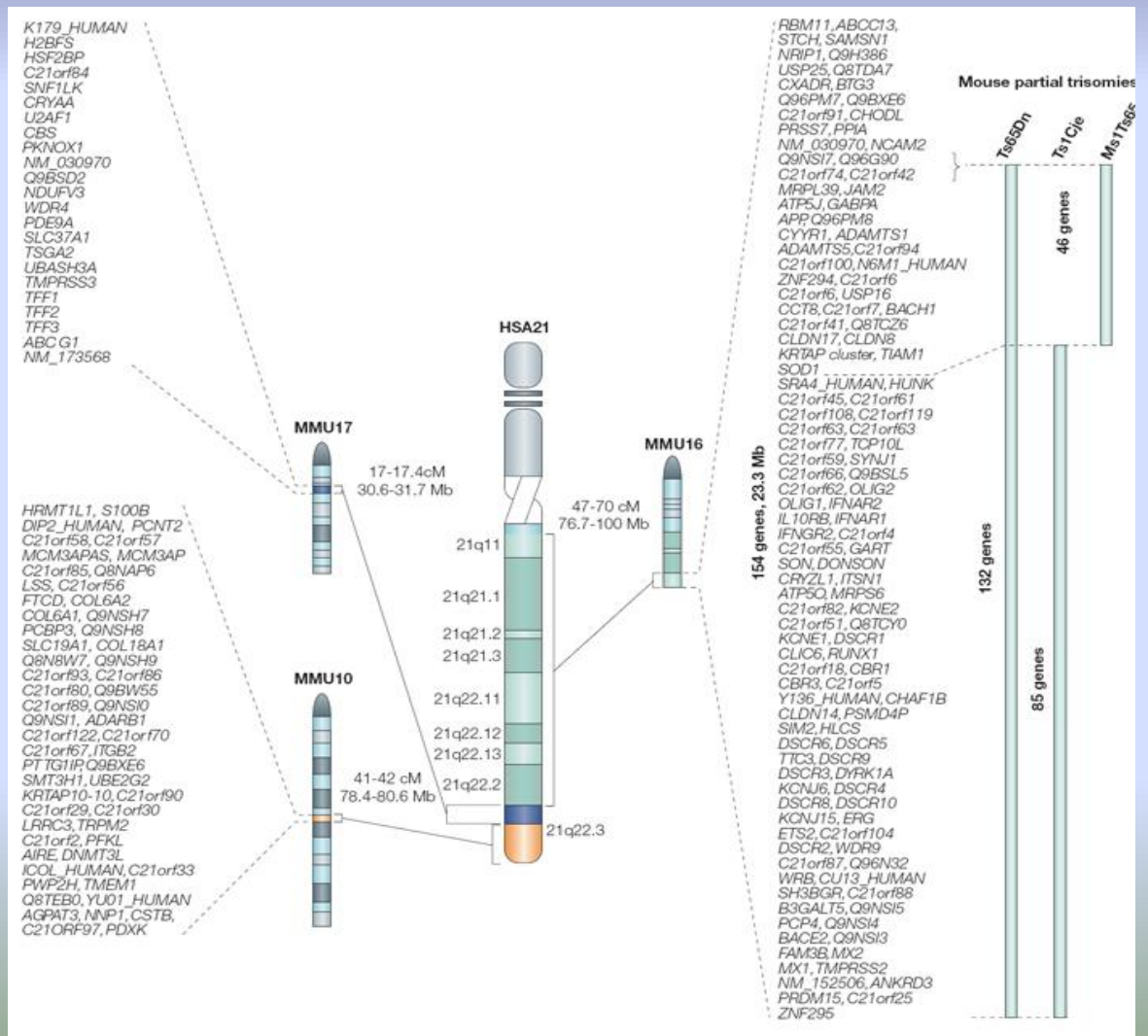
DALLA GENETICA...

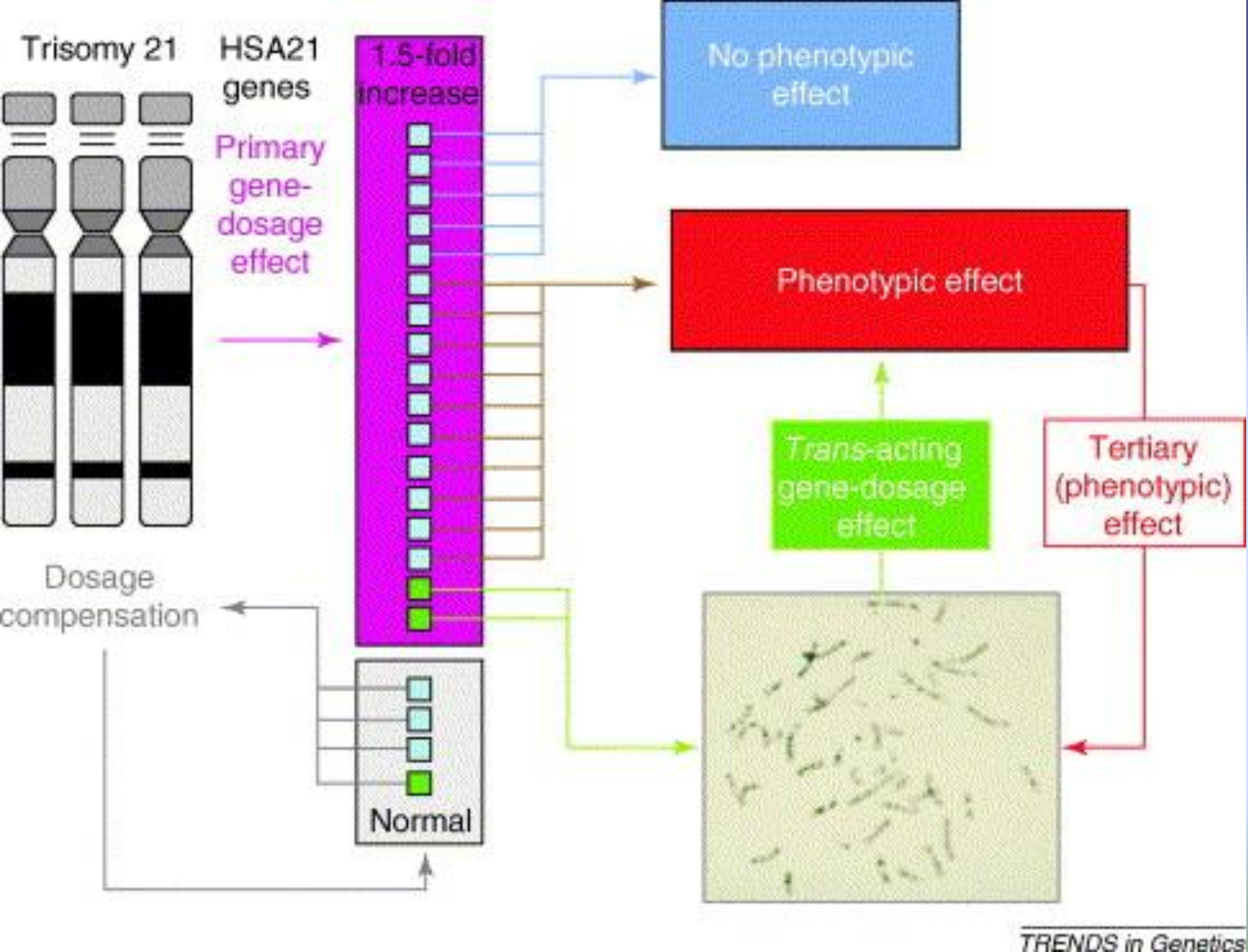
- **TRISOMIA 21 VUOL DIRE 3 COPIE DEL CROMOSOMA 21**

Ci sono circa 400 geni sul cromosoma 21

AVERE 3 COPIE DEL CR 21 SIGNIFICA AVERE TRE COPIE DEI GENI IVI CONTENUTI

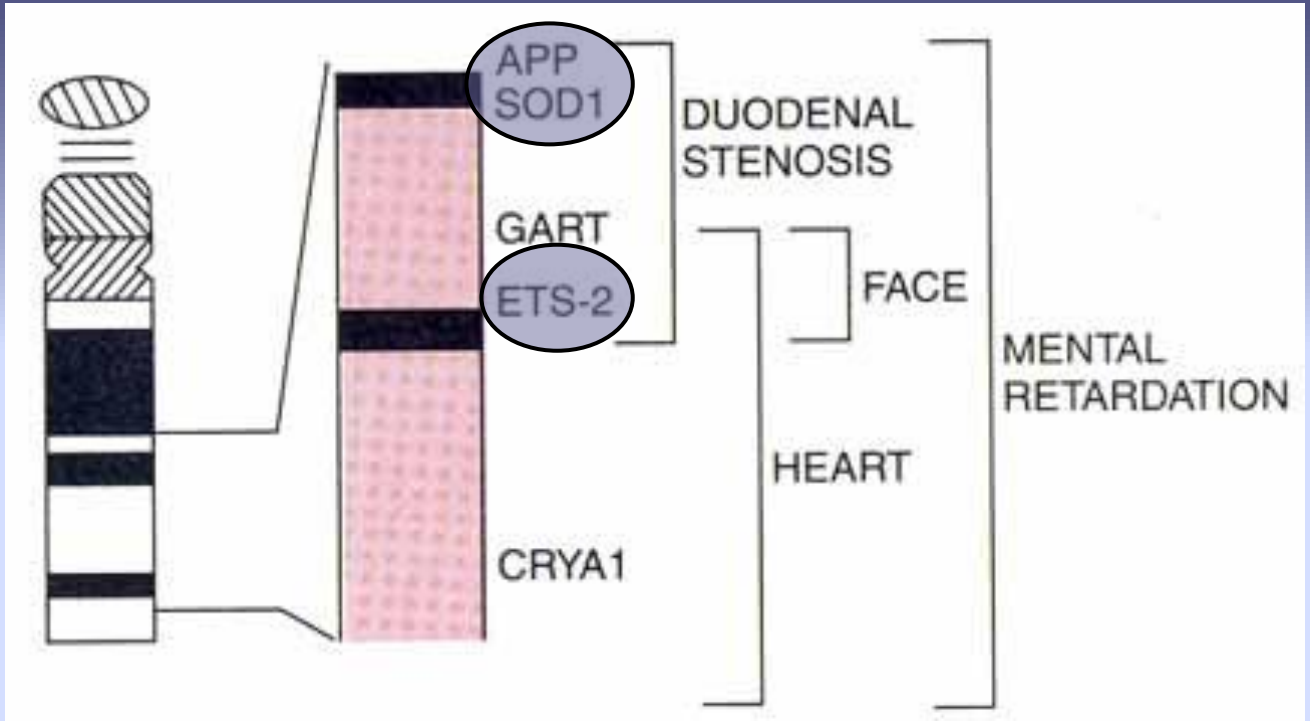
COSA COMPORTA?




Trisomy 21
HSA21 genes
1.5-fold increase
Primary gene-dosage effect
No phenotypic effect
Phenotypic effect
Trans-acting gene-dosage effect
Tertiary (phenotypic) effect
Dosage compensation
Normal
TRENDS in Genetics

DALLA GENETICA...

CROM. 21



- **APP** Amiloid Precursor Protein (Alzheimer)
- **ETS2** (anomalie scheletriche e cardiache)
- **SOD1** Superossido Dismutasi (stress ox e diminuita funzionalità del sistema immunitario)

DALLA GENETICA...

LA RICERCA IN AMBITO CELLULARE, GENETICO E BIOMOLECOLARE SULLA SINDROME DI DOWN È MOLTO VIVACE…

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PLOS ONE

Mitotic Spindle Defects and Chromosome Mis-Segregation Induced by LDL/Cholesterol—Implications for Niemann-Pick C1, Alzheimer's Disease, and Atherosclerosis

Antoneta Granic[1,2], **Huntington Potter**[1*]

1 Department of Neurology and Linda Crnic Institute for Down Syndrome, University of Colorado School of Medicine, Aurora, Colorado, United States of America, 2 Institute for Ageing and Health, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, United Kingdom

Abstract

Elevated low-density lipoprotein (LDL)-cholesterol is a risk factor for both Alzheimer's disease (AD) and Atherosclerosis (CVD), suggesting a common lipid-sensitive step in their pathogenesis. Previous results show that AD and CVD also share a cell cycle defect: chromosome instability and up to 30% aneuploidy–in neurons and other cells in AD and in smooth muscle cells in atherosclerotic plaques in CVD. Indeed, specific degeneration of aneuploid neurons accounts for 90% of neuronal loss in AD brain, indicating that aneuploidy underlies AD neurodegeneration. Cell/mouse models of AD develop similar aneuploidy through amyloid-beta (Aß) inhibition of specific microtubule motors and consequent disruption of mitotic spindles. Here we tested the hypothesis that, like upregulated Aß, elevated LDL/cholesterol and altered intracellular cholesterol homeostasis also causes chromosomal instability. Specifically we found that: 1) high dietary cholesterol induces aneuploidy in mice, satisfying the hypothesis' first prediction, 2) Niemann-Pick C1 patients accumulate aneuploid fibroblasts, neurons, and glia, demonstrating a similar aneugenic effect of intracellular cholesterol accumulation in humans 3) oxidized LDL, LDL, and cholesterol, but not high-density lipoprotein (HDL), induce chromosome mis-segregation and aneuploidy in cultured cells, including neuronal precursors, indicating that LDL/cholesterol directly affects the cell cycle, 4) LDL-induced aneuploidy requires the LDL receptor, but not Aß, showing that LDL works differently than Aß, with the same end result, 5) cholesterol treatment disrupts the structure of the mitotic spindle, providing a cell biological mechanism for its aneugenic activity, and 6) ethanol or calcium chelation attenuates lipoprotein-induced chromosome mis-segregation, providing molecular insights into cholesterol's aneugenic mechanism, specifically through its rigidifying effect on the cell membrane, and potentially explaining why ethanol consumption reduces the risk of developing atherosclerosis or AD. These results suggest a novel, cell cycle mechanism by which aberrant cholesterol homeostasis promotes neurodegeneration and atherosclerosis by disrupting chromosome segregation and potentially other aspects of microtubule physiology.

Citation: Granic A, Potter H (2013) Mitotic Spindle Defects and Chromosome Mis-Segregation Induced by LDL/Cholesterol—Implications for Niemann-Pick C1, Alzheimer's Disease, and Atherosclerosis. PLoS ONE 8(4): e60718. doi:10.1371/journal.pone.0060718

Editor: Ken Arai, Massachusetts General Hospital/Harvard Medical School, United States of America

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Competing Interests: The authors have declared that no competing interests exist.

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Cell Stem Cell
Brief Report

Trisomy Correction in Down Syndrome Induced Pluripotent Stem Cells

Li B. Li,[1] Kai-Hsin Chang,[1] Pei-Rong Wang,[1] Roli K. Hirata,[1] Thalia Papayannopoulou,[1] and David W. Russell[1,2,*]
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http://dx.doi.org/10.1016/j.stem.2012.08.004

SUMMARY

Human trisomies can alter cellular phenotypes and produce congenital abnormalities such as Down syndrome (DS). Here we have generated induced pluripotent stem cells (iPSCs) from DS fibroblasts and introduced a *TKNEO* transgene into one copy of chromosome 21 by gene targeting. When selecting against *TKNEO*, spontaneous chromosome loss was the most common cause for survival, with a frequency of $\sim 10^{-4}$, while point mutations, epigenetic silencing, and *TKNEO* deletions occurred at lower frequencies in this unbiased comparison of inactivating mutations. Mitotic recombination events resulting in extended loss of heterozygosity were not observed in DS iPSCs. The derived, disomic cells proliferated faster and produced more endothelia in vivo than their otherwise isogenic trisomic counterparts, but in vitro hematopoietic differentiation was not consistently altered. Our study describes a targeted removal of a human trisomy, which could prove useful in both clinical and research applications.

nature medicine

Loss of sorting nexin 27 contributes to excitatory synaptic dysfunction by modulating glutamate receptor recycling in Down's syndrome

Xin Wang[1,2], Yingjun Zhao[1,3], Xiaofei Zhang[1], Hedieh Badie[4], Ying Zhou[2], Yangling Mu[5], Li Shen Loo[6], Lei Cai[6], Robert C Thompson[1], Bo Yang[1], Yaomin Chen[1], Peter F Johnson[7], Chengbiao Wu[8], Guojun Bu[3], William C Mobley[8], Dongxian Zhang[1], Fred H Gage[5], Barbara Ranscht[4], Yun-wu Zhang[1,3], Stuart A Lipton[1,8], Wanjin Hong[6,9] & Huaxi Xu[1,3]

Sorting nexin 27 (SNX27), a brain-enriched PDZ domain protein, regulates endocytic sorting and trafficking. Here we show that *Snx27*$^{-/-}$ mice have severe neuronal deficits in the hippocampus and cortex. Although *Snx27*$^{+/-}$ mice have grossly normal neuroanatomy, we found defects in synaptic function, learning and memory and a reduction in the amounts of ionotropic glutamate receptors (NMDA and AMPA receptors) in these mice. SNX27 interacts with these receptors through its PDZ domain, regulating their recycling to the plasma membrane. We demonstrate a concomitant reduced expression of SNX27 and CCAAT/enhancer binding protein β (C/EBPβ) in Down's syndrome brains and identify C/EBPβ as a transcription factor for *SNX27*. Down's syndrome causes overexpression of miR-155, a chromosome 21–encoded microRNA that negatively regulates C/EBPβ, thereby reducing SNX27 expression and resulting in synaptic dysfunction. Upregulating SNX27 in the hippocampus of Down's syndrome mice rescues synaptic and cognitive deficits. Our identification of the role of SNX27 in synaptic function establishes a new molecular mechanism of Down's syndrome pathogenesis.

THE EMBO JOURNAL

Have you seen?

The EMBO Journal (2012) 31, 3647–3649 | © 2012 European Molecular Biology Organization | All Rights Reserved 0261-4189/12
www.embojournal.org

Down syndrome DSCR1 causes spine pathology via the Fragile X-related protein FMRP

Francesco Roselli

Friedrich Miescher Institute for Biological Research, Basel, Switzerland. Correspondence to: francesco.roselli@fmi.ch

The EMBO Journal (2012) **31**, 3647–3649. doi:10.1038/emboj.2012.239; Published online 21 August 2012

A new study by Wang *et al* (2012) published in *The EMBO Journal* reports that the Down Syndrome Critical Region 1 (DSCR1) protein interacts with the Fragile X-related protein (FMRP) to regulate spine morphology and local protein synthesis. These findings highlight a convergence of Down syndrome (DS) and Fragile X pathogenic pathways, and provide insights on potential therapeutic approaches.

(Wang *et al*, 2012) and synaptic plasticity is altered. HSAq21 genes involved in synaptic physiology are therefore attractive candidates to account for intellectual disability in DS. Among them, *DSCR1* (also known as *RCAN1*) is strongly expressed in the brain and its overexpression or knockout causes memory impairment and LTP derangement in mice. DSCR1 is a negative regulator of calcineurin phosphatase and, as such, has been implicated in a large number of functions both in

The EMBO Journal (2012), 1–12 | © 2012 European Molecular Biology Organization | All Rights Reserved 0261-4189/12
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THE EMBO JOURNAL

DSCR1 interacts with FMRP and is required for spine morphogenesis and local protein synthesis

Wei Wang[1,3], John Z Zhu[1], Karen T Chang[2] and Kyung-Tai Min[1,3,*]

[1]Department of Biology, Indiana University, Bloomington, IN, USA, [2]Department of Cell and Neurobiology, Zilkha Neurogenetic Institute, University of Southern California, Los Angeles, CA, USA and [3]School of Nano-Bioscience and Chemical Engineering, UNIST (Ulsan National Institute of Science and Technology), Ulsan, Korea

Most common genetic factors known to cause intellectual disability are Down syndrome and Fragile X syndrome. However, the underlying cellular and molecular mechanisms of intellectual disability remain unclear. Recently, dendritic spine dysmorphogenesis and impaired local protein synthesis are posited to contribute to the cellular mechanisms of intellectual disability. Here, we show that Down syndrome critical region1 (DSCR1) interacts with Fragile X mental retardation protein (FMRP) and regulates both dendritic spine morphogenesis and local protein synthesis. Interestingly, decreasing the level of FMRP restores the DSCR1-induced changes in dendritic spine morphology. Our results imply that DSCR1 is a novel regulator of FMRP and that Fragile X syndrome and Down syndrome may share disturbances in common pathways that regulate dendritic spine morphology and local protein synthesis.

The EMBO Journal advance online publication, 3 August 2012; doi:10.1038/emboj.2012.190

Subject Categories: neuroscience; molecular biology of disease

Keywords: down syndrome; DSCR1; FMRP; Fragile X syndrome; local protein synthesis

Bassell and Warren, 2008; Waung and Huber, 2009). However, the molecular mechanisms regulating dendritic spine morphogenesis are not well understood and it is not known whether the two disorders share common disturbances in molecular pathways.

Recent studies propose that in addition to spine dysmorphogenesis, defects in local protein synthesis at dendritic spines may also contribute to the cellular and molecular mechanisms of intellectual disability. One protein implicated in spine morphogenesis and intellectual disability is the Fragile X mental retardation protein (FMRP) (Dierssen and Ramakers, 2006; Bassell and Warren, 2008; Waung and Huber, 2009). The absence of the mRNA-binding protein FMRP, encoded by the *fmr1* gene, causes mental impairment in Fragile X syndrome patients (Bagni and Greenough, 2005; Bassell and Warren, 2008; Garber *et al*, 2008; Waung and Huber, 2009). The *fmr1* knockout mice have deficits in learning behaviour, altered synaptic activity, as well as abnormal spine morphology characterized by a high density of thin and elongated spines (Comery *et al*, 1997; Penagarikano *et al*, 2007). FMRP is located in the cell body, dendrites, and dendritic spines in neurons and emerging evidence suggest that FMRP is involved in local protein synthesis in dendritic spines, although its regulatory mechanism is not well understood (Bagni and Greenough, 2005; Bassell and Warren, 2008; Muddashetty *et al*, 2011; Nalavadi *et al*, 2012; Niere *et al*, 2012).

Down syndrome critical region1 (DSCR1, also called RCAN1 or regulator of calcineurin) is located on human chromosome 21 and highly expressed in the brain, especially enriched in hippocampal neurons (Fuentes *et al*, 1995).

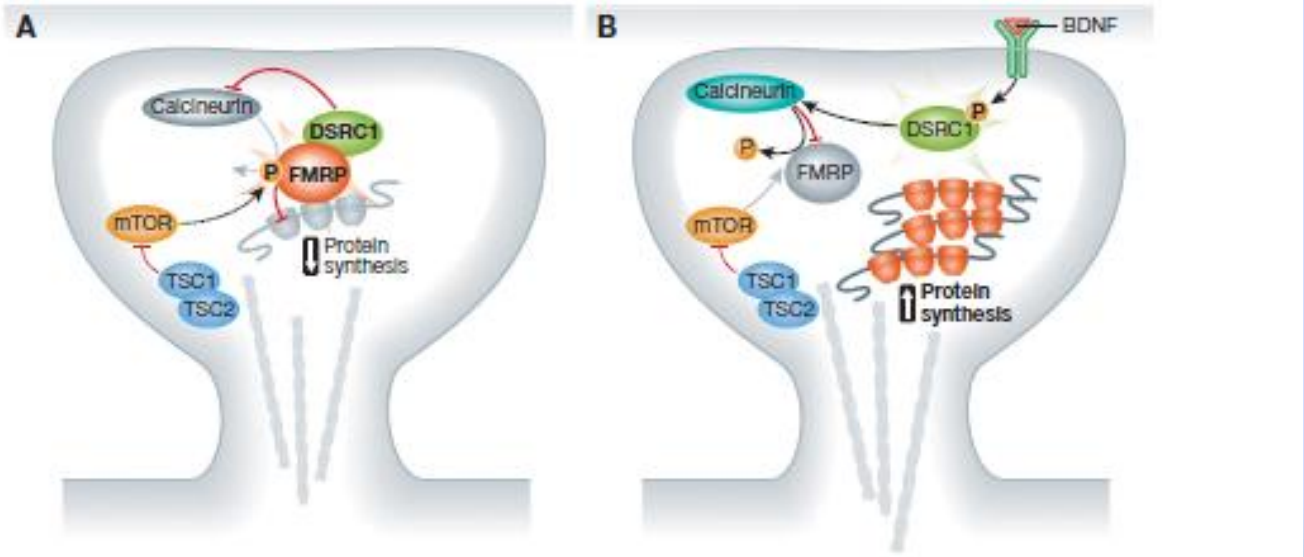

Figure 1 DSCR1 regulates mRNA translation at synapses through FMRP. (**A**) At rest, DSCR1 inhibits calcineurin that, in turn, does not dephosphorylate FMRP. Both mGluR5 and mTOR signalling cascades contribute to regulate FMRP phosphorylation; in its phosphorylated form, FMRP depresses mRNA translation. (**B**) Upon BDNF application, DSCR1 is phosphorylated and shifts to activate calcineurin, which efficiently dephosphorylates FMRP, relieving its inhibitory effect on mRNA translation.

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ALLA CLINICA

Natività
(Anonimo, circa 1515)

HA SENSO PARLARE ANCORA DI SINDROME DI DOWN?

DIPENDE DALL'ASSUNTO DI PARTENZA…

«Ah….ti occupi di persone con sindrome di Down…

Ma ne nascono ancora?»

Anonimo 2012

QUANTE SONO LE PERSONE CON SINDROME DI DOWN?

Attualmente in Italia circa 1 bambino su 1000 nasce con questa condizione.
Grazie allo sviluppo della medicina e alle maggiori cure dedicate a queste persone la durata della loro vita si è molto allungata così che si può ora parlare di un'aspettativa di vita di almeno 62 anni, destinata ulteriormente a crescere in futuro.
Si stima che oggi vivano in Italia circa 38.000 persone con sindrome di Down di cui li 61% ha più di 25 anni.

MA ⟹ NON ESISTONO STIME PRECISE UFFICIALI

ESEMPIO DI INCREMENTO DELLA POPOLAZIONE CON D.I.: LA SINDROME DI DOWN

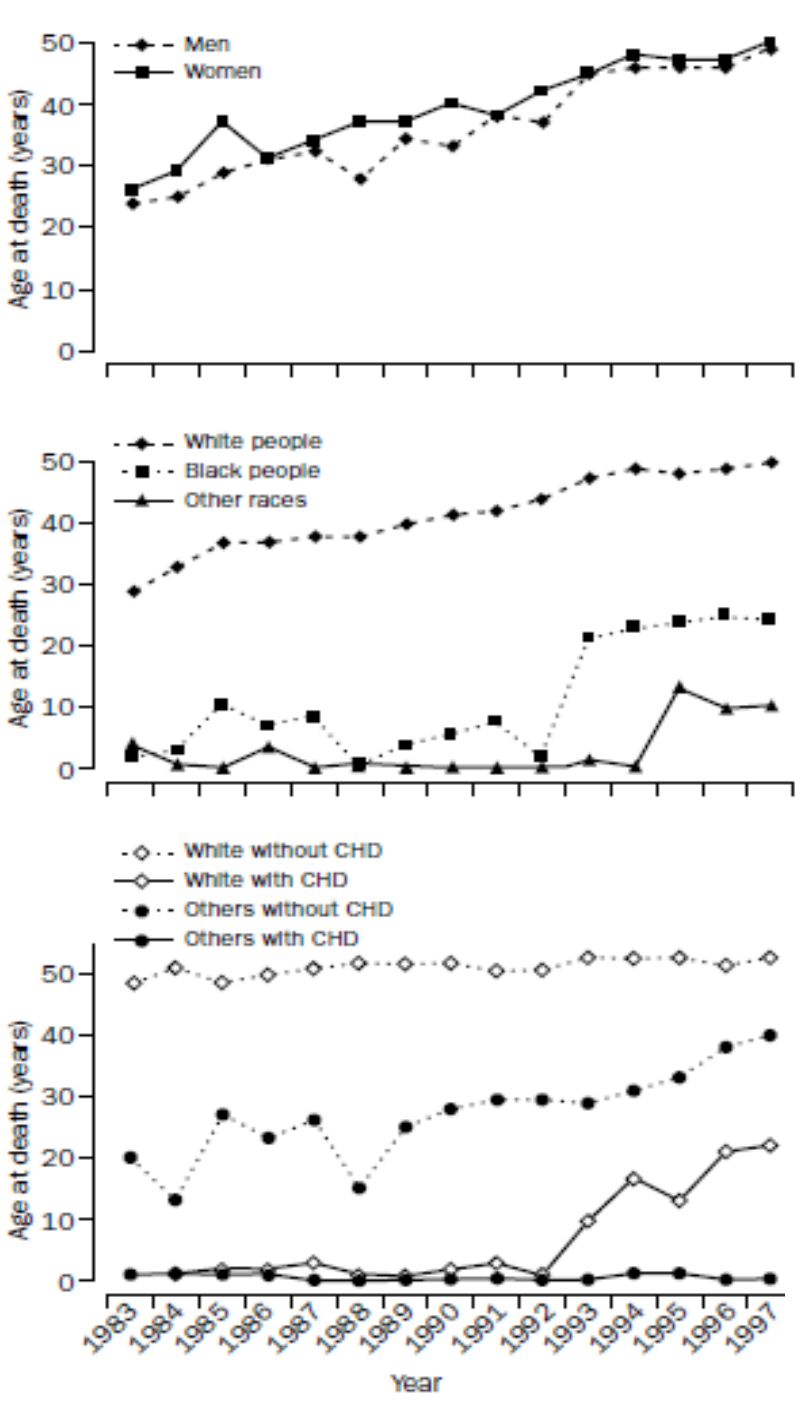

Figure 2: **Median age at death of people with Down's syndrome by sex (upper), racial group (middle), and with or without congenital heart defects (CHD) by racial group (lower)**

Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study

Quanhe Yang, Sonja A Rasmussen, J M Friedman

Lancet 2002; **359:** 1019–25

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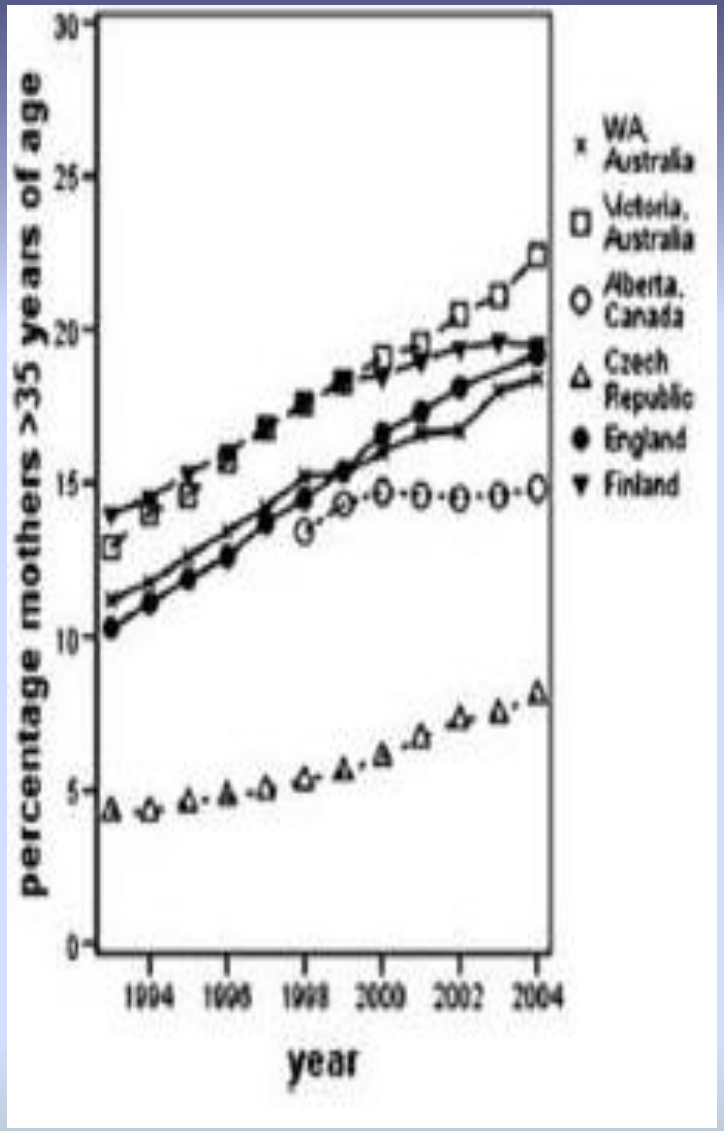
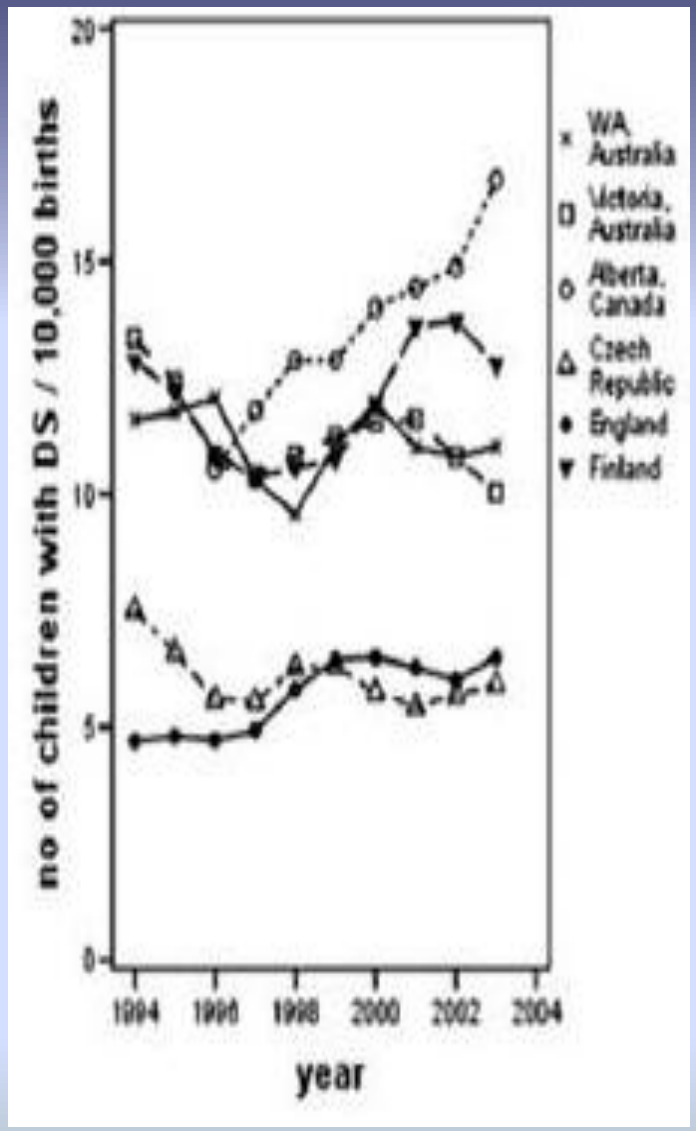
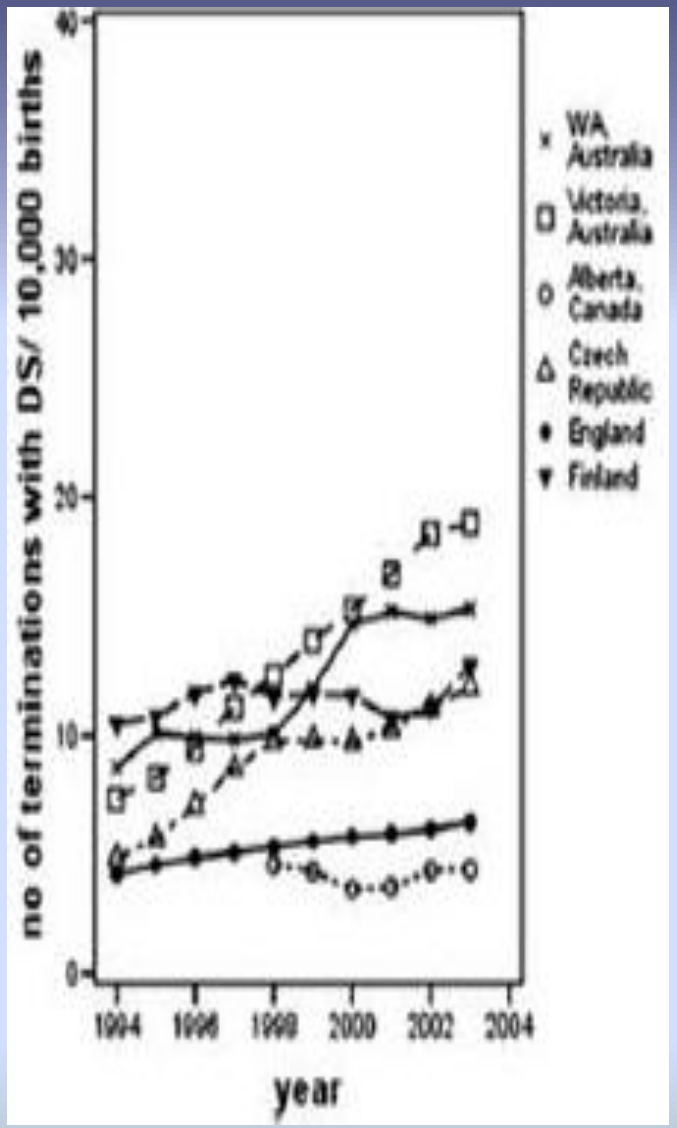
Birth Defects Research (Part A) 88:474–479 (2010)

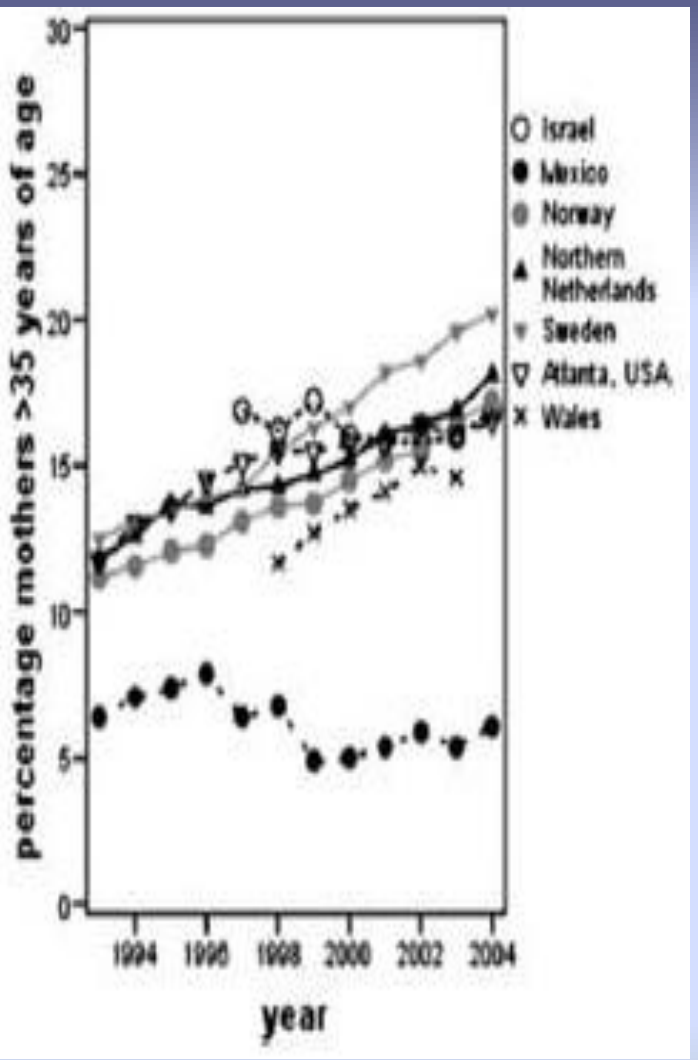
International Trends of Down Syndrome 1993–2004: Births in Relation to Maternal Age and Terminations of Pregnancies

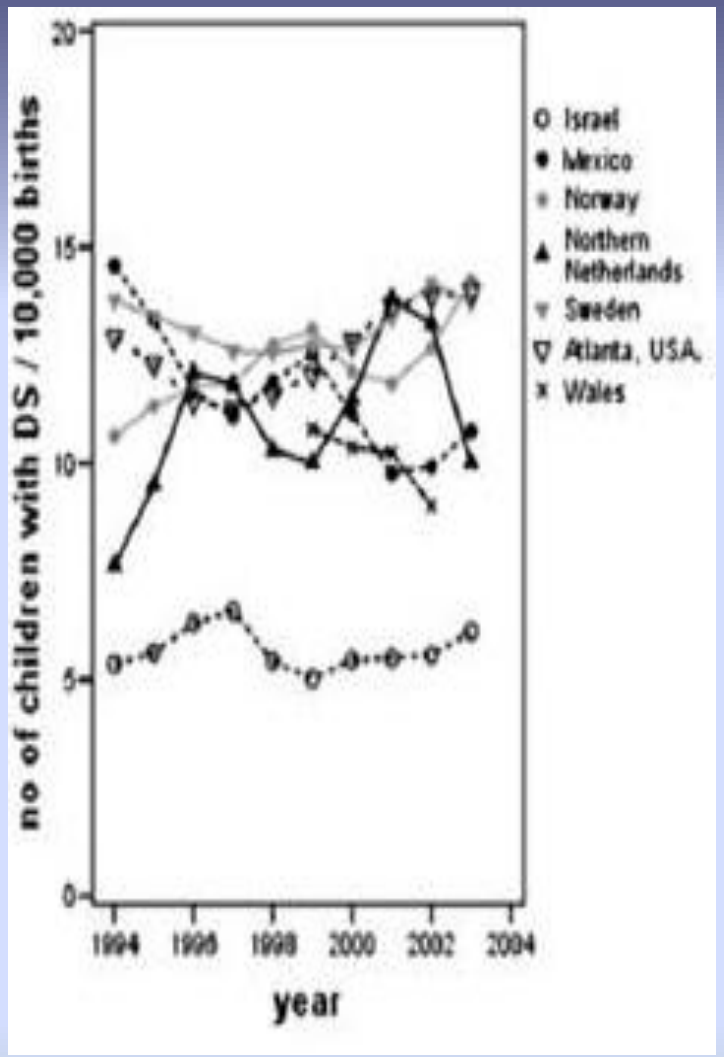
Guido Cocchi,[1] Silvia Gualdi,[1] Caroline Bower,[2] Jane Halliday,[3] Björn Jonsson,[4] Åsa Myrelid,[4] Pierpaolo Mastroiacovo,[5] Emmanuelle Amar,[6] Marian K. Bakker,[7] Andrea Correa,[8] Berenice Doray,[9] Kari Klungsør Melve,[10] Babak Koshnood,[11] Daniella Landau,[12] Osvaldo M. Mutchinick,[13] Anna Pierini,[14] Anukka Ritvanen,[15] Vera Ruddock,[16] Giocchino Scarano,[17] Barbara Sibbald,[18] Antonin Sípek,[19] Romano Tenconi,[20] Dave Tucker,[21] and Göran Annerén[4*]


percentage mothers >35 years of age
year
WA, Australia
Victoria, Australia
Alberta, Canada
Czech Republic
England
Finland


no of children with DS / 10,000 births
year
WA, Australia
Victoria, Australia
Alberta, Canada
Czech Republic
England
Finland


no of terminations with DS/ 10,000 births
year
WA, Australia
Victoria, Australia
Alberta, Canada
Czech Republic
England
Finland


percentage mothers >35 years of age
year
Israel
Mexico
Norway
Northern Netherlands
Sweden
Atlanta, USA
Wales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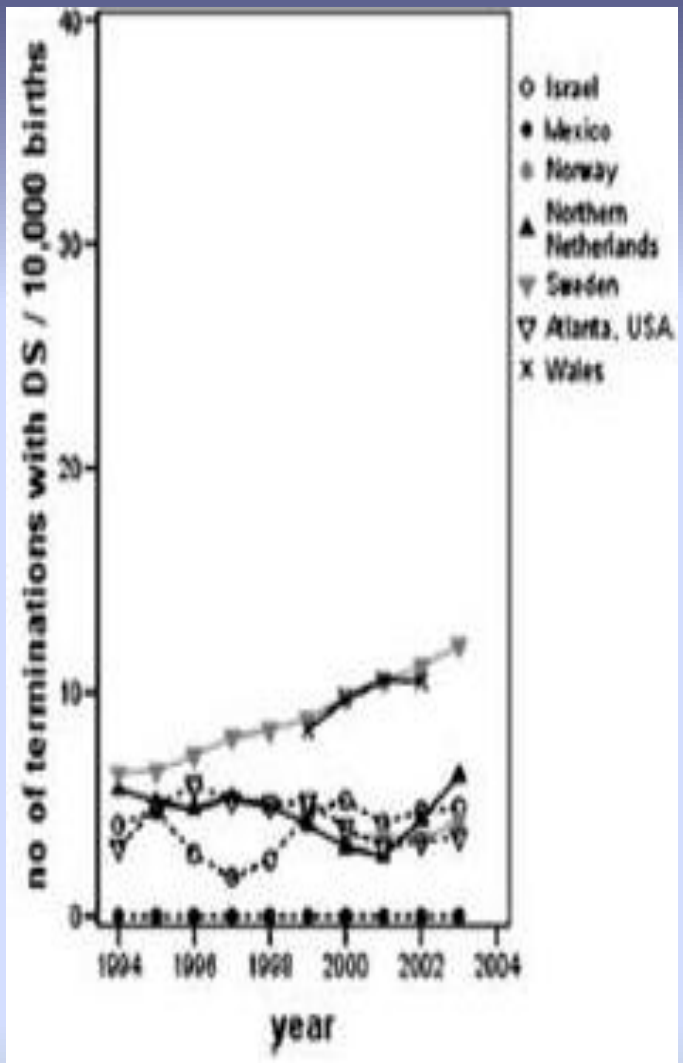
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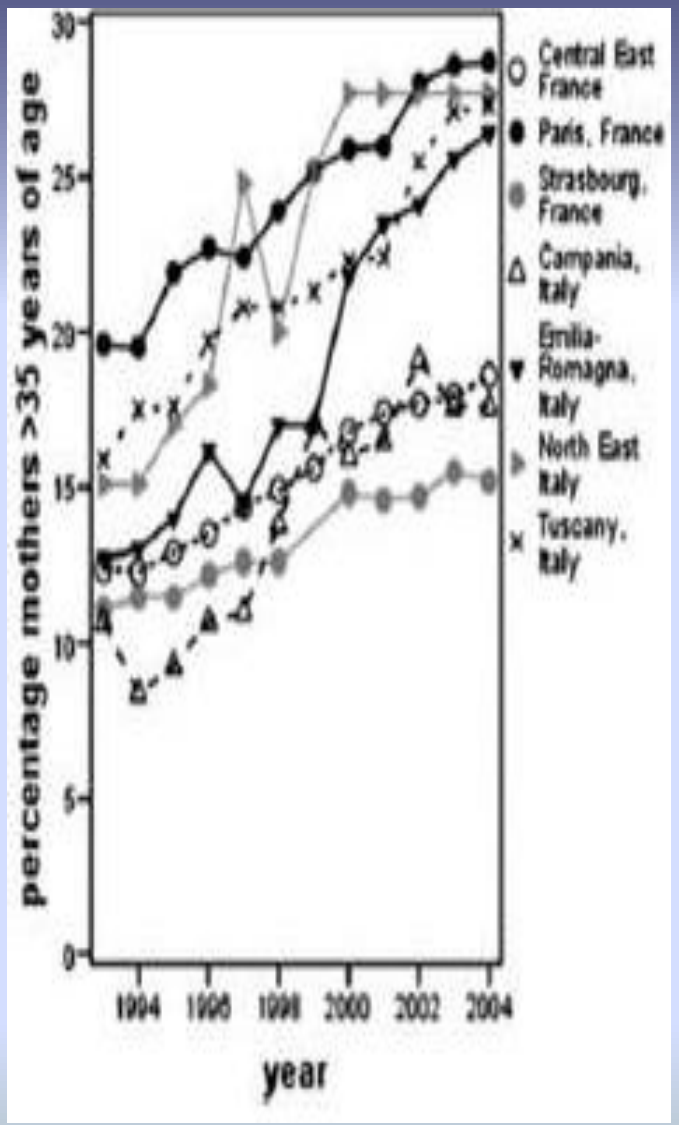
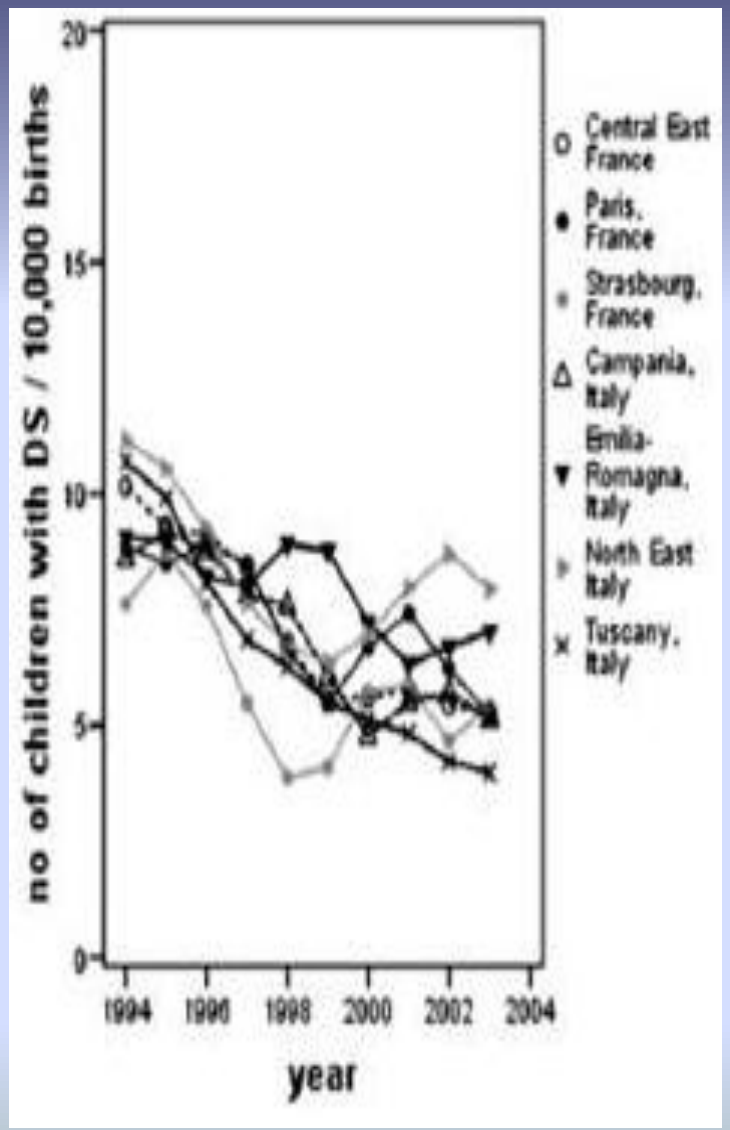
Sweden
Atlanta, USA
Wales


percentage mothers >35 years of age
year
Central East France
Paris, France
Strasbourg, France
Campania, Italy
Emilia-Romagna, Italy
North East Italy
Tuscany, Italy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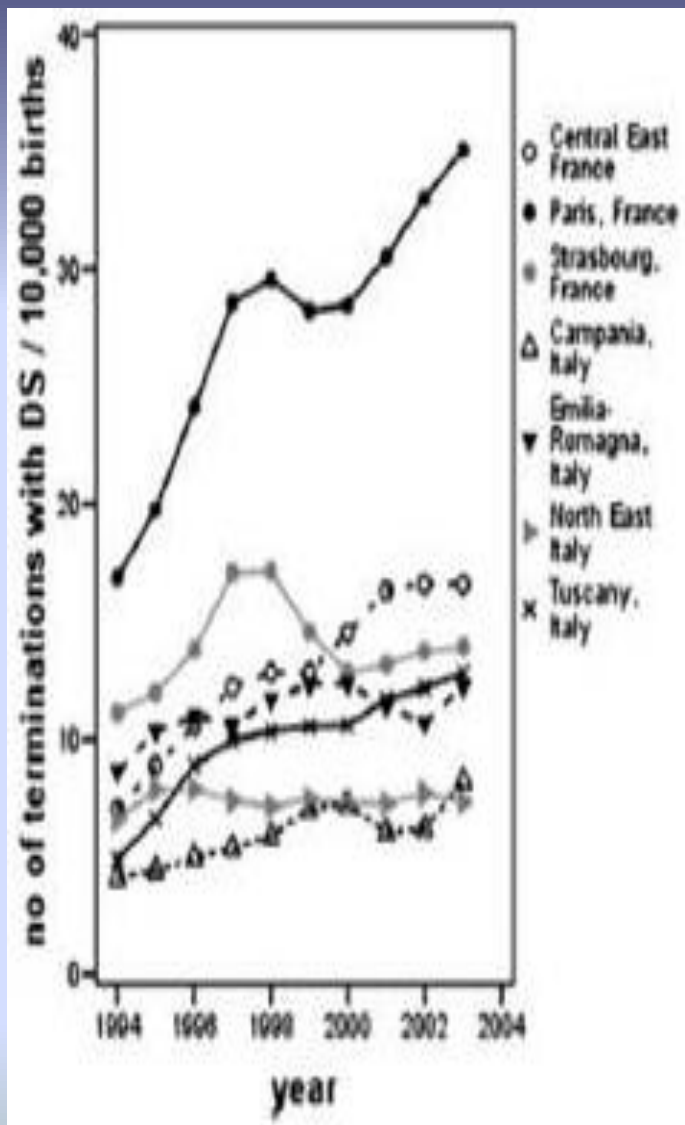
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Central East France
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Emilia-Romagna, Italy
North East Italy
Tuscany, Italy

DOI: 10.1002/pd.2910

ORIGINAL ARTICLE

Prenat
termin

Jaime L. Natoli

[1]University of So
[2]Oregon Colleg
*Correspondenc

ABSTRACT

Objective Th
prenatal diag

Method A sys
studies that r
pregnancy te
models, were

Results Twent
population-ba
eight anomaly
also varied wi

Conclusion This systematic review presents the largest synthesis of United States data on termination rates following a prenatal diagnosis of Down syndrome. Evidence suggests that termination rates are lower than noted in a previous review that was based on less contemporary studies and had an international focus. Heterogeneity across studies suggests that a summary termination rate may not be applicable to the entire US population. © 2012 John Wiley & Sons, Ltd.

Funding sources: None
Conflicts of interest: None declared

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- A prior international systematic review found that 92% of pregnancies with a prenatal diagnosis of Down syndrome were terminated.

WHAT DOES THIS STUDY ADD?

- This systematic review presents updated data on this topic and is the largest synthesis of data on termination rates following a prenatal diagnosis of Down syndrome in the United States.
- Overall, termination rates were lower than previously reported, and evidence suggests that termination rates have decreased in recent years.

DOI: 10.1002/pd.4001

ORIGINAL ARTICLE

Low uptake of the combined test in the Netherlands – which factors contribute?

Merel Bakker[1]*, Erwin Birnie[1,4], Eva Pajkrt[2], Caterina Maddalena Bilardo[1] and Rosalinde Johanna Maria Snijders[3]

[1]Department of Obstetrics and Gynecology, Fetal Medicine Unit, University Medical Center, Groningen, The Netherlands
[2]Department of Obstetrics and Gynecology, Fetal Medicine Unit, Academic Medical Center, Amsterdam, The Netherlands

Conclusion The uptake of the CT in this study is low. The main reason for the low uptake is the relatively positive attitude towards Down syndrome and a negative attitude towards TOP. Moreover, the perception of maternal age as strong predictor of Down syndrome risk and the inequality of access to care, due to the financial threshold for younger women, are likely to affect participation in screening. © 2012 John Wiley & Sons, Ltd.

Results Analyses were based on 820 questionnaires (73% response rate). Women from the NW region opted more often for the CT than women from the NE region (52.1% and 16.5%, respectively, $p < 0.001$). Women of 36 years and older opted more often for the CT than younger women (59.4% and 28.2%, respectively, $p < 0.001$). Women's socio-demographic background and their attitude towards Down syndrome and termination of pregnancy (TOP) had contributed independently on CT choice.

Conclusion The uptake of the CT in this study is low. The main reason for the low uptake is the relatively positive attitude towards Down syndrome and a negative attitude towards TOP. Moreover, the perception of maternal age as strong predictor of Down syndrome risk and the inequality of access to care, due to the financial threshold for younger women, are likely to affect participation in screening. © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Funding sources: None
Conflicts of interest: None declared

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IL PROSSIMO FUTURO...

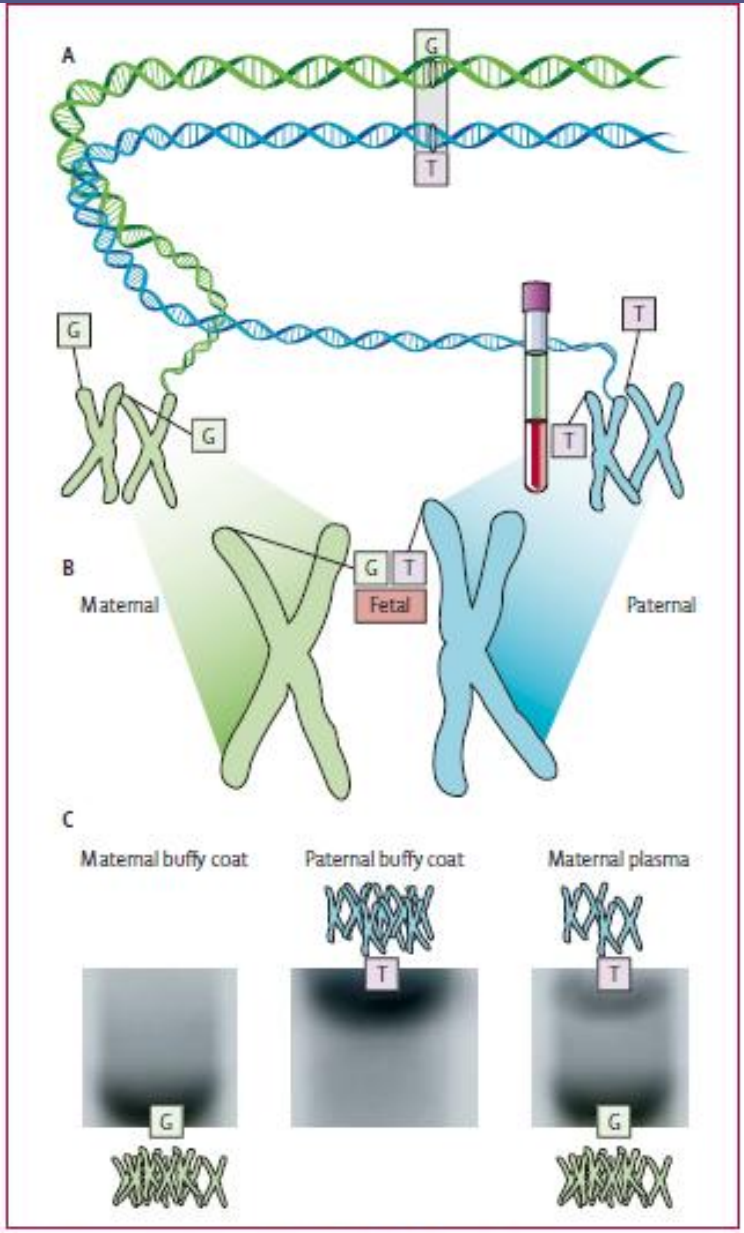


Figure 1: **Inheritance of single nucleotide polymorphisms**
(A) Single nucleotide polymorphisms (SNPs) are the greatest single source of natural variation in the human genome and can be used to determine the copy number of fetal chromosomes. (B) At certain sites within the fetal genome, the inherited paternal allele ("T") will differ from the inherited maternal allele ("G"). (C) Presence of the paternal allele in the plasma provides a genetic beacon to distinguish fetal DNA from maternal DNA.

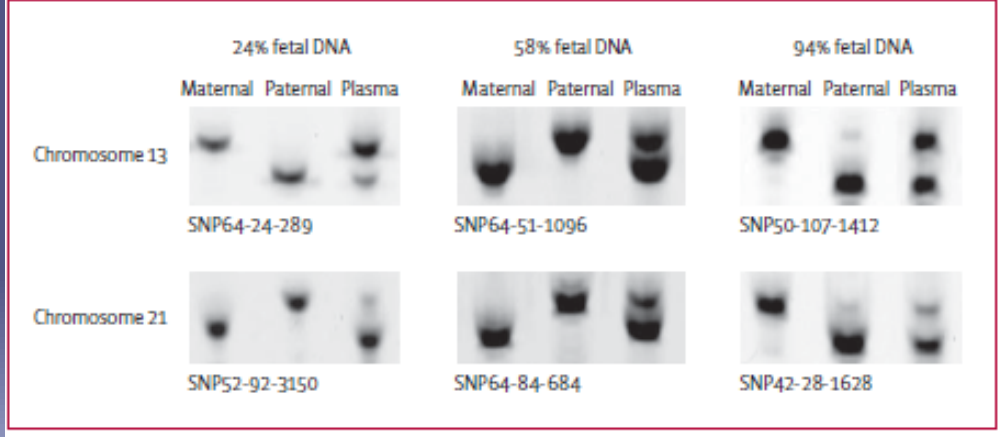
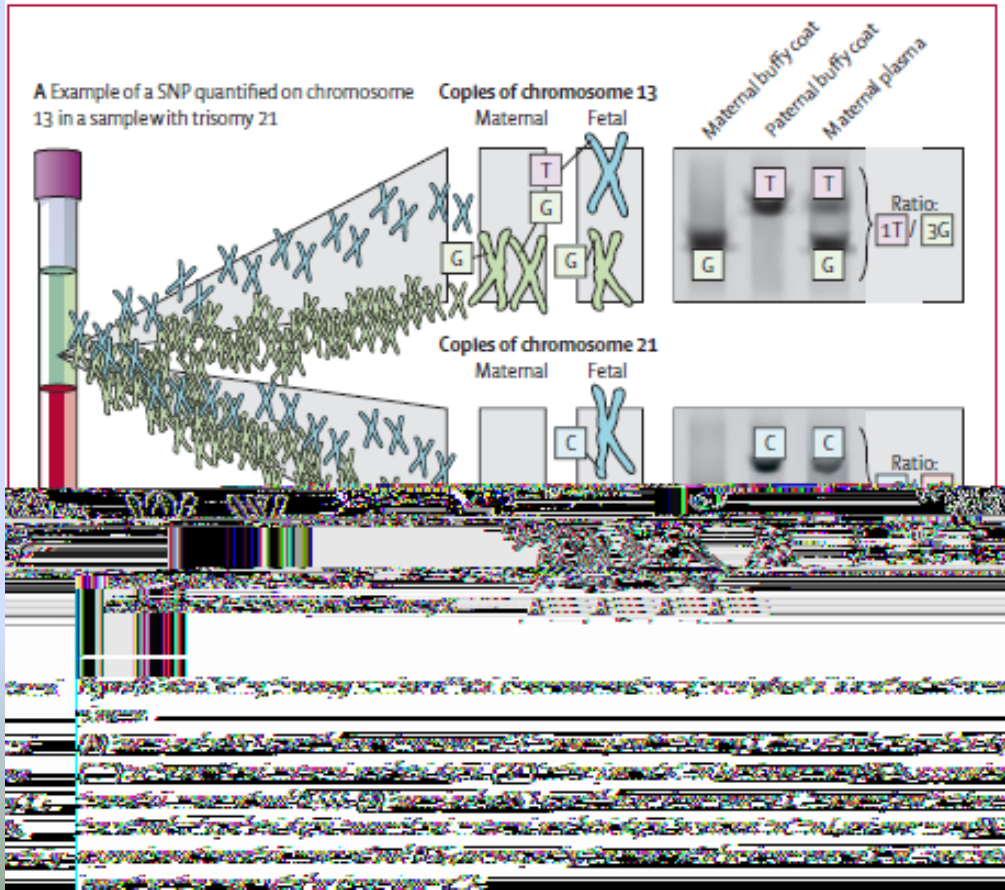
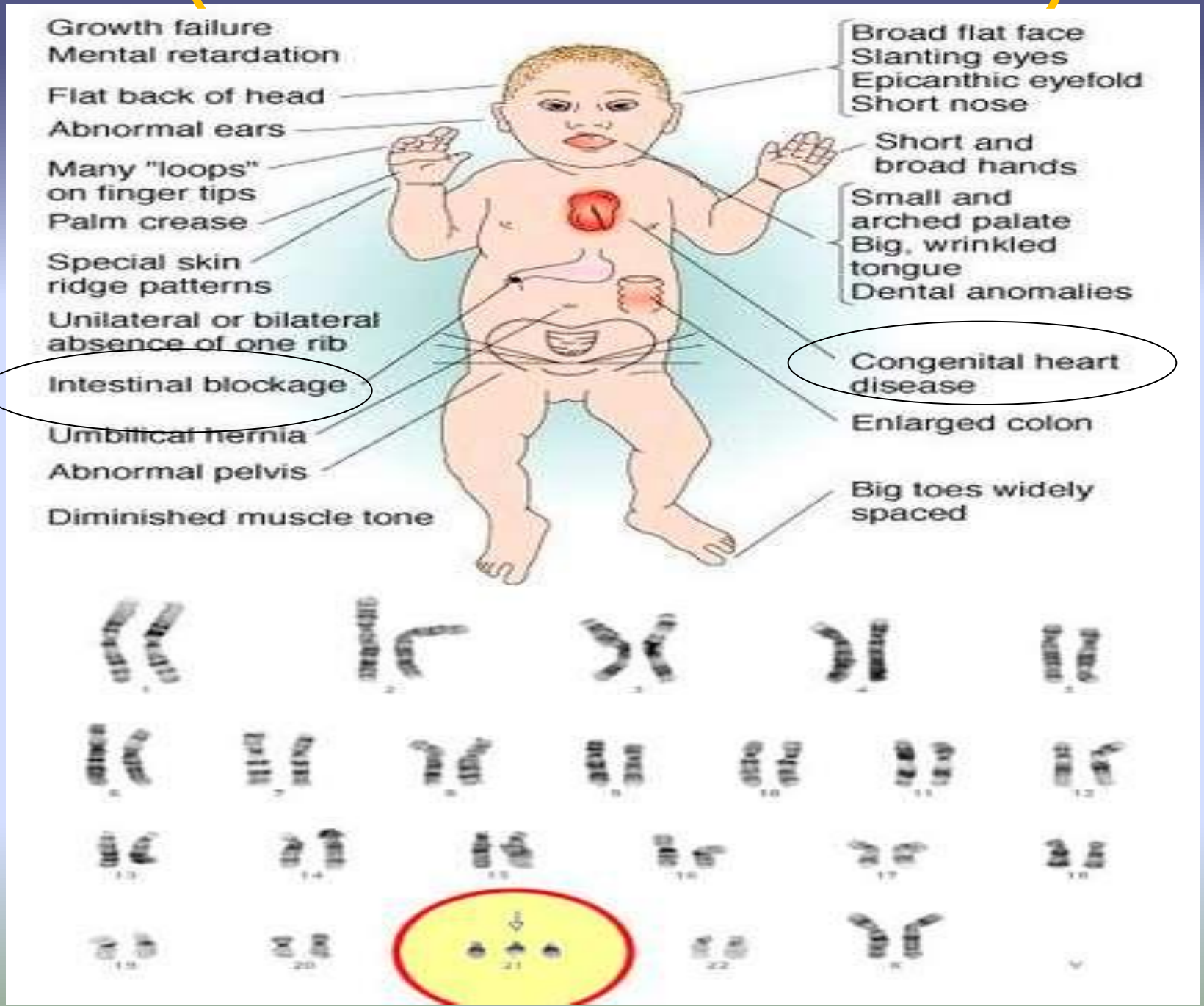


Figure 2: **SNPs on chromosomes 13 and 21 at various fetal DNA percentages in maternal plasma samples**
In a maternal plasma sample, the inherited paternal allele represents a unique marker, which distinguishes fetal DNA from maternal DNA. A homozygous allele signal from maternal genomic DNA (maternal), a homozygous allele signal from paternal genomic DNA (paternal) and signals from heterozygous alleles in maternal plasma DNA (plasma) are shown. The 94% fetal DNA example is sample 4, which was identified as trisomy 21. By contrast with the roughly 1 to 1 ratio of maternal (upper) and unique fetal (lower) alleles in the chromosome 13 panel (top), an indication of the presence of an additional, paternally inherited allele, is visible in the chromosome 21 panel (bottom), in which the ratio of maternal to unique fetal alleles is greater than 1 to 1.



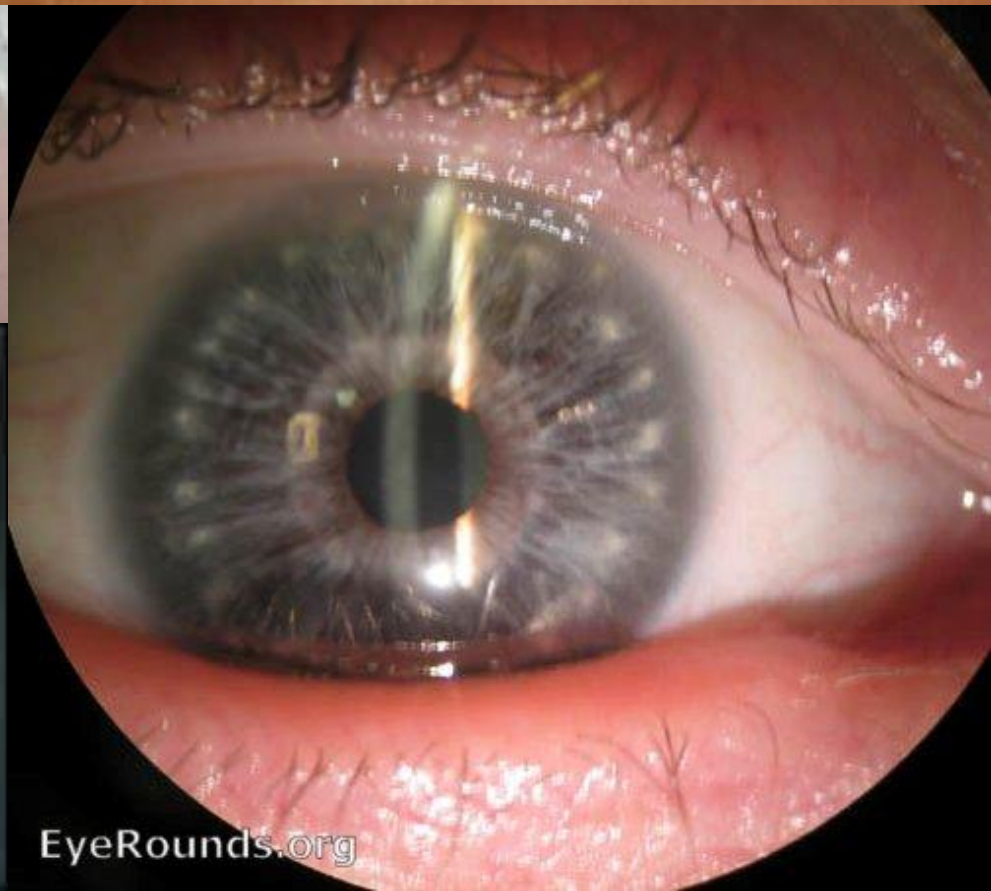
ALLA CLINICA

SEGNI TIPICI (VISIBILI GIÀ ALLA NASCITA)



1

2


EyeRounds.org

PER L'ETÀ PEDIATRICA ESISTONO DELLE LINEE GUIDA ACCETTATE A LIVELLO INTERNAZIONALE

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Health Supervision for Children With Down Syndrome

Marilyn J. Bull and the Committee on Genetics

Pediatrics 2011;128;393; originally published online July 25, 2011;
DOI: 10.1542/peds.2011-1605

	Prenatal	Birth–1 mo	1 mo–1 y	1–5 y	5–13 y	13–21 y
Counseling regarding prenatal screening test & imaging results						
Plan for delivery						
Referral to geneticist						
Parent-to-parent contact, support groups, current books and pamphlets						
Physical exam for evidence of trisomy 21						
Chromosomal analysis to confirm dx						
Discuss risk of recurrence of Down syndrome						
Echocardiogram						
Radiographic swallowing assessment if marked hypotonia, slow feeding, choking with feeds, recurrent or persistent respiratory sx, FTT						
Eye exam for cataracts						
Newborn hearing screen and follow-up						
Hx and PE assessment for duodenal or anorectal atresia						
Reassure parents delayed and irregular dental eruption, hypodontia are common						
If constipation, evaluate for limited diet or fluids, hypotonia, hypothyroidism, GI malformation, Hirschsprung		Any visit				
CBC to R/O transient myeloproliferative disorder, polycythemia						
Hb annually; CRP & ferritin or CHr if possible risk iron deficiency or Hb <11 g.				Annually		
Hemoglobin						Annually
TSH (may be part of newborn screening)			6 and 12 mo	Annually		
Discuss risk of respiratory infection						
If cardiac surgery or hypotonic: evaluate apnea, bradycardia, or oxygen desaturation in car seat before discharge						
Discuss complementary & alternative therapies		All health maint. visits				
Discuss cervical spine positioning, especially for anesthesia or surgical or radiologic procedures		All health maint. visits				
Review signs and symptoms of myopathy		All health maint. visits				
If myopathic signs or symptoms: obtain neutral position spine films and, if normal, obtain flexion & extension films & refer to pediatric neurosurgeon or orthopedic surgeon with expertise in evaluating and treating atlanto-axial instability		Any visit				

Instruct to contact physician for change in gait, change in use of arms or hands, change in bowel or bladder function, neck pain, head tilt, torticollis, or new-onset weakness				Biennially		
Advise risk of some contact sports, trampolines				All health maint. visits		
Audiology evaluation at 6 mo						
If normal hearing established, behavioral audiogram and tympanometry until bilateral ear specific testing possible. Refer child with abnormal hearing to ot				Every 6 mo		
If normal ear-specific hearing established, behavioral audiogram				Annually		
Assess for obstructive sleep apnea Sx				All health maint. visits		
Sleep study by age 4 years						
Ophthalmology referral to assess for strabismus, cataracts, and nystagmus						
Refer to pediatric ophthalmologist or ophthalmologist with experience with Down syndrome				Annually	Every 2 y	Every 3 y
If congenital heart disease, monitor for signs & Sx of Congestive heart failure		All visits				
Assess the emotional status of parents and intrafamilial relationships		All health maint. visits				
Check for Sx of celiac disease; if Sx present, obtain tissue transglutaminase IgA & quantitative IgA				All health maint. visits		
Early intervention: physical, occupational, and speech therapy				Health maint. visits		
At 30 months, discuss transition to preschool and development of IEP						
Discuss behavioral and social progress				Health maint. visits		
Discuss self-help skills, ADHD, OCD, wandering off, transition to middle school					Health maint. visits	
If chronic cardiac or pulmonary disease, 23-valent pneumococcal vaccine at age >2 y						
Reassure regarding delayed and irregular dental eruption						
Establish optimal dietary and physical exercise patterns				Health maint. visits		
Discuss dermatologic issues with parents						
Discuss physical and psychosocial changes though puberty, need for gynecologic care in the pubescent female						
Facilitate transition: guardianship, financial planning, behavioral problems, school placement, vocational training, independence with hygiene and self-care, group homes, work settings						Health maint. visits
Discuss sexual development and behaviors, contraception, sexually transmitted diseases, recurrence risk for offspring						Health maint. visits
		Do once at this age				
		Do if not done previously				
		Repeat at indicated intervals				

E IN ETÀ ADULTA?

Transizione e tappe determinanti nella vita delle persone con SD

Tappe fondamentali

Infanzia

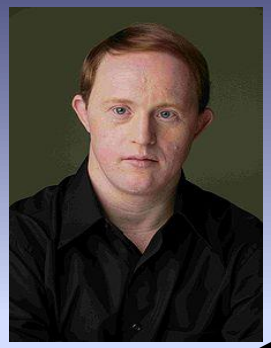
Conclusione studi
Autonomia
Indipendenza dalla famiglia

Vita in famiglia
Aiuto alle famiglie
Scuola
Cure mediche
Svago

Adolescenza

Vita in famiglia
Aiuto ai famigliari
Inserimento lavorativo
Cure mediche
Vvta in comunità

Maturità



Autonomia
Cambiamenti nello stato di salute
Mutamento stile di vita
Invecchiamento della famiglia e del caregiver

Vecchiaia

Pensionamento
Declino fisico e mentale
Perdita dei caregiver

Vita autonoma o in gruppo
Ritiro dal lavoro
Cure mediche
Coinvolgimento nella comunità

Transizioni

LINEE GUIDA FOLLOW-UP CLINICO PERSONE CON SD

ETA' PEDIATRICA (fino ai 21 anni)

- Bull MJ; Committee on Genetics

Health supervision for children with Down syndrome

Pediatrics. 2011 Aug;128(2):393-406

- Weijerman ME et al Eur J Pediatr. 2010 Dec;169(12):1445-52

ETA' ADULTA

EXPERT OPINION, GOOD CLINICAL PRACTICE, ECC…

SD COME SINDROME PROGEROIDE (Madan et al 2006)

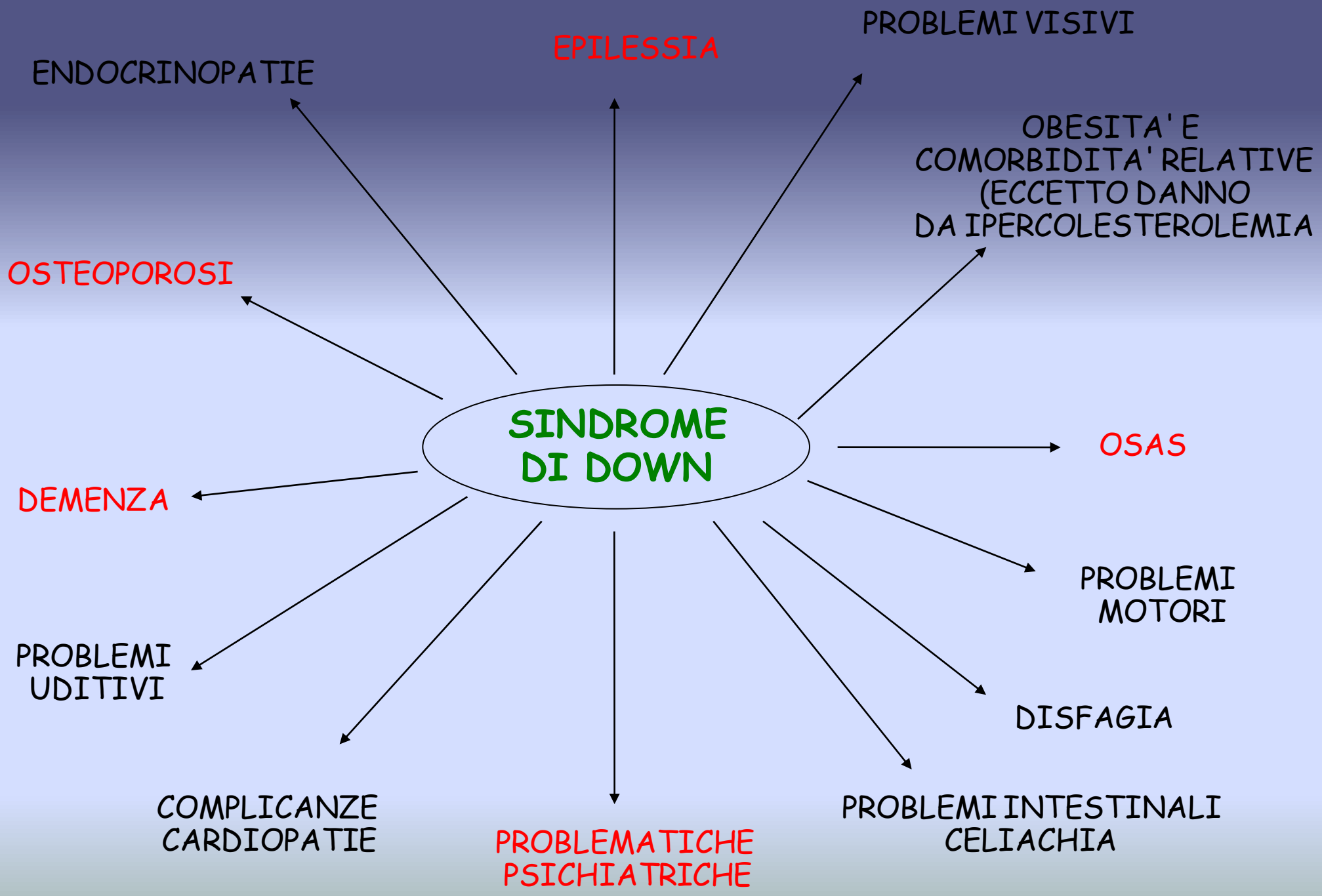
- INVECCHIAMENTO CUTANEO
- MENOPAUSA
- OSTEOPOROSI
- OSTEOARTRITE
- IPOGONADISMO
- PATOLOGIE AUTOIMMUNI
- CATARATTA

AD UN'ETA' SIGNIFICATIVAMENTE INFERIORE RISPETTO A POPOLAZIONE GENERALE (<40 ANNI)

PROBLEMATICHE MEDICHE

NEI SOGGETTI CON SD

IN ETA' AVANZATA


SINDROME DI DOWN
ENDOCRINOPATIE
EPILESSIA
PROBLEMI VISIVI
OBESITA' E COMORBIDITA' RELATIVE (ECCETTO DANNO DA IPERCOLESTEROLEMIA
OSTEOPOROSI
OSAS
DEMENZA
PROBLEMI MOTORI
PROBLEMI UDITIVI
DISFAGIA
COMPLICANZE CARDIOPATIE
PROBLEMATICHE PSICHIATRICHE
PROBLEMI INTESTINALI CELIACHIA

PROBLEMI VISIVI

- Calo visione periferica
- Perdita acuità visiva nella visione notturna
- Ridotta capacita di distinzione dei colori
- Xeroftlamia

Hindawi Publishing Corporation
Current Gerontology and Geriatrics Research
Volume 2012, Article ID 974253, 9 pages
doi:10.1155/2012/974253

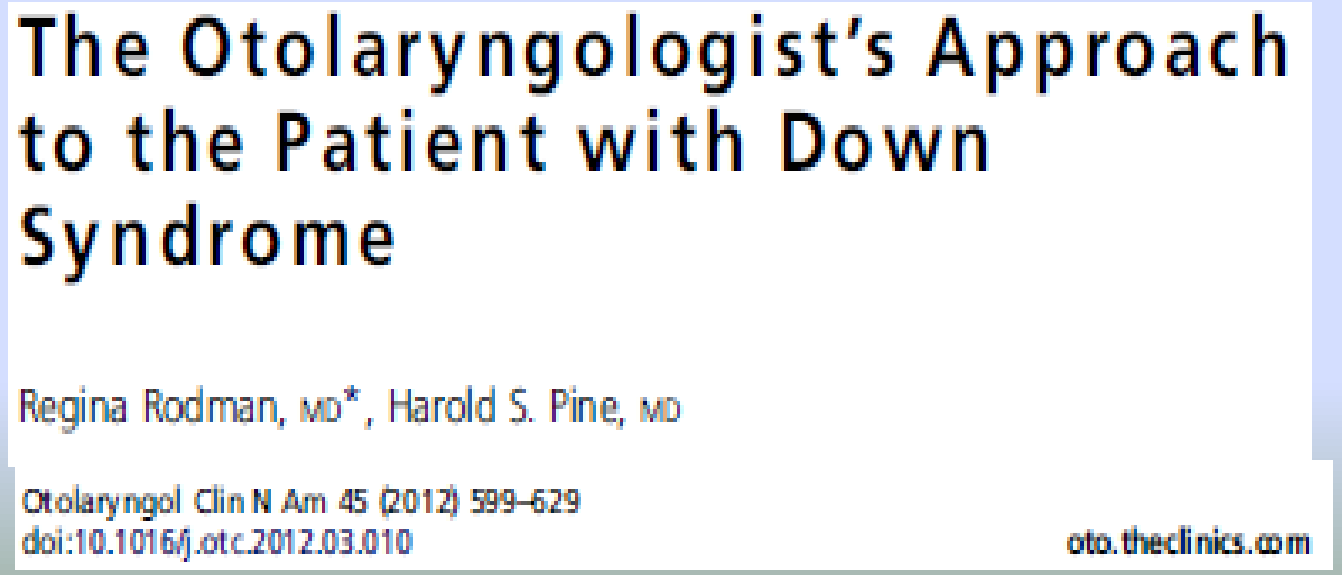
Research Article

Ophthalmic Disorders in Adults with Down Syndrome

Sharon J. Krinsky-McHale,[1] Edmund C. Jenkins,[2] Warren B. Zigman,[1] and Wayne Silverman[3]

PROBLEMI UDITIVI

- Maggior sensibilità ai rumori
- Difficoltà di loclizzazione delle sorgenti sonore
- Maggior suscettibilità a sviluppo di formazioni ceruminose



The Otolaryngologist's Approach to the Patient with Down Syndrome

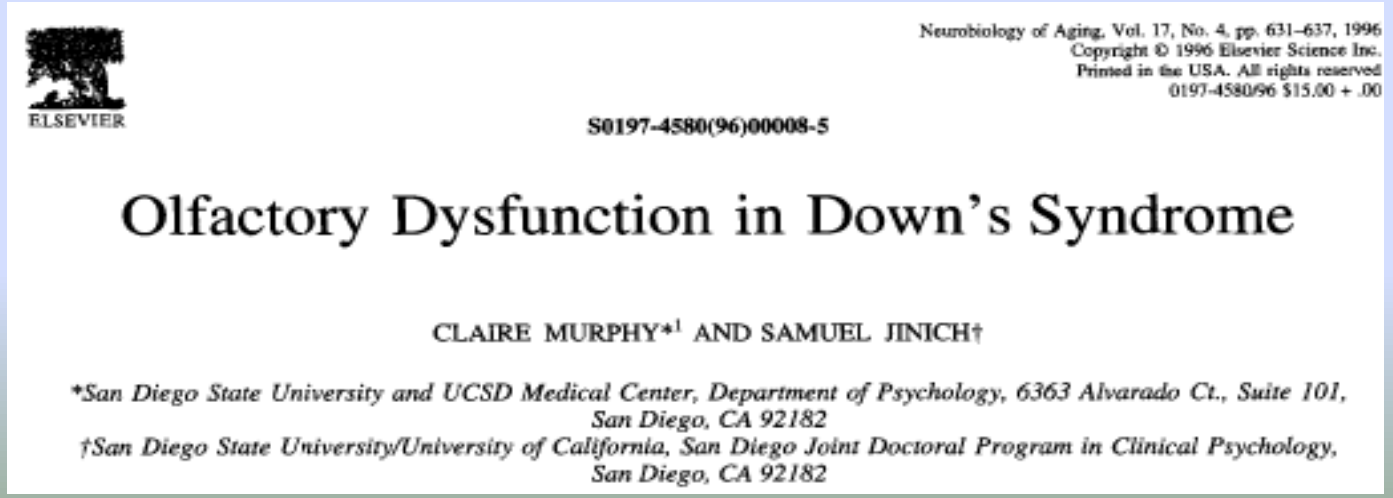
Regina Rodman, MD*, Harold S. Pine, MD

Otolaryngol Clin N Am 45 (2012) 599–629
doi:10.1016/j.otc.2012.03.010

oto.theclinics.com

ALTERAZIONI DEL GUSTO E DELL'OLFATTO

- Diminuzione delle papille gustative e della secrezione di saliva (xerostomia)
- Diminuita percezione degli odori



Neurobiology of Aging, Vol. 17, No. 4, pp. 631–637, 1996
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ELSEVIER

S0197-4580(96)00008-5

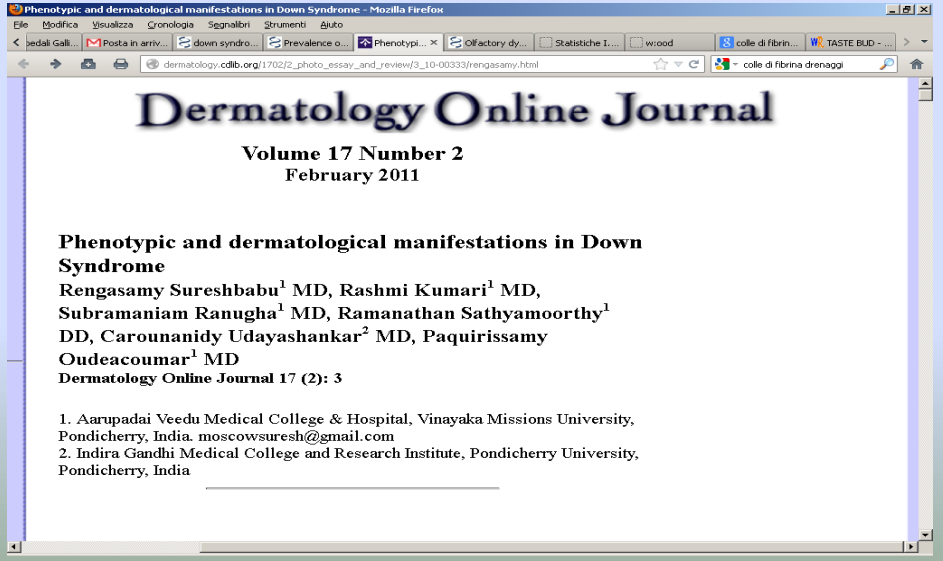
Olfactory Dysfunction in Down's Syndrome

CLAIRE MURPHY*[1] AND SAMUEL JINICH†

*San Diego State University and UCSD Medical Center, Department of Psychology, 6363 Alvarado Ct., Suite 101, San Diego, CA 92182
†San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA 92182

COINVOLGIMENTO CUTANEO

- Ridotta idratazione ed elasticità
- Fragilità cutanea
- Ridotta rappresentazione del PAS
- Ridotto numero ghiandole sudoripare- difetti nella termoregolazione.
- Ridotta sensibilità tattile
- Facile vulnerabilità



Phenotypic and dermatological manifestations in Down Syndrome - Mozilla Firefox

Dermatology Online Journal

Volume 17 Number 2
February 2011

Phenotypic and dermatological manifestations in Down Syndrome

Rengasamy Sureshbabu[1] MD, Rashmi Kumari[1] MD, Subramaniam Ranugha[1] MD, Ramanathan Sathyamoorthy[1] DD, Carounanidy Udayashankar[2] MD, Paquirissamy Oudeacoumar[1] MD

Dermatology Online Journal 17 (2): 3

1. Aarupadai Veedu Medical College & Hospital, Vinayaka Missions University, Pondicherry, India. moscowsuresh@gmail.com
2. Indira Gandhi Medical College and Research Institute, Pondicherry University, Pondicherry, India

ALTERAZIONI METABOLICHE

- Ridotta risposta allo stress ossidativo
- Riduzione metabolismo basale

Journal of Intellectual Disability Research doi: 10.1111/j.1365-2788.2004.00616.x

VOLUME 49 PART 2 pp 125–133 FEBRUARY 2005

Obesity in adults with Down syndrome: a case–control study

C.A. Melville,[1] S.-A. Cooper,[1] C.W. McGrother,[2] C. F. Thorp[2] & R. Collacott[3]

The identification of protein biomarkers for oxidative stress in Down syndrome

Expert Rev. Proteomics 8(4), 427–429 (2011)

Perluigi & Butterfield

10.1586/EPR.11.36 © 2011 Expert Reviews Ltd ISSN 1478-9450

TURBE ALVO/DIURESI

- Atrofia vescicale
- Stipsi
- Pollachiuria (prostata)
- Deficitario controllo sfinteriale

Pediatr Surg Int (2008) 24:873–883
DOI 10.1007/s00383-008-2188-7

REVIEW ARTICLE

Down syndrome and the enteric nervous system

S. W. Moore

0022-5347/04/1713-1250/0
THE JOURNAL OF UROLOGY®
Copyright © 2004 by AMERICAN UROLOGICAL ASSOCIATION
Vol. 171, 1250–1253, March 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000112915.69436.91

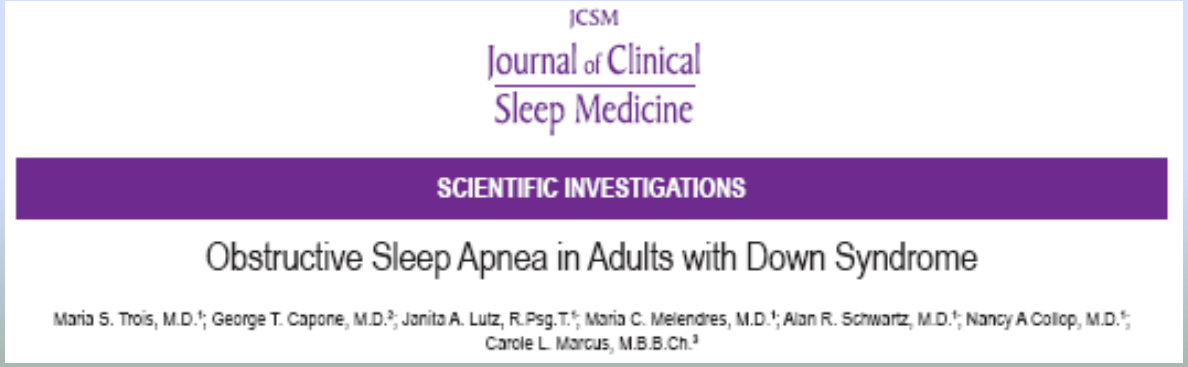
Review Article

UROLOGICAL MANIFESTATIONS OF DOWN SYNDROME

ERICA SCHALOW MERCER, BRUCE BROECKER,* EDWIN A. SMITH, ANDREW J. KIRSCH, HAL C. SCHERZ AND CHARLOTTE A. MASSAD

MODIFICAZIONI APPARATO RESPIRATORIO

- Diminuzione di volume e funzione polmonare
- Suscettibilità alle infezioni polmonari soprattutto se il soggetto non è attivo
- **OSAS**
- Aumentata probabilità di inalazione corpi estranei da alterazioni della deglutizione



JCSM
Journal of Clinical Sleep Medicine

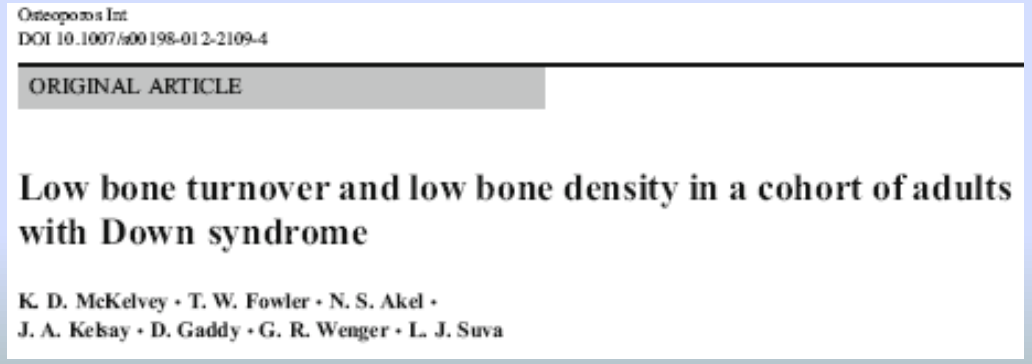
SCIENTIFIC INVESTIGATIONS

Obstructive Sleep Apnea in Adults with Down Syndrome

Maria S. Trois, M.D.[1]; George T. Capone, M.D.[2]; Janita A. Lutz, R.Psg.T.[1]; Maria C. Melendres, M.D.[1]; Alan R. Schwartz, M.D.[1]; Nancy A Collop, M.D.[1]; Carole L. Marcus, M.B.B.Ch.[3]

ALTERAZIONI DEI TESSUTI OSSEO ED ARTICOLARE

- Aumento del rischio di fratture da fragilità ossea
- Alterazioni di assorbimento del calcio
- Dolore da pregresse cadute e/o fratture
- Alterazioni della "lubrificazione" delle cartilagini


Osteoporos Int
DOI 10.1007/s00198-012-2109-4

ORIGINAL ARTICLE

Low bone turnover and low bone density in a cohort of adults with Down syndrome

K. D. McKelvey · T. W. Fowler · N. S. Akel · J. A. Kelsay · D. Gaddy · G. R. Wenger · L. J. Suva

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2012, Article ID 469235, 10 pages
doi:10.1155/2012/469235

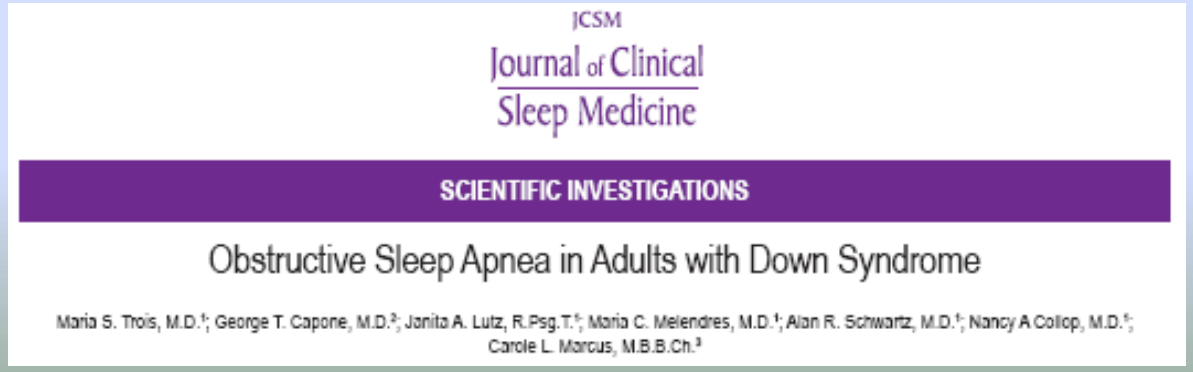
Review Article

Aging and Bone Health in Individuals with Developmental Disabilities

Joan Jasien,[1,2] Caitlin M. Daimon,[1] Stuart Maudsley,[3] Bruce K. Shapiro,[2] and Bronwen Martin[1]

ALTERAZIONI DEL SNC

- Alterazioni del ciclo sonno/veglia con riduzione della durata e della qualità del riposo notturno
- Diminuzione di circa il 20% dell'apporto di ossigeno al cervello
- OSAS



JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

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Maria S. Trois, M.D.[1]; George T. Capone, M.D.[2]; Janita A. Lutz, R.Psg.T.[1]; Maria C. Melendres, M.D.[1]; Alan R. Schwartz, M.D.[1]; Nancy A Collop, M.D.[1]; Carole L. Marcus, M.B.B.Ch.[3]

PROTEZIONE DA

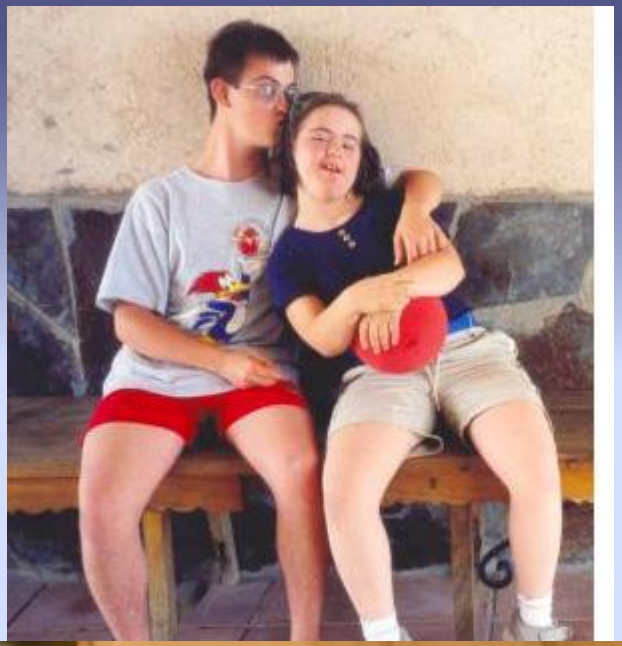
VARI TIPI DI TUMORI SOLIDI (eccetto K testicolo e stomaco)

- Baek KH et al. Nature. 2009 Jun 25;459(7250):1126-30
- Sussan TE et al. Nature. 2008 Jan 3;451(7174):73-5
- Nizetic D et al. Nat Rev Cancer. 2012 Oct;12(10):721-32

DANNI DA IPERCOLESTEROLEMIA

- Draheim CC et al. Am J Cardiol. 2010 Nov 15;106(10):1512-6

SESSUALITÀ E SD



RAPPRESENTA UN ASPETTO IMPORTANTE E SPESSO SOTTOVALUTATO

NON TUTTI I MASCHI CON SD SONO STERILI

RUOLO IMPORTANTE DELLA CONTRACCEZIONE

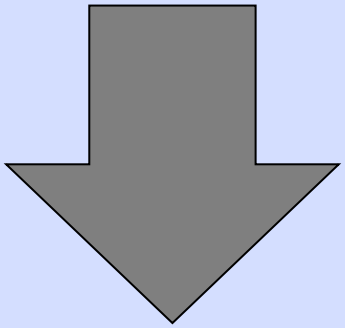
Table 5. **Reported results of pregnancy in Down syndrome**

Paper	Parent	Offspring
Sheridan et al, 1989	1 man with Down syndrome	1 normal male
Bovicelli et al, 1982	26 women with Down syndrome	10 normal
		10 Down syndrome
		2 mentally retarded
		1 set of premature, nonviable normal twins
		3 malformed
		1 slightly microcephaly
		1 still born
		2 abortion, phenotype unknown
Rani et al, 1990	1 woman with Down syndrome	1 normal
Zühlke et al, 1996	1 man with Down syndrome	1 normale female
Pradhan M et al, 2006	1 man with Down syndrome	1 normal male

SICURAMENTE IL PROBLEMA PIÙ IMPORTANTE PER LE

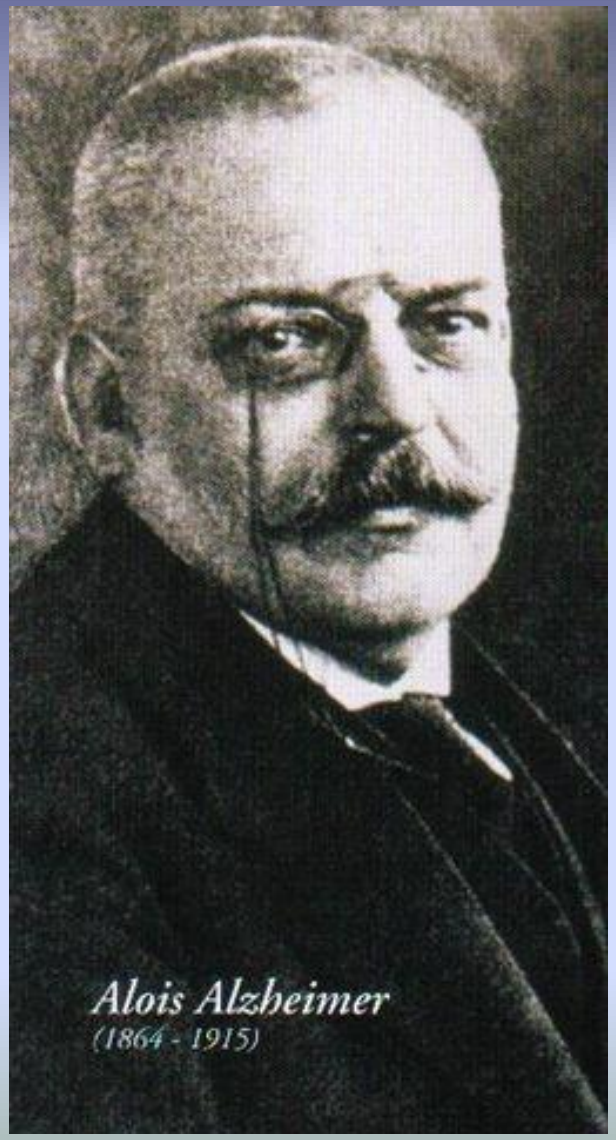
PERSONE CON SD E PER I

LORO CAREGIVER È RAPPRESENTATO DA



MALATTIA DI ALZHEIMER

ALZHEIMER E SINDROME DI DOWN



- 40-49 Years –9.4%
- 50-59 Years-36.1%
- 60-69 Years-54.4%

SD & AMILOIDE

- ACCUMULO DI AMILOIDE GIA' IN EPOCA FETALE

- INCREMENTO CONSISTENTE ATTORNO AI 35-45 ANNI DI ETA'

- INIZIALMENTE ACCUMULO
  - LOBI FRONTALI (Nelson et al. 2001)
  - CORTECCIA ENTORINALE (Azizeh et al. 2000)

PATOGENESI AD IN SD

MECCANISMI GENETICI PROBABILMENTE DETERMINANTI

- DNA REPAIR DEFECTS (Subba Rao 2007)
- TRIPLA DOSE APP
- TRIPLA DOSE SOD-1 e IPERPRODUZIONE RADICALI LIBERI (Kowald e Klipp 2004)
- TELOMERI

MECCANISMI GENETICI PREDISPONENTI

- Allele ε4 APO E
- Polimorfismi gene HSD17B1
- DYRK1A

COMPRENDENDO LE BASI NEUROPATOLOGICHE DELLA PATOLOGIA DI ALZHEIMER NELLA SINDROME DI DOWN

MIGLIOR COMPRENSIONE DELLA STESSA PATOLOGIA NELLA POPOLAZIONE GENERALE

Wallace and Dalton *Alzheimer's Research & Therapy* 2011, **3**:13
http://alzres.com/content/3/2/13

REVIEW

What can we learn from study of Alzheimer's disease in patients with Down syndrome for early-onset Alzheimer's disease in the general population?

Robyn A Wallace[1,2] and Arthur J Dalton[3*]

CARATTERISTICHE DELL'ALZHEIMER NELLA SINDROME DI DOWN

- Insorgenza di epilessia
- Alcuni aspetti di decadimento cognitivo possono essere sfumati
- Insorgenza precoce (45-50 anni)
- Impatto significativo su indipendenza, iniziativa personale e comunicazione

DIAGNOSI DIFFERENZIALE

- Anomalie tiroide
- Depressione
- Perdita vista ed udito
- Reazioni a farmaci
- Problemi vie urinarie
- Problemi G-I
- Deficit nutrizionali
- Deficit vitaminici
- Trauma cranico
- Tumore cerebrale
- Bassi valori di folati in coloro che assumono terapia anticomiziale

COSA RENDE DIFFICILE LA DIAGNOSI?

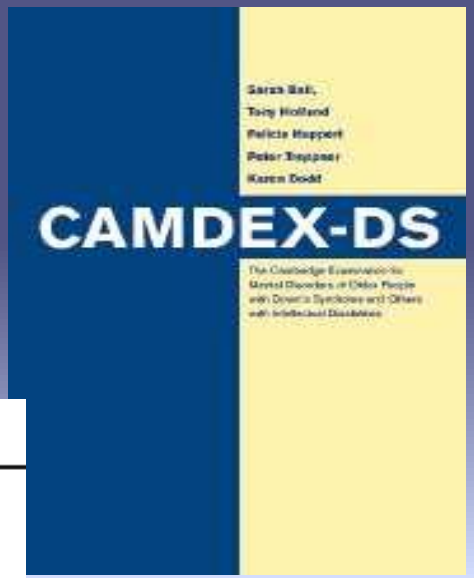
- Difficoltà a riferire i sintomi
- Lievi alterazioni possono passare inosservate
- Condizioni associate al ritardo di sviluppo possono essere confuse con sintomi di demenza
- La maggior parte delle batterie di test non sono applicabili ai soggetti con D.I.

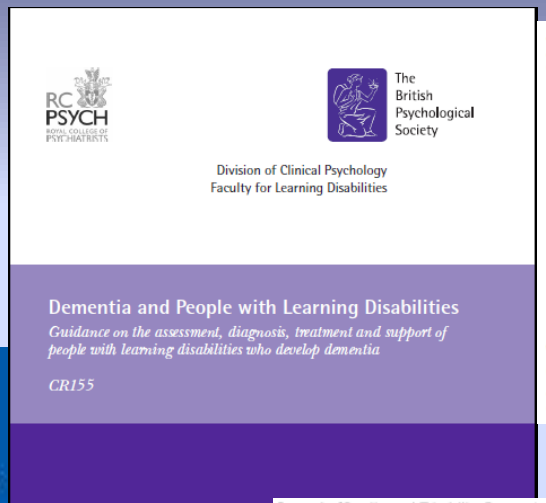
Journal of Intellectual Disability Research

VOLUME 48 PART 6 pp 611–620 SEPTEMBER 2004

The modified CAMDEX informant interview is a valid and reliable tool for use in the diagnosis of dementia in adults with Down's syndrome

S. L. Ball,[1] A. J. Holland,[1] F.A. Huppert,[2] P. Treppner,[1] P. Watson,[3] & J. Hon[1]

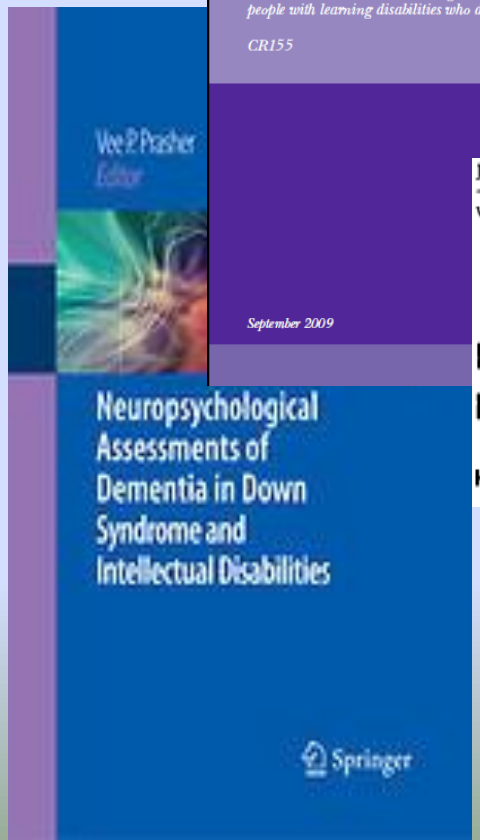




J Neurodevelop Disord (2010) 2:149–164
DOI 10.1007/s11689-010-9054-3

Development and validation of the Arizona Cognitive Test Battery for Down syndrome

Jamie O. Edgin · Gina M. Mason · Melissa J. Allman · George T. Capone · Iser DeLeon · Cheryl Maslen · Roger H. Reeves · Stephanie L. Sherman · Lynn Nadel



Journal of Intellectual Disability Research

VOLUME 40 PART 4 pp 369–373 AUGUST 1996

Further evaluation of the Dementia Questionnaire for Persons with Mental Retardation (DMR)

H. M. Evenhuis

British Journal of Clinical Psychology (1999), 38, 155–165 Printed in Great Britain
© 1999 The British Psychological Society

Neuropsychological assessment of older adults with Down's Syndrome: An epidemiological study using the Cambridge Cognitive Examination (CAMCOG)

Johnny Hon
Section of Developmental Psychiatry, Cambridge University, UK

Felicia A. Huppert
Department of Psychiatry, Addenbrooke's Hospital, Cambridge, UK

Anthony J. Holland*
Section of Developmental Psychiatry, Cambridge University, UK

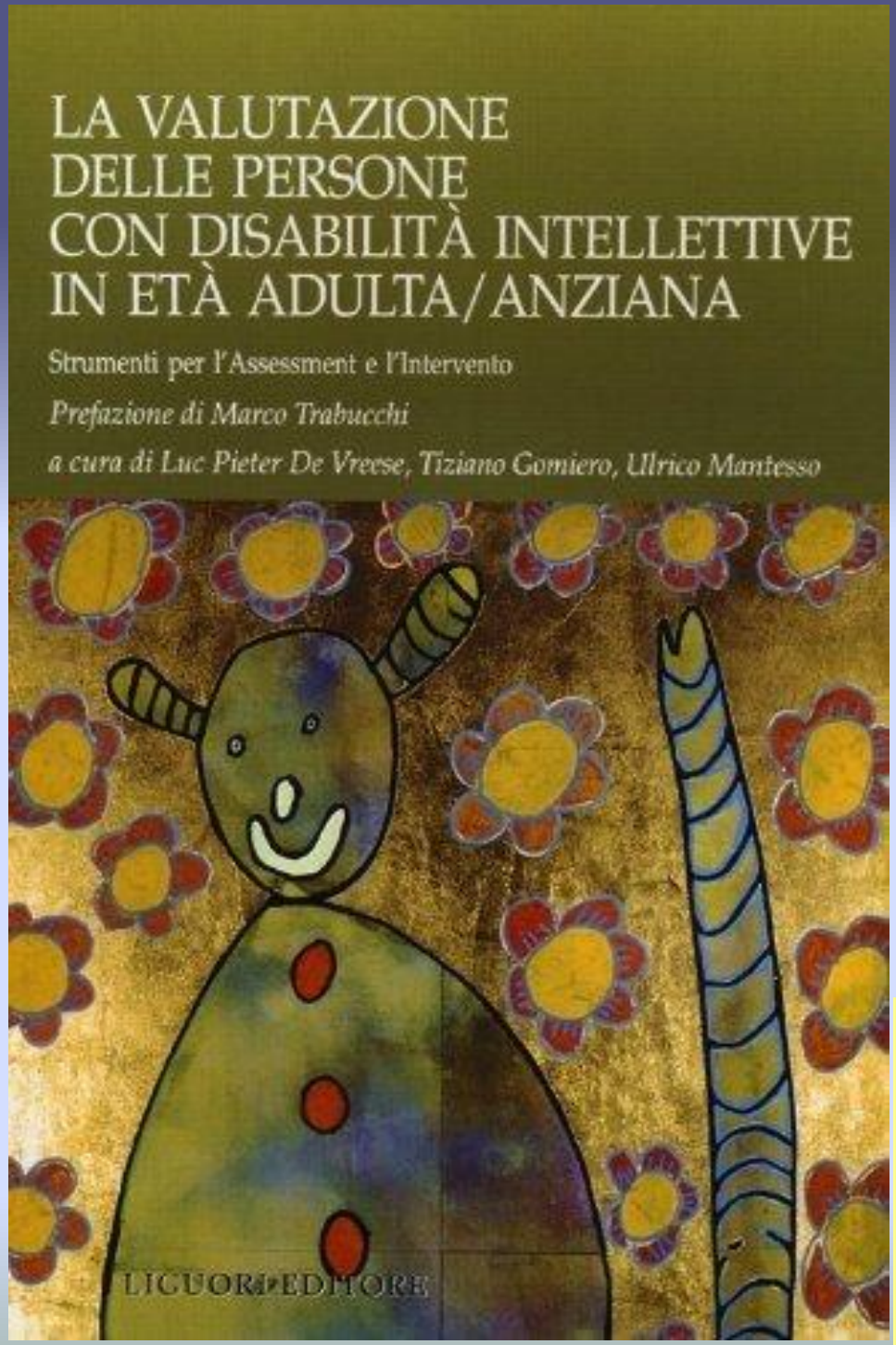
Peter Watson
Cognition Brain Sciences Unit, Cambridge University, UK

Journal of Intellectual Disability Research

VOLUME 43 PART 5 pp 400–407 OCTOBER 1999

Comparison of rating scales for the diagnosis of dementia in adults with Down's syndrome

S. Deb & J. Braganza



Editore: Liguori (5 dicembre 2012)

E IN ITALIA?

DMR (Dementia Questionnaire for Persons With Intellectual Disabilities (Evenhuis et al., 2004)

AFAST (Alzheimer's Functional Assessment Tool) (Wrentham Developmental Center, Dep of Mental Retardation – Massachusetts)

AADS (Assessment for Adults with Developmental Disanbilities) (Kalsy et al., 2002)

CDS-DI (Caregiver Difficulty Scale-Intellectual Disanbilities) (Mc Callion et al., 2005)

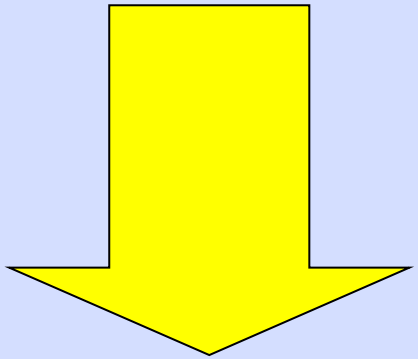
QUALID (Quality of Life in Late-Stage Dementia)

DAD
DOWN ALZHEIMER DEMENZA

Anffas
dal 1965
AnffAS TRENTINO ONLUS

SINDROME DI DOWN

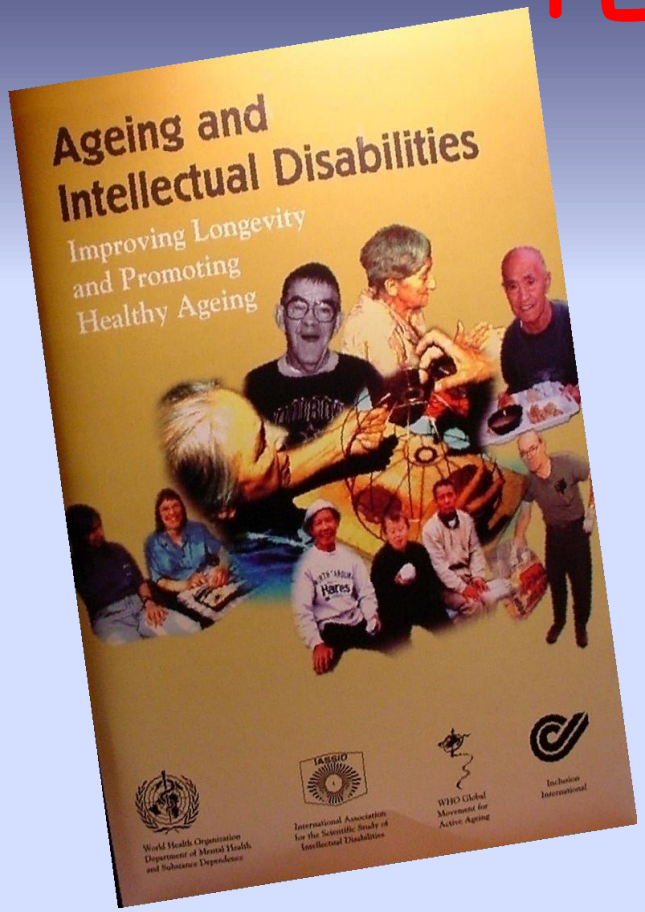
- più frequente;
- abbondantemente e correntemente studiata;
- bisogni e tematiche affini ad altre patologie genetiche accompagnate da DI

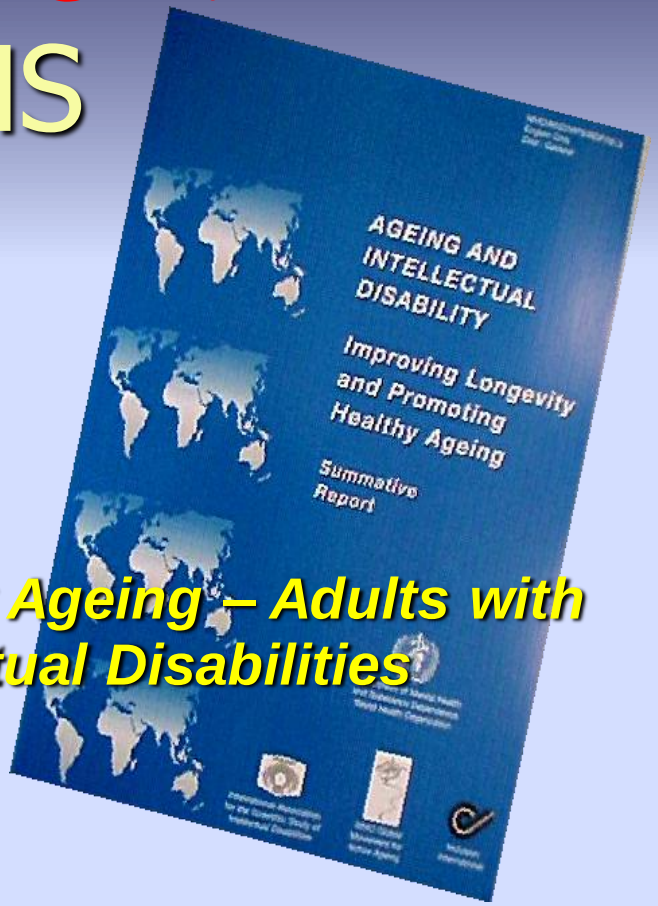


SINDROME DI DOWN COME PARADIGMA DELLE DIFFICOLTA' DEL SOGGETTO CON DI IN TERZA ETA'

QUALI PREOCCUPAZIONI DELL'OMS SULL'INVECCHIAMENTO DELLE PERSONE CON DI ?

Reports OMS

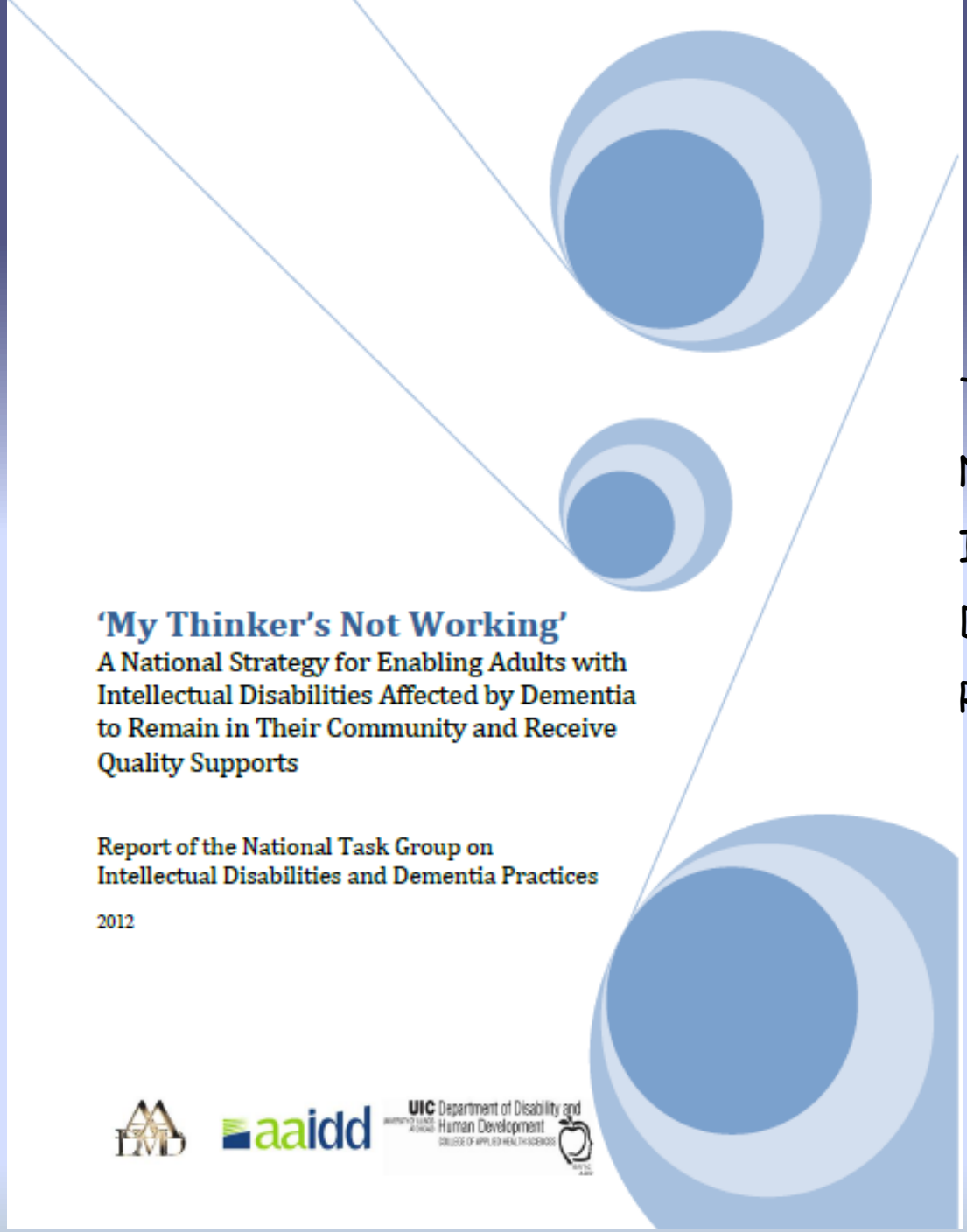




Healthy Ageing – Adults with Intellectual Disabilities

Journal of Applied Research in Intellectual Disabilities (JARID), 2001, Vol. 14(3), 171-275

Ageing & Intellectual Disability – Improving Longevity and Promoting Healthy Ageing – *Summative report* (WHO, 2000)



The report, "'My Thinker's Not Working': A National Strategy for Enabling Adults with Intellectual Disabilities Affected by Dementia to Remain in Their Community and Receive Quality Supports,"

http://aadmd.org/sites/default/files/NTG_Thinker_Report.pdf

http://dad2011.pinp.it/attachments/article/45/Dimentica%20la%20Disabilit%C3%A0%281%29.pdf

LA RICERCA

Terapie(1)

DONEPEZIL Mohan M et AL. Cochrane Database Syst Rev. 2009

Kondoh T et al. Int J Psychiatry Med 2011; 41(1):71-89

RIVASTIGMINA Mohan ET AL. Cochrane Database Syst Rev. 2009

GALANTAMINA Mohan M, Cochrane Database Syst Rev. 2009

ANTIOX Lott IT et al Am J Med Genet A. 2011 Aug;155A(8):1939-48

MEMANTINA Hanney M et al Lancet. 2012 Feb 11;379(9815):528-36

Boada R et al Transl Psychiatry. 2012 Jul 17;2:e141

Donepezil for dementia in people with Down syndrome (Review)

Mohan M, Carpenter PK, Bennett C

THE COCHRANE COLLABORATION®

Galantamine for dementia in people with Down syndrome (Review)

Mohan M, Bennett C, Carpenter PK

THE COCHRANE COLLABORATION®

Rivastigmine for dementia in people with Down syndrome (Review)

Mohan M, Bennett C, Carpenter PK

THE COCHRANE COLLABORATION®

Memantine for dementia in people with Down syndrome (Review)

Mohan M, Bennett C, Carpenter PK

THE COCHRANE COLLABORATION®

THE INTERNATIONAL JOURNAL OF
PSYCHIATRY IN MEDICINE
BIOPSYCHOSOCIAL ASPECTS OF PATIENT CARE

Editor: DANA E. KING, M.D.

Volume 41, Number 1 — 2011

Donepezil Significantly Improves Abilities in Daily Lives of Female Down Syndrome Patients with Severe Cognitive Impairment: A 24-Week Randomized, Double-Blind, Placebo-Controlled Trial

Tatsuro Kondoh, Atsushi Kanno, Hiroshi Itoh, Mikiro Nakashima, Ryoko Honda, Michio Kojima, Mitsuru Noguchi, Hideyuki Nakane, Hidetsugu Nozaki, Hitoshi Sasaki, Toshiro Nagai, Riko Kosaki, Naoko Kaltee, Tomoyuki Okuyama, Masafumi Fukuda, Masayuki Ikeda, Yoshisada Shibata, and Hiroyuki Moriuchi

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

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

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Down Syndrome and Dementia: A Randomized, Controlled Trial of Antioxidant Supplementation

Ira T. Lott,[1,2]* Eric Doran,[1] Vinh Q. Nguyen,[3] Anne Tournay,[1] Elizabeth Head,[4,5] and Daniel L. Gillen[3]

[1]Department of Pediatrics, School of Medicine, University of California, Irvine (UCI), Orange, California
[2]Department of Neurology, School of Medicine, University of California, Irvine (UCI), Irvine, California
[3]Department of Statistics, University of California, Irvine (UCI), Irvine, California
[4]Institute for Memory Impairments and Neurological Disorders, University of California, Irvine (UCI), Irvine, California
[5]Sanders-Brown Center on Aging, University of Kentucky (UKY), Lexington, Kentucky

Received 22 November 2010; Accepted 22 April 2011

Articles

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

Marisa Mansey, Vivi Proctor, Rosalind Williams, Emma Evans, Peig Kardiol, Anne Corbett, Dale Lawrence, Ly Mee Yu, Stephen Tyrer, Paul 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

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, Norway (Prof D Aarsland PhD); Alzheimer's Society, London, UK (A Corbett PhD); University of Newcastle, Newcastle, UK (S Tyrer FRCPsych); Medical Research Council Biostatistics Unit, Cambridge, UK (T Johnson PhD); and Kingshill Research Centre, Swindon, UK (R Bullock MRCPsych)

Correspondence to: Prof Clive Ballard, Wolfson Centre for Age-Related Diseases, Wolfson Wing, Hodgkin Building,

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-significant differences between groups of −4·1 (95% CI −13·1 to 4·8) in DAMES scores, −8·5 (−20·1 to 3·1) in ABS I scores, and 2·0 (−7·2 to 11·3) in ABS II scores, all in favour of controls. 10 (11%) of 88 participants in the memantine group and six (7%) of 85 controls had serious adverse events (p=0·33). Five participants in the memantine group and four controls died from serious adverse events (p=0·77).

Interpretation There is a striking absence of evidence about pharmacological treatment of cognitive impairment and dementia in people older than 40 years with Down's syndrome. Despite promising indications, memantine is not an effective treatment. Therapies that are effective for Alzheimer's disease are not necessarily effective in this group of patients.

Funding Lundbeck.

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

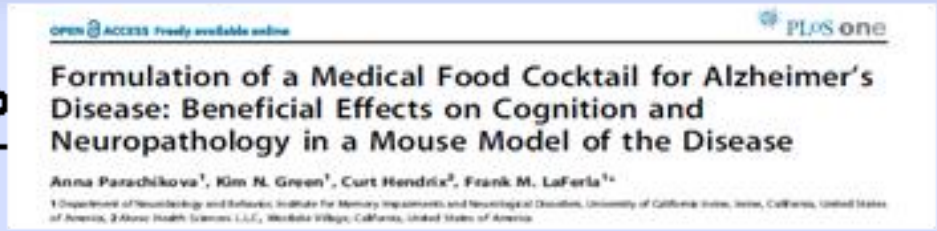
Terapie (2)

ECGG?

Available online at www.sciencedirect.com
SciVerse ScienceDirect
Journal of Nutritional Biochemistry
Epigallocatechin-3-gallate prevents systemic inflammation-induced memory deficiency and amyloidogenesis via its anti-neuroinflammatory properties

Biochimica et Biophysica Acta
Epigallocatechin-3-gallate prevents oxidative phosphorylation deficit and promotes mitochondrial biogenesis in human cells from subjects with Down's syndrome

MEDICAL FOOD COCKTAIL?


PLoS one
Formulation of a Medical Food Cocktail for Alzheimer's Disease: Beneficial Effects on Cognition and Neuropathology in a Mouse Model of the Disease

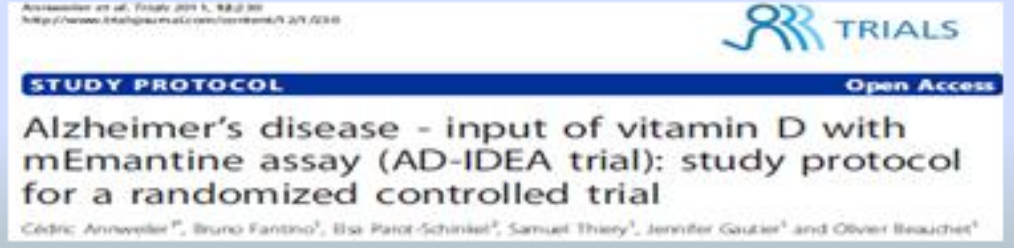
LITIO?

Research article
Lithium rescues synaptic plasticity and memory in Down syndrome mice
The Journal of Clinical Investigation http://www.jci.org

STUDIO "DOWNSLIT"

VITAMINA D?

VITAMINA D +


TRIALS
STUDY PROTOCOL Open Access
Alzheimer's disease - input of vitamin D with mEmantine assay (AD-IDEA trial): study protocol for a randomized controlled trial

Terapie (2)

ECGG? Lee YJ et al J Nutr Biochem. 2013 Jan;24(1):298-310

MEDICAL FOOD COCKTAIL? Parachikova A et al PLoS One. 2010 Nov 17;5(11):e14015

LITIO? Contestabile A et al J Clin Invest. 2012 Dec 3. doi:pii: 64650. 10.1172/JCI64650.

VITAMINA D?

VITAMINA D + MEMANTINA?

Terapie (3)

FLUOXETINA?

Hindawi Publishing Corporation
Neural Plasticity
Volume 2012, Article ID 467251, 10 pages
doi:10.1155/2012/467251

Research Article

Adult-Onset Fluoxetine Treatment Does Not Improve Behavioral Impairments and May Have Adverse Effects on the Ts65Dn Mouse Model of Down Syndrome

Markus Heinen, Moritz M. Hettich, Devon P. Ryan, Susanne Schnell, Katharina Paesler, and Dan Ehninger

OPEN ACCESS Freely available online PLOS ONE

Pharmacotherapy with Fluoxetine Restores Functional Connectivity from the Dentate Gyrus to Field CA3 in the Ts65Dn Mouse Model of Down Syndrome

Fiorenza Stagni[1☯], Jacopo Magistretti[2☯], Sandra Guidi[1], Elisabetta Ciani[1], Chiara Mangano[3], Laura Calzà[3], Renata Bartesaghi[1*]

1 Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy, 2 Department of Biology and Biotechnology "L. Spallanzani", University of Pavia, Pavia, Italy, 3 Health Sciences and Technologies - Interdepartmental Center for Industrial Research (HST-ICIR), University of Bologna, Bologna, Italy

Brain Pathology ISSN 1015-6305

RESEARCH ARTICLE

Early Pharmacotherapy with Fluoxetine Rescues Dendritic Pathology in the Ts65Dn Mouse Model of Down Syndrome

Sandra Guidi[1*]; Fiorenza Stagni[1*]; Patrizia Bianchi[1]; Elisabetta Ciani[1]; Elena Ragazzi[1]; Stefania Trazzi[1]; Gabriele Grossi[2]; Chiara Mangano[3]; Laura Calzà[3]; Renata Bartesaghi[1]

[1] Department of Human and General Physiology, University of Bologna, Bologna, Italy.
[2] Center for Applied Biomedical Research (CRBA), S.Orsola-Malpighi University Hospital, Bologna, Italy.
[3] Health Sciences and Technologies—Interdepartmental Center for Industrial Research (HST-ICIR), University of Bologna, Bologna, Italy.

VIP IN PRENATALE?

OPEN ACCESS Freely available online PLOS ONE

Prenatal Treatment Prevents Learning Deficit in Down Syndrome Model

Maddalena Incerti[1,2*], Kari Horowitz[1,3], Robin Roberson[1], Daniel Abebe[1], Laura Toso[1], Madeline Caballero[1], Catherine Y. Spong[1]

1 Unit on Perinatal and Developmental Neurobiology, National Institute of Child and Human Development, National Institute of Health, Bethesda, Maryland, United States of America, 2 Department of Obstetrics and Gynaecology, University of Milano-Bicocca, Ospedale S. Gerardo, Fondazione MBBM, Monza, Italy, 3 Department of Obstetrics and Gynecology, University of Connecticut, Groton, Connecticut, United States of America

COLINA IN PRENATALE?

Neurobiology of Disease xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Maternal choline supplementation improves spatial learning and adult hippocampal neurogenesis in the Ts65Dn mouse model of Down syndrome

Ramon Velazquez [a], Jessica A. Ash [a,1], Brian E. Powers [a], Christy M. Kelley [b], Myla Strawderman [a], Zoe I. Luscher [a], Stephen D. Ginsberg [c,d,e], Elliott J. Mufson [b], Barbara J. Strupp [a,*]

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[b] Dept. Neurological Science and Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, 60612, USA
[c] Center for Dementia Research, Nathan Kline Institute, Orangeburg, NY, USA
[d] Department of Psychiatry, New York University Langone Medical Center, New York, NY, 10962, USA
[e] Department of Physiology & Neuroscience, New York University Langone Medical Center, New York, NY, 10962, USA

PROOF

« Troveremo. È impossibile non trovare. È uno sforzo intellettuale molto meno difficile che mandare un uomo sulla luna » (Jerôme Lejeune)

Risposta alla domanda di un giornalista sulla possibilità di trovare una cura per la sindrome di Down

Current Gerontology and Geriatrics Research

Journal Menu

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- Article Processing Charges
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Published Special Issues [6 issues]

- Active Aging: A Global Goal
  Guest Editors: Rocío Fernández-Ballesteros, Jean Marie Robine, Alan Walker, and Alex Kalache
- Apathy in the Elderly: From Assessment to Treatment
  Guest Editors: Iracema Leroi and Philippe H. Robert
- Aging and Down Syndrome
  Guest Editors: Elizabeth Head, Wayne Silverman, David Patterson, and Ira T. Lott
- Nutrition and Dementia
  Guest Editors: Fabio Coppedè, Paolo Bosco, Andrea Fuso, and Aron M. Troen
- Mechanisms and Implications of Age-Related Changes in the Liver
  Guest Editors: Victoria C. Cogger, Sarah N. Hilmer, and Dmitri Svistounov
- Centenarian Studies: Important Contributors to Our Understanding of the Aging Process and Longevity
  Guest Editors: Donald Craig Willcox, Bradley J. Willcox, and Leonard W. Poon

Aging and Down Syndrome

Guest Editors: Elizabeth Head, Wayne Silverman, David Patterson, and Ira T. Lott

- Aging and Down Syndrome, Elizabeth Head, Wayne Silverman, David Patterson, and Ira T. Lott
  Volume 2012 (2012), Article ID 412536, 6 pages
- Gait Parameter Adjustments for Walking on a Treadmill at Preferred, Slower, and Faster Speeds in Older Adults with Down Syndrome, Beth A. Smith, Masayoshi Kubo, and Beverly D. Ulrich
  Volume 2012 (2012), Article ID 782671, 7 pages
- Clinical Predictors of Mortality in Adults with Intellectual Disabilities with and without Down Syndrome, Lilian Thorpe, Punam Pahwa, Vernon Bennett, Andrew Kirk, and Josephine Nanson
  Volume 2012 (2012), Article ID 943890, 11 pages
- Sterol Lipid Metabolism in Down Syndrome Revisited: Down Syndrome Is Associated with a Selective Reduction in Serum Brassicasterol Levels, Gavin Tansley, Daniel T. Holmes, Dieter Lütjohann, Elizabeth Head, and Cheryl L. Wellington
  Volume 2012 (2012), Article ID 179318, 11 pages
- Oxidative Stress and Mitochondrial Dysfunction in Down's Syndrome: Relevance to Aging and Dementia, Pinar E. Coskun and Jorge Busciglio
  Volume 2012 (2012), Article ID 383170, 7 pages
- Ophthalmic Disorders in Adults with Down Syndrome, Sharon J. Krinsky-McHale, Edmund C. Jenkins, Warren B. Zigman, and Wayne Silverman
  Volume 2012 (2012), Article ID 974253, 9 pages
- Age-Related Neurodegeneration and Memory Loss in Down Syndrome, Jason P. Lockrow, Ashley M. Fortress, and Ann-Charlotte E. Granholm
  Volume 2012 (2012), Article ID 463909, 13 pages
- Polymorphisms in *HSD17B1*: Early Onset and Increased Risk of Alzheimer's Disease in Women with Down Syndrome, Joseph H. Lee, Susan Gurney, Deborah Pang, Alexis Temkin, Naeun Park, Sarah C. Janicki, Warren B. Zigman, Wayne Silverman, Benjamin Tycko, and Nicole Schupf
  Volume 2012 (2012), Article ID 361218, 8 pages
- β-Secretases, Alzheimer's Disease, and Down Syndrome, Robin L. Webb and M. Paul Murphy
  Volume 2012 (2012), Article ID 362839, 8 pages
- The Use of Mouse Models for Understanding the Biology of Down Syndrome and Aging, Guido N. Vacano, Nathan Duval, and David Patterson
  Volume 2012 (2012), Article ID 717315, 20 pages
- Neuroinflammation in the Aging Down Syndrome Brain; Lessons from Alzheimer's Disease, Donna M. Wilcock
  Volume 2012 (2012), Article ID 170276, 10 pages
- Alzheimer's Disease and Vascular Deficiency: Lessons from Imaging Studies and Down Syndrome, Arlene Reed-Cossairt, Xiongwei Zhu, Hyoung-Gon Lee, Charles Reed, George Perry, and Robert B. Petersen
  Volume 2012 (2012), Article ID 929734, 5 pages
- Oxidative Stress and Down Syndrome: A Route toward Alzheimer-Like Dementia, Marzia Perluigi and D. Allan Butterfield
  Volume 2012 (2012), Article ID 724904, 10 pages

JIDR Journal of Intellectual Disability Research
Published on behalf of mencap and in association with IASSID

Journal of Intellectual Disability Research doi: 10.1111/j.1365-2788.2011.01432.x

VOLUME 55 PART 8 pp 801–820 AUGUST 2011

Needs and challenges of daily life for people with Down syndrome residing in the city of Rome, Italy

M. Bertoli,[1] G. Biasini,[2] M.T. Calignano,[3] G. Celani,[4] G. De Grossi,[4] M. C. Digilio,[5] C. C. Fermariello,[6] G. Loffredo,[7] F. Luchino,[2,4] A. Marchese,[7] S. Mazotti,[7] B. Menghi,[8] C. Razzano,[7] C. Tiano,[3] A. Zambon Hobart,[7] G. Zampino[9] & G. Zuccalà[10]

1 *Genetica Medica, Ospedale San Pietro Fatebenefratelli, Roma, Italy*
2 *Associazione Culturale Pediatri, Italy*
3 *Coordinamento Nazionale Associazioni Persone con sindrome di Down, Roma, Italy*
4 *Associazione Italiana Persone con sindrome di Down, Roma, Italy*
5 *Genetica Medica, Ospedale Pediatrico Bambino Gesù, Roma, Italy*
6 *Comitato Siblings Roma, Italy*
7 *Fondazione Italiana Verso il Futuro, Roma, Italy*
8 *Servizio Studi Socio-Economici, Comune di Roma, Ufficio di Statistica, Roma, Italy*
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- Difficoltà dell'adulto con sindrome di Down e dei caregivers
- Difficoltà nel reperire informazioni cliniche e di censimento
- Coinvolgimento delle associazioni di famiglie

CONCLUSIONI (1)

- La sindrome di Down è una patologia con prevalenza in crescita soprattutto nelle fasce d'età più avanzate.

- Il problema più rilevante per la persona Down adulta è il declino cognitivo

- Ruolo fondamentale della ricerca

✓ nella spiegazione delle basi neuropatologiche del decadimento cognitivo,

✓ nella validazione di test utili per la diagnosi precoce di demenza e

✓ nell'organizzazione di trials clinici nel tentativo di offrire approcci farmacologici efficaci

CONCLUSIONI (2)

Tuttavia…

- La gerontologia raramente si occupa dell' invecchiamento delle persone con disabilità intellettiva

- Scarsa attenzione per gli studi sull'invecchiamento nelle persone con disabilità intellettiva

NEUROLOGY / CLINICAL PRACTICE

Down syndrome in the neurology clinic: Too much? Too little? Too late?

Andrew J Larner

DOWN SYNDROME IN THE GERIATRICS CLINIC: WHEN?