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Diagnostica genetica e immunologica, biomarkers, trial clinici per terapie farmacologiche innovative

I DISTURBI DELLO SPETTRO AUTISTICO: LO STATO DELL'ARTE
FOBAP ONLUS & Ordine dei Medici di Brescia, 18 Marzo, 2017

Dichiarazione di conflitto di interessi

L’autore non ha conflitti di interessi

Le ricerche dell’autore sono state finanziate dal Ministero della Salute e dall’IMI (consorzio europeo EU-AIMS)

L'autismo di Leo Kanner

PATHOLOGY

To understand and measure emotional qualities is very difficult. Psychologists and educators have been struggling with that problem for years but we are still unable to measure emotional and personality traits with the exactness with which we can measure intelligence.
—Rose Zeligs in *Glimpses into Child Life**

AUTISTIC DISTURBANCES OF AFFECTIVE CONTACT

By Leo Kanner

Nervous Child 2:217-50, 1942

SINCE 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits—and, I hope, will eventually receive—a detailed consideration of its fascinating peculiarities. In this place, the limitations neces-

Eleven cases with "…a number of essential common characteristics. These characteristics form a unique "syndrome", not heretofore reported….it is quite possible that some such children have been viewed as feebleminded or schizophrenic" (pg. 241-242)

Leo Kanner (1894-1981)

(1) Autismi sindromici "Classici"

- **Sindrome dell'X fragile**
- **Sclerosi tuberosa**
- **Neurofibromatosi**
- **Fenilchetonuria non trattata**
- **Sindrome di Angelman**
- **Sindrome di Cornelia de Lange**
- **Sindrome di Down**
- **Sindrome di Smith-Lemli-Opitz**
- **Riarrangiamenti cromosomici *de novo***
- **Esposizione prenatale ad alcuni agenti ambientali (virus o farmaci)**

10% dei casi

Persico AM & Napolioni V, Behav Brain Res 251:95-112, 2013

(2) "Nuovi" autismi sindromici monogenici dovuti a mutazioni *de novo* o CNV

Sinaptogenesi
- **NLGN3 and NLGN4** (Xq13, Xp22.3)
- **SHANK3** (22q13.3)
- **NRXN1** (2q32)

Struttura della cromatina
- **MECP2** (Xq28)

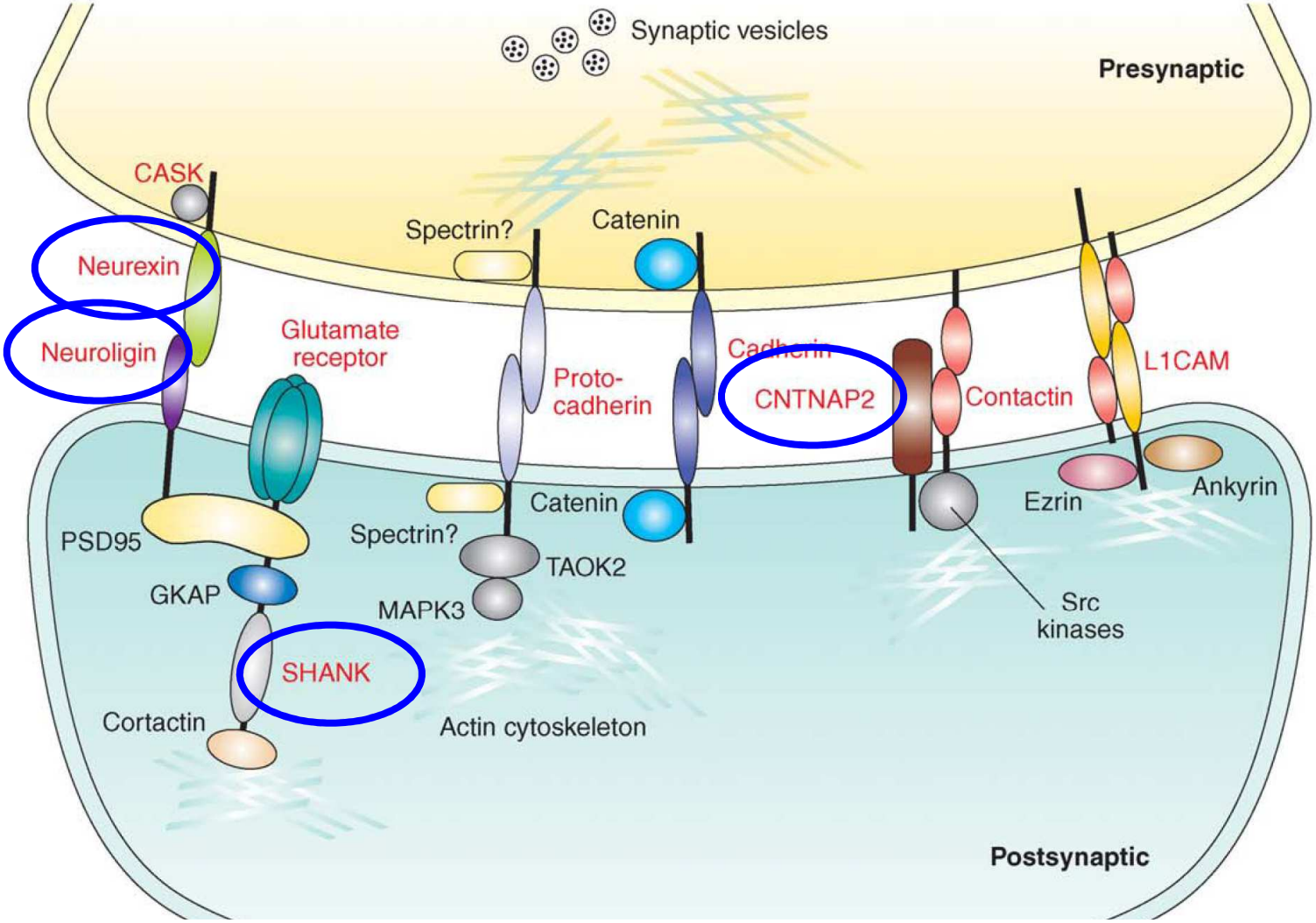
Morfogenesi e ciclo cellulare
- **HOXA1** (7p15.3)
- **PTEN** (10q23)
- **RAY1, IMMP2L** (7q31-q33)
- **EIF4E** (4q21-q25)

Omeostasi del calcio
- **CACNA1C** (12p13.3), **CACNA1F** (Xp11.23),
- **KCNMA1** (10q22.3), **[CACNA1H, SCN2A]**

Screening nelle femmine (MECP2) e nei macrocefalici (PTEN)

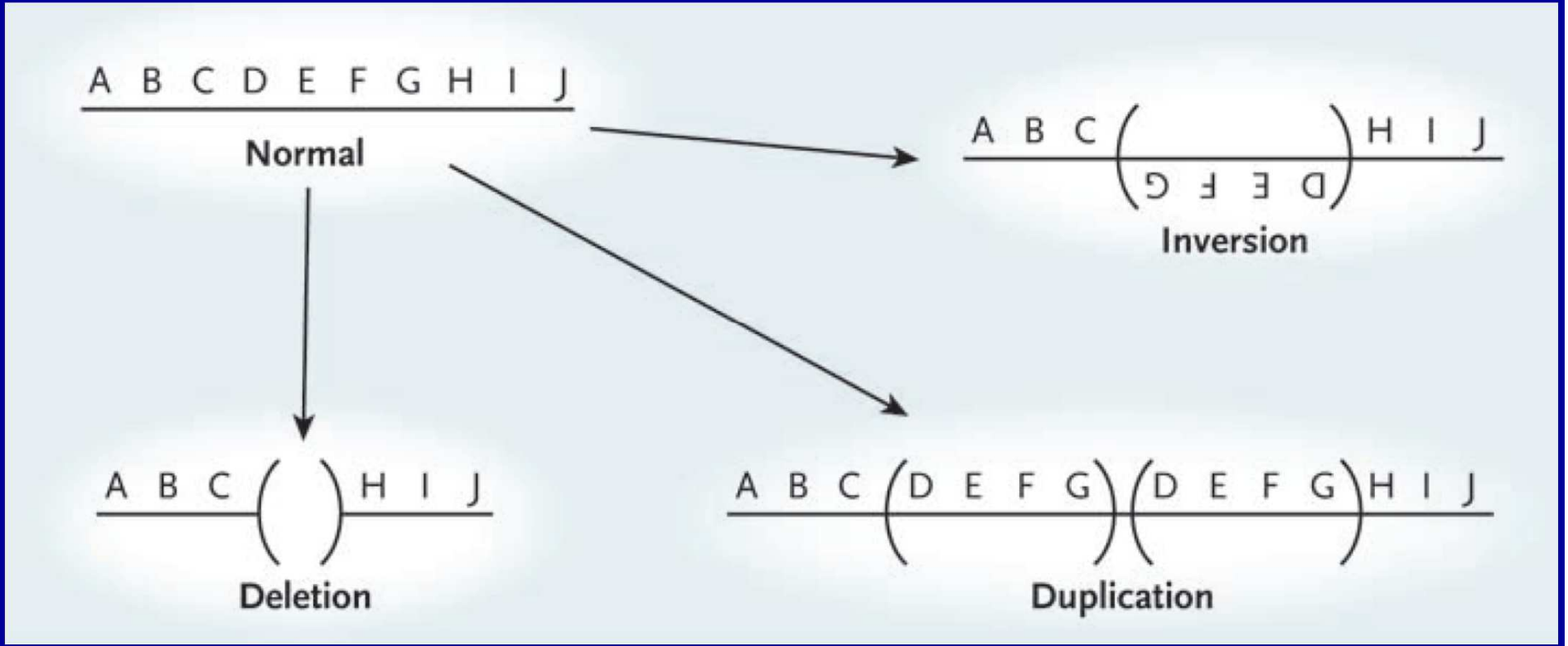
Lintas C & Persico AM, J Med Genet, 46:1-8, 2009

Il complesso delle neurolighine e la sinaptogenesi



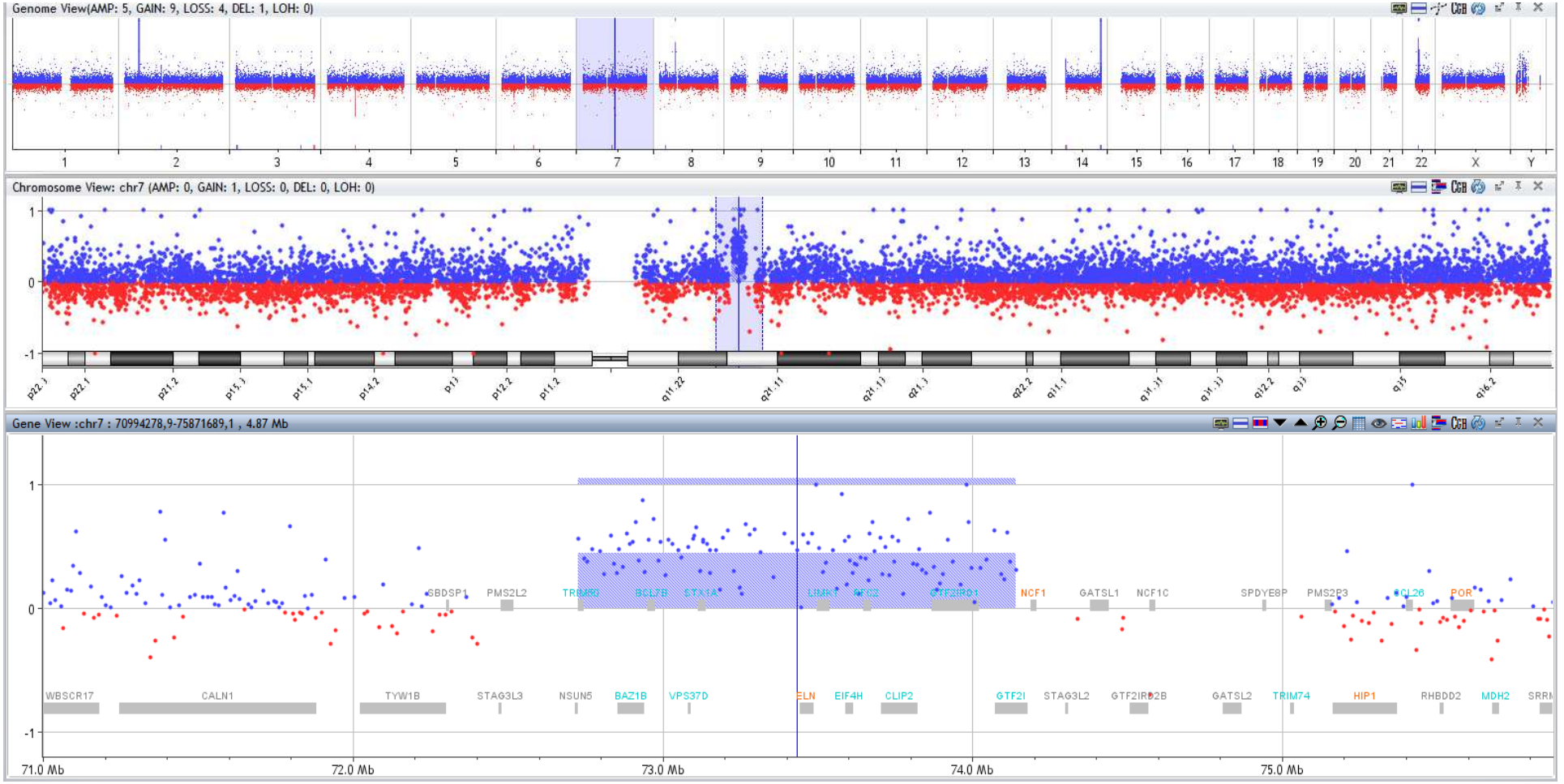
Betancur C et al, Trends Neurosci, 32:402, 2009

(3) Sindromi autistiche ricorrenti da CNV

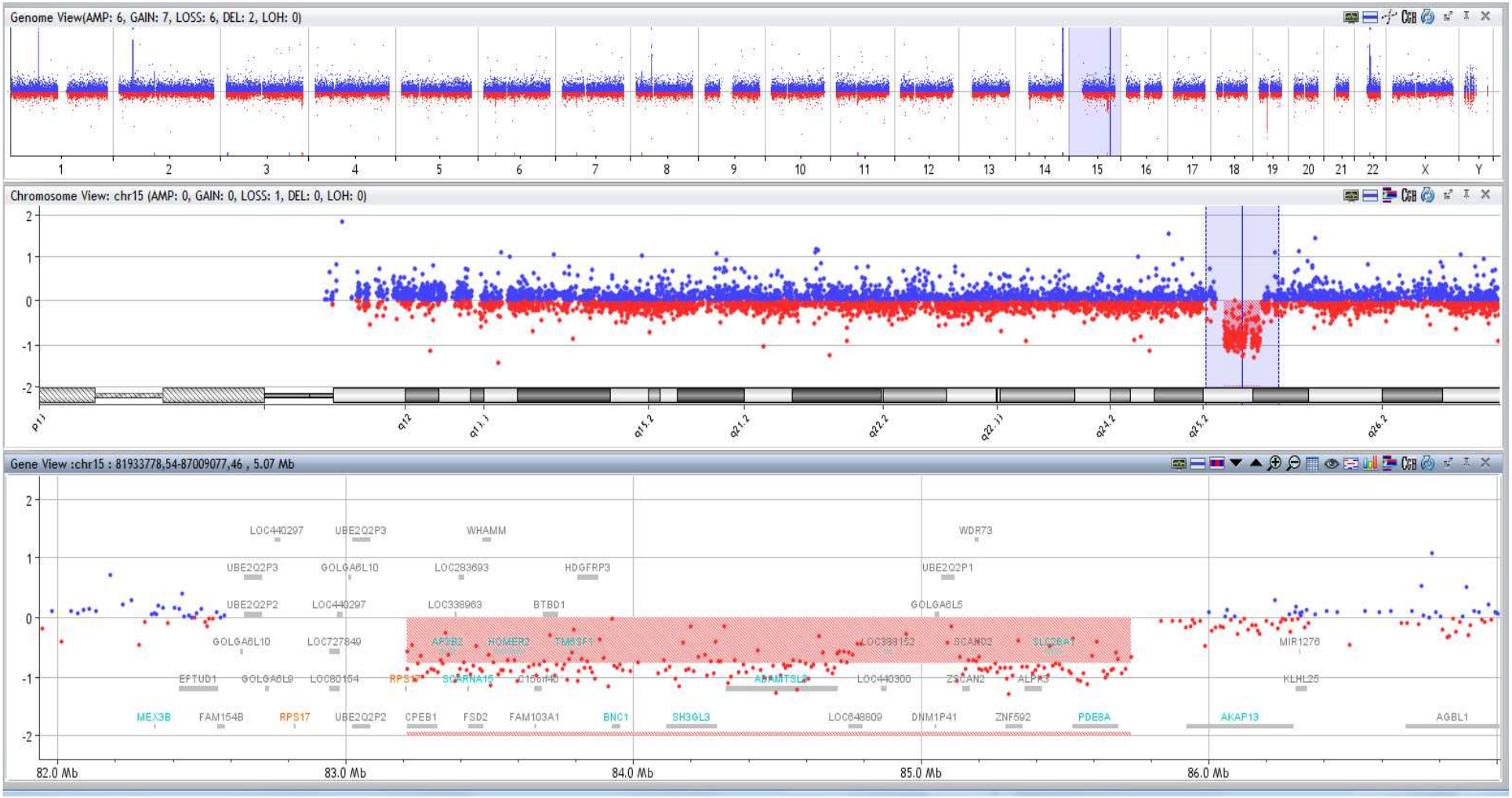


Lupski JR, N Engl J Med 356:1169-71, 2007

Copy Number Variants (microdelezioni e microduplicazioni) possono causare l'autismo (forme monogeniche) oppure aumentare il rischio (forme oligogeniche/poligeniche)



M.G.: 1.4 Mb *de novo* duplication (chr. 7q11.23)



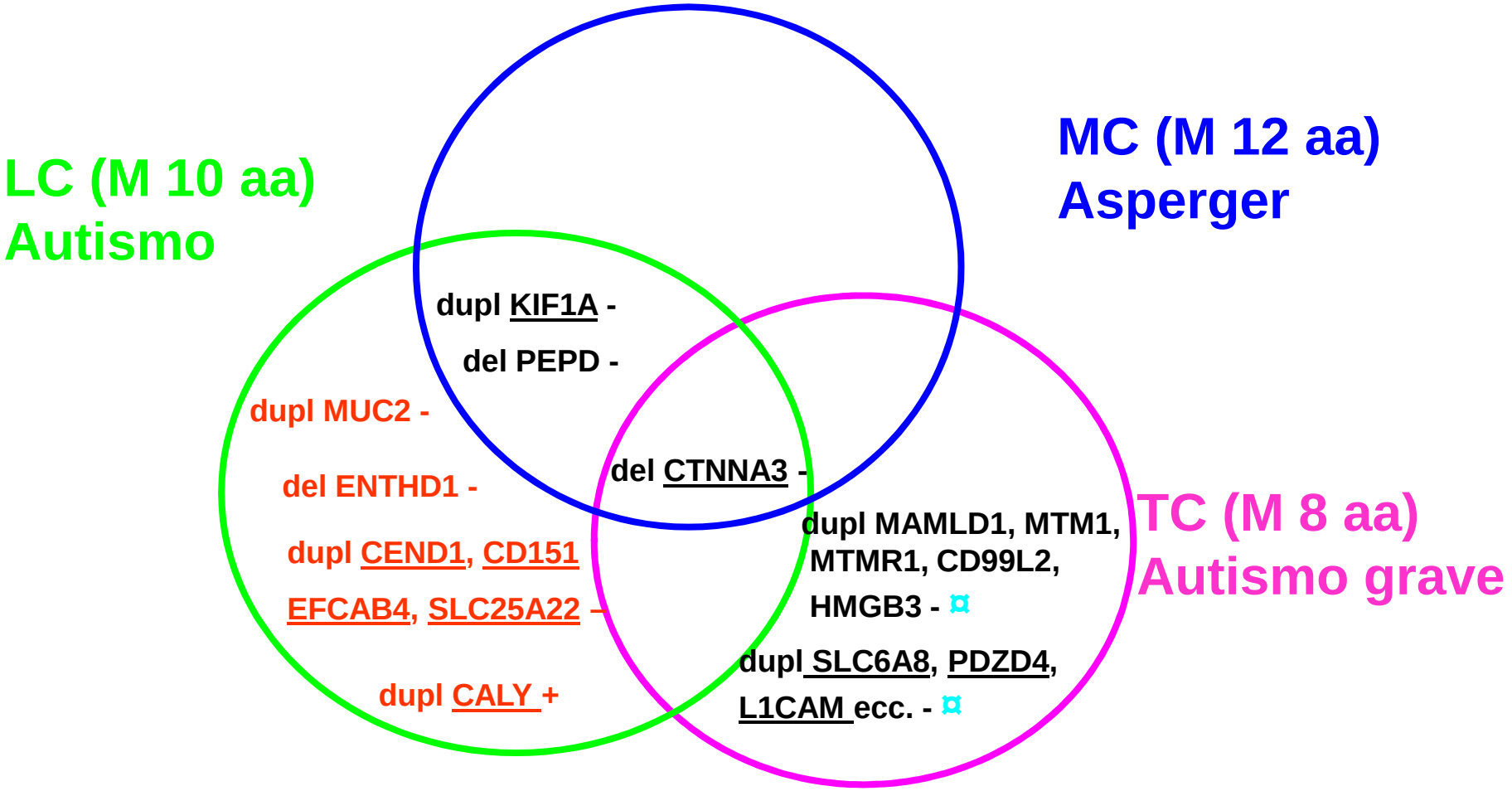
D.R.: 2.5 Mb *de novo* deletion (chr. 15q25.2-15q25.3)

(3) Sindromi autistiche ricorrenti da CNV

Regione Ch	Del/Dup	segni e sintomi relativi al neurosviluppo	Altri segni e sintomi
1q21	**Del**	Autismo, ADHD, comportamento antisociale, ansia, epilessia, ritardo mentale, ritardo dello sviluppo, depressione, allucinazioni, schizofrenia.	**Dismorfismi** minori, difetti cardiaci, cataratta, **malformazioni** multiple congenite.
	Dup	Autismo, ADHD, epilessia, ritardo mentale, ritardo dello sviluppo, deficit del linguaggio, disturbi dell'apprendimento.	Dismorfismi minori, malformazioni multiple congenite.
2p15-2p16.1	**Del**	Autismo, ritardo dello sviluppo	Microsomia, microcefalia, caratteristiche dismorfiche
15q13	**Del**	Autismo, ADHD, aggressività, ansia, epilessia, ritardo mentale, ritardo dello sviluppo, deficit del linguaggio, schizofrenia.	DIsmorfismi minori, difetti cardiaci.
	Dup	Autismo, ansia, disturbo bipolare, ritardo mentale, ritardo dello sviluppo, disturbo ossessivo compulsivo, ritardo del linguaggio.	Dismorfismi minori, ipotonia, obesità, infezioni ricorrenti dell'orecchio
16p11.2	**Del**	Autismo, sindrome di Asperger, ADHD, dislessia, disturbo bipolare, ansia, epilessia, ritardo mentale, ritardo dello sviluppo, deficit del linguaggio, schizofrenia.	Dismorfismi minori, ipotonia, malformazioni congenite multiple.
	Dup	Autismo, ADHD, ansia, epilessia, ritardo mentale, ritardo dello sviluppo, disturbo ossessivo-compulsivo.	

Persico AM & Napolioni V, Behav Brain Res 251:95-112, 2013

Correlazioni genotipo- fenotipo nella famiglia CA



CNV ereditati

CNV de novo

+ CNV localizzato in zona ipervariabile

-CNV localizzato in zona poco ipervariabile o ipovariabile

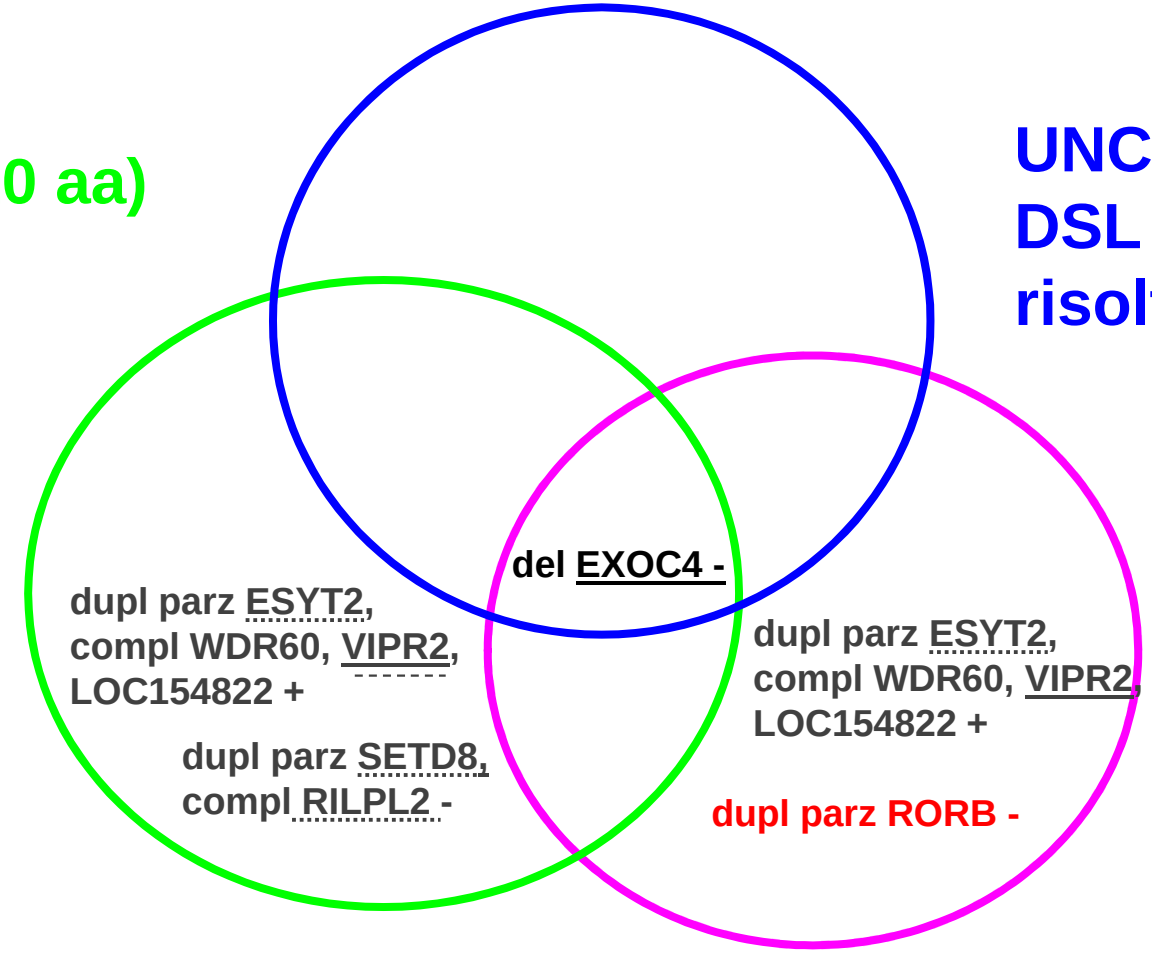
geni autismo o neurosviluppo

¤ geni soggetti a inattivazione cromosoma X nelle femmine

Correlazioni genotipo- fenotipo nella famiglia CO

VPC (M 10 aa)
Autismo

UNC (M 7 aa)
DSL espressivo
risolto



CCC (F 5 aa)
autismo grave

CNV ereditati dalla madre

CNV ereditati dal padre

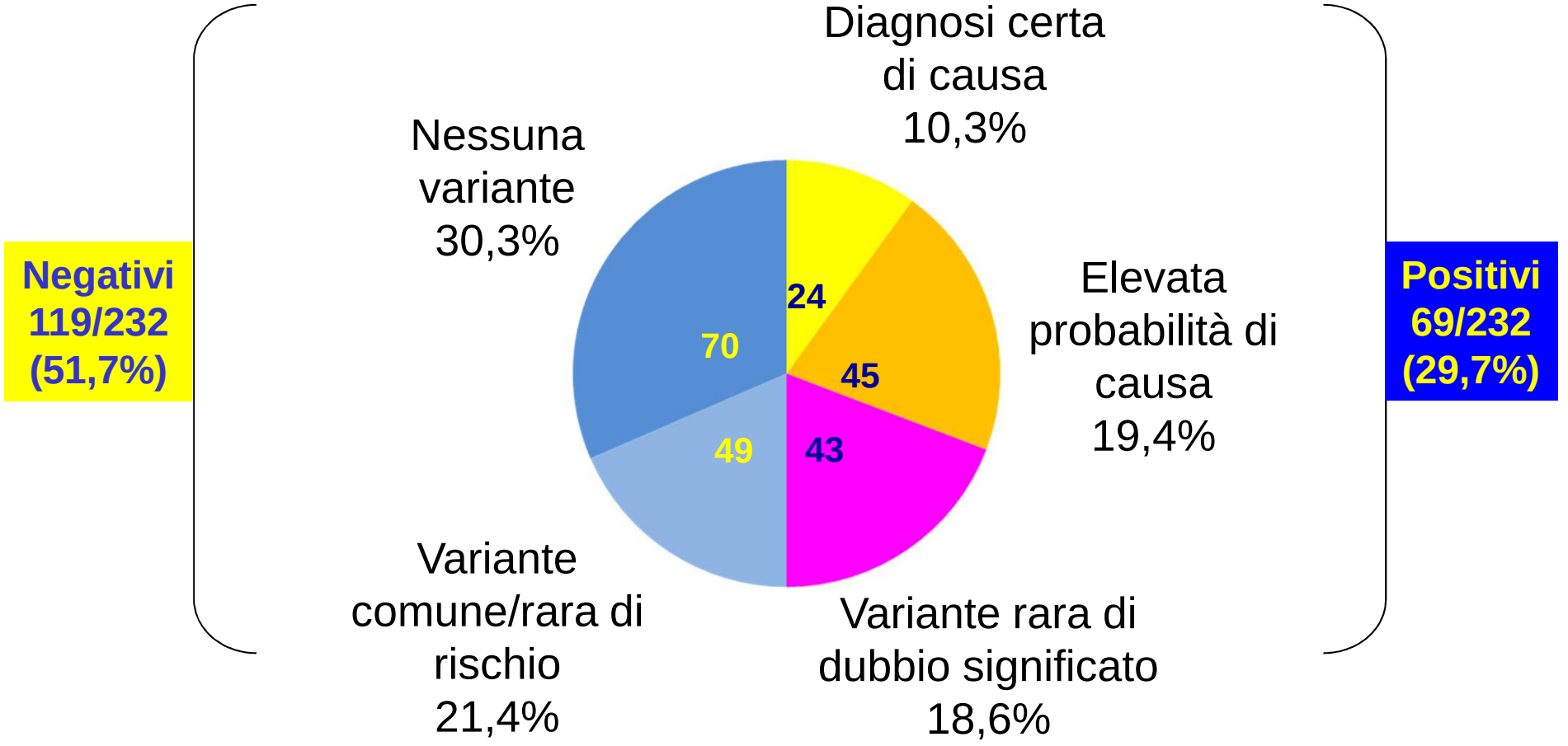
CNV de novo

+ CNV localizzato in zona ipervariabile

- CNV localizzato in zona poco ipervariabile o ipovariabile

geni autismo o schizofrenia o neurosviluppo

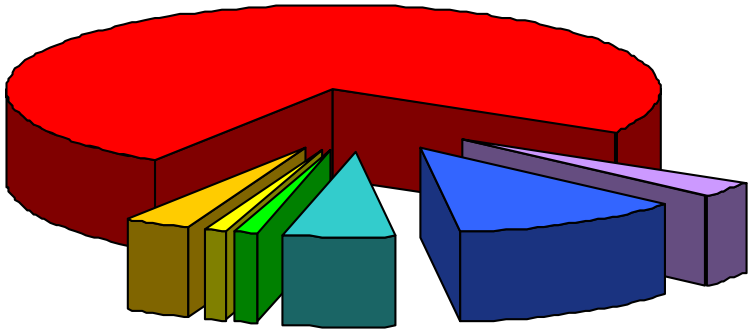
Esito degli array-CGH nei pazienti autistici (N=232)



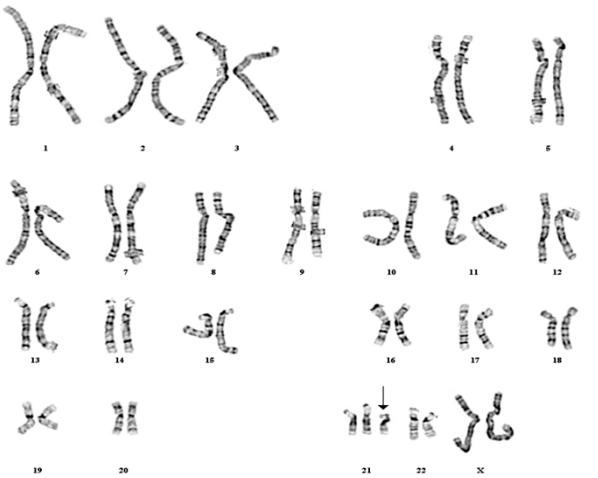
(4) Sindromi autistiche mitocondriali

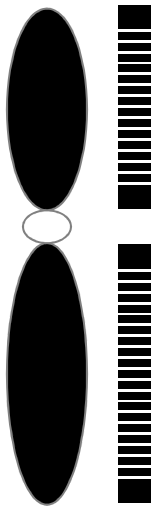
Ref.	Mutation	mtDNA gene	N. of patients	Signs and symptoms
Graf *et al* (2000)	8363G>A	$tRNA^{Lys}$	2 siblings	*Brother*: autism, behavioral **regression**, extreme hyperactivity, lack of attention, mild fine and gross motor dyspraxia *Sister*: partial complex seizures, unsteady gait, myoclonus, swallowing dysfunction, moderate mental retardation.
Fillano *et al* (2002)	Large mtDNA deletions		5 ASD	Autism, ataxia, cardiomyopathy.
Pons *et al* (2004)	3243A>G	$tRNA^{Leu(UUR)}$	2 ASD & their 2 mothers	**Highly heterogeneous**: typically mit. encephalopathy with lactic acidosis and stroke-like episodes (MELAS), or maternally inherited progressive external ophthalmoplegia. In these two patients: autism, **dev. delay**, clumsiness, attention deficit, **neurologic deterioration in the presence of fever**, microcephaly or macrocephaly.
	?	mtDNA? Genomic DNA?	1 with mit. DNA depletion	Autism, **muscle hypotonia**, seizures, myoclonus, and developmental delay.
Weissman *et al* (2008)	3397A>G 4295A>G 11984T>C	ND1 subunit of $ItRNA^{Ileu}$ ND4 subunit of complex I	25 with primary mit. disorder (3/25 carry mtDNA mutation)	Autism, **excessive fatigability and/or exercise intolerance**, gastrointestinal dysfunction, cardiovascular abnormalities, facial dysmorphisms, **microcephaly or macrocephaly**, gross motor dev. delays, growth retardation.

Difetti genetici e genomici nei Disturbi dello Spettro Autistico



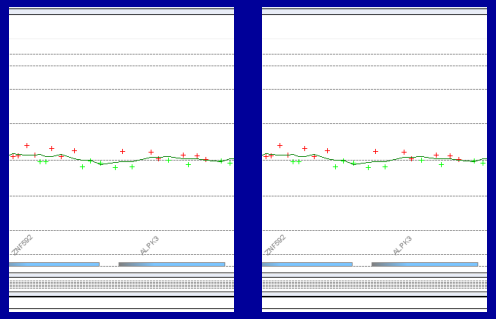
- Karyotypic
- Submicroscopic
- Fragile X
- Rett syndrome
- Neuroligins
- Tuberous Sclerosis
- Unknown

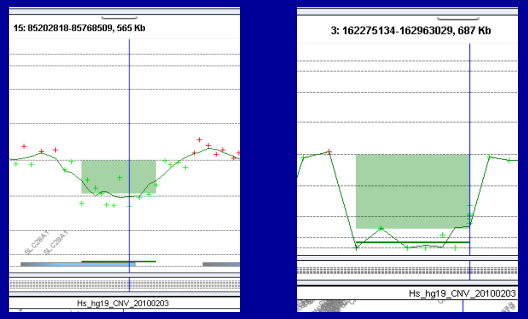


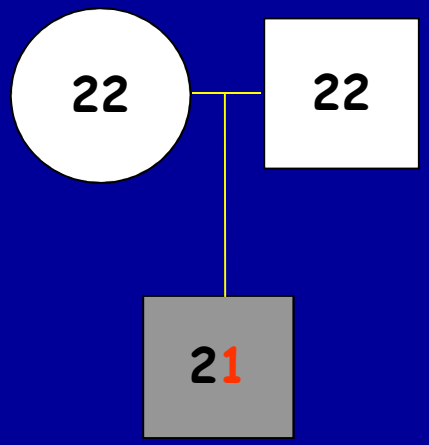


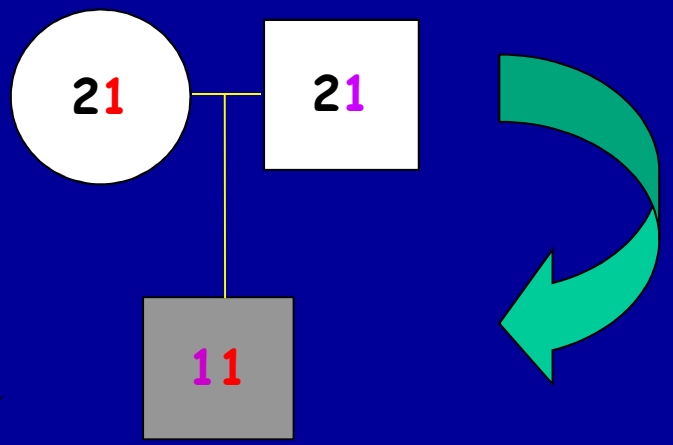
Prof. Bei-Lin Wu, Harvard Univ.

Genetica semplice e complessa





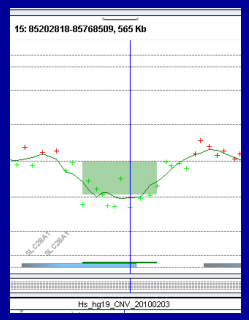


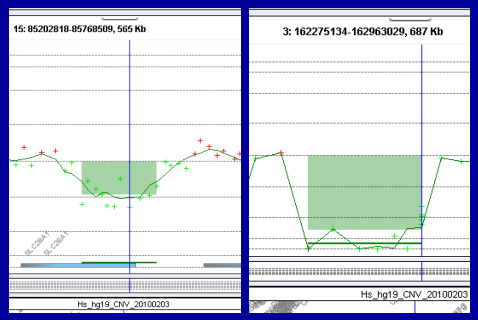


Mutazione o delezione de novo

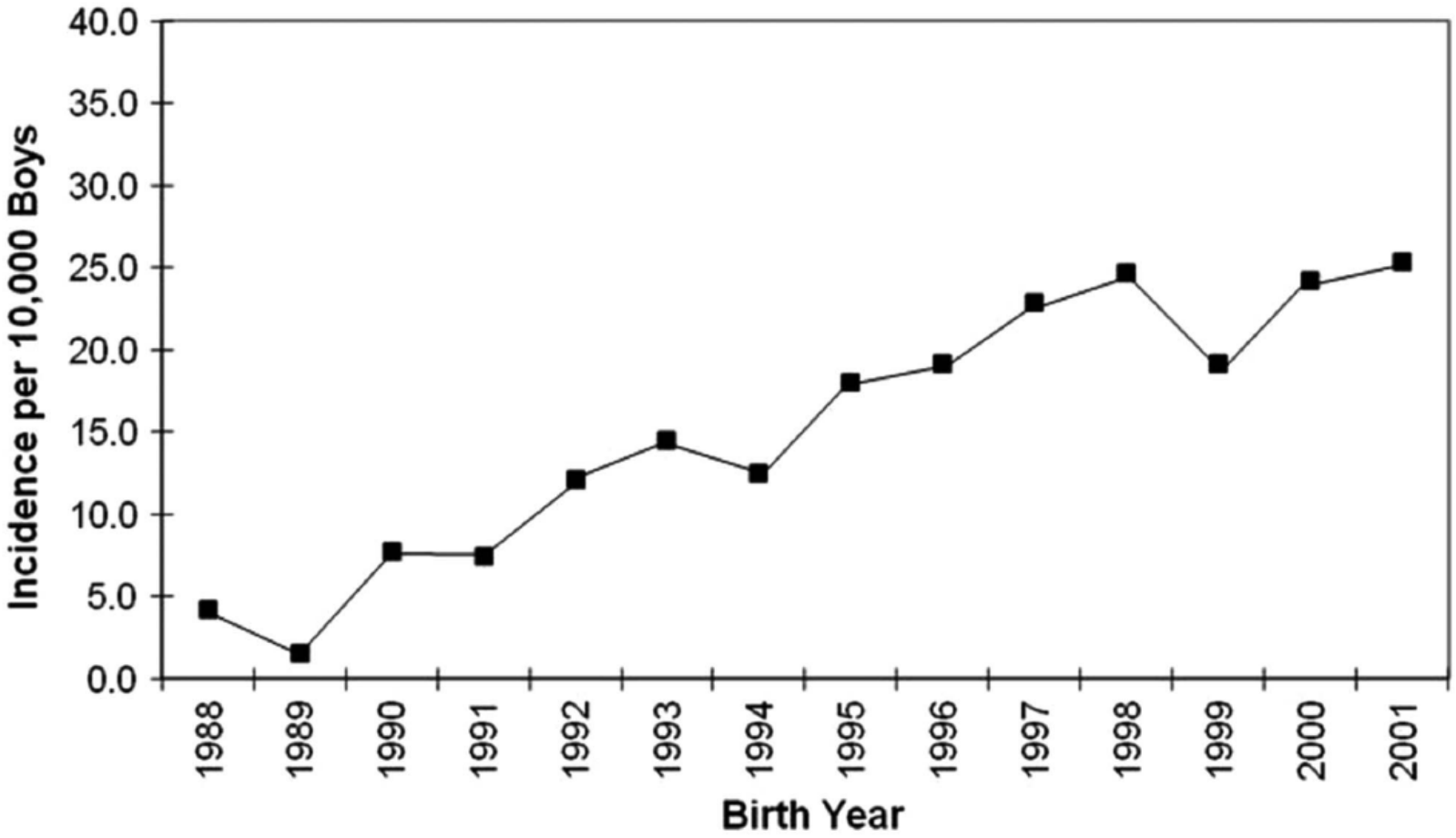
Fattori ambientali

Delezioni trasmesse dai genitori al figlio





Incidenza di autismo nel Regno Unito



Taylor et al., *BMJ Open* 3:e003219, 2013

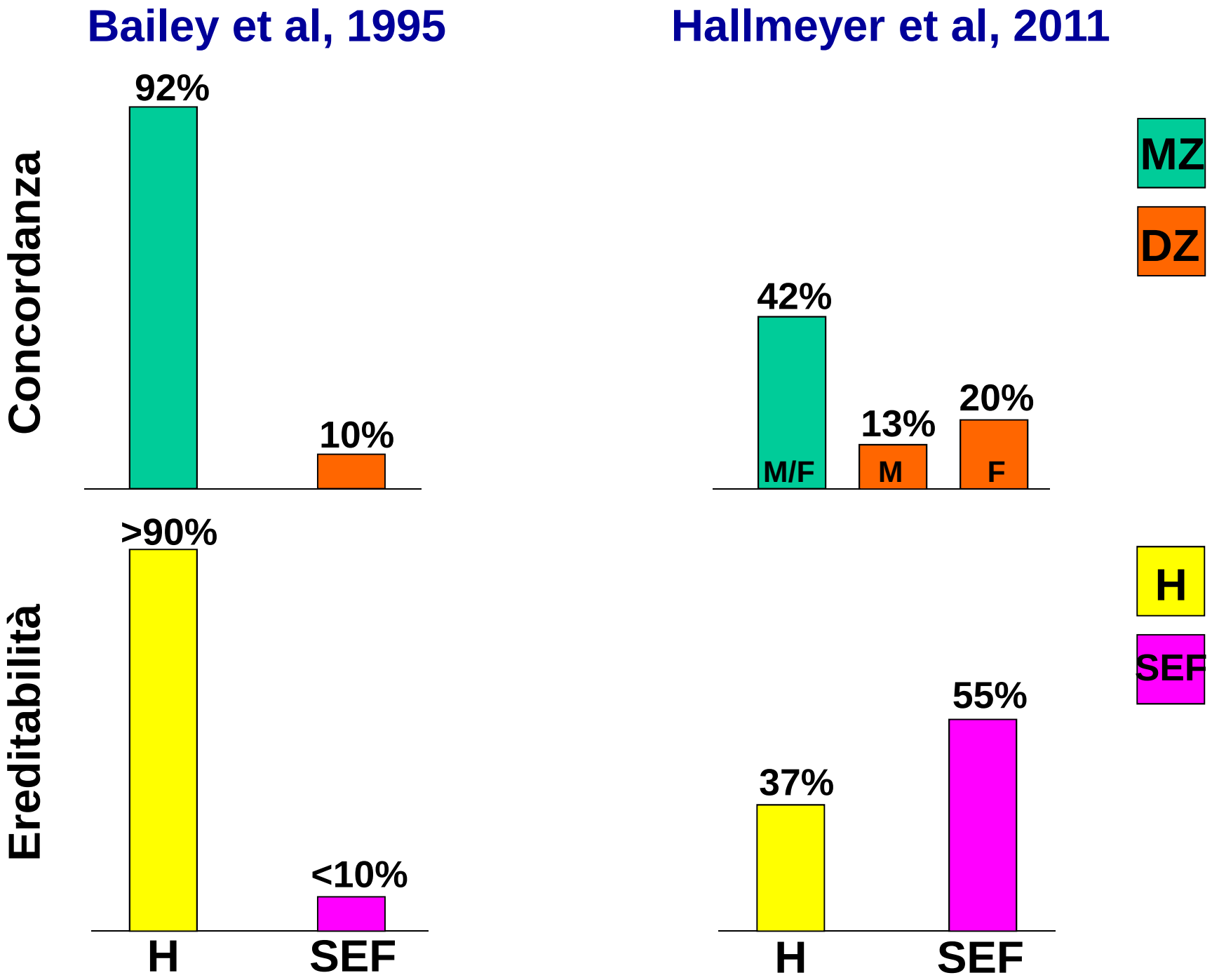
Fattori Ambientali e Autismo: prove certe di causalità diretta

Fattore Ambientale	Periodo critico	Meccanismo
Acido Valproico	Giorno embrionale 18-30 post-fertilizzazione	Alterazione della espressione genica Ipometilazione del DNA Stress ossidativo Anti-metabolismo dell'acido folico
Talidomide	Giorno embrionale 20-30 post-fertilizzazione	Alterazione della espressione genica Danno al DNA mediato da radicali dell'O_2 Inibizione dell'angiogenesi
Misoprostol	Giorno embrionale 18-42 post-fertilizzazione	Alterazione della espressione genica Inibizione dell'angiogenesi
Rosolia	Settimana embrionale 1-8 post-fertilizzazione	Danno diretto del virus sul neurosviluppo Risposta immune materna e fetale
Citomegalovirus	Tutta la gravidanza	Danno diretto del virus sul neurosviluppo Risposta immune materna e fetale

Persico AM & Merelli S, Key Issues in Mental Health, vol. 179/Chapter 10

Fattori Ambientali e Autismo: indizi di causalità diretta

Fattore Ambientale	Periodo critico	Meccanismo
Inquinamento dell'aria	Tutta la gravidanza + periodo postnatale precoce	Stress ossidativo nel sistema nervoso centrale Attivazione immunitaria sistemica e nel sist. nervoso Danno vascolare cerebrale Neurodegenerazione Alterazione della espressione genica Alterata metilazione del DNA
Organofosfati	Tutta la gravidanza	Attivazione infiammatoria sistemica e nel sist. nervoso Alterazione della proliferazione neurogliale da perossidazione Inibizione della trascrizione e dell'attività di reelin Ridotta espressione di BDNF Interferenza con la gestione del calcio intracellulare Alterazione della neurotrasmissione GABAergica
Bifenili policlorinati (PCB) e eteri difenili polibrominati (PBDE)	Tutta la gravidanza	Interferenza endocrina Stress ossidativo nel sistema nervoso centrale Interferenza con la gestione del calcio intracellulare Ridotta metilazione del DNA Attivazione immunitaria sistemica e nel sist. nervoso
Metalli pesanti	Tutta la gravidanza	Neurotossicità Attivazione del sistema immune, autoimmunità Alterazione della espressione genica
Antidepressivi	Tutta la gravidanza + periodo postnatale precoce	Squilibrio serotoninergico


Bailey et al, 1995
Hallmeyer et al, 2011
Concordanza
92%
10%
42%
13%
20%
M/F
M
F
MZ
DZ
Ereditabilità
>90%
<10%
37%
55%
H
SEF
H
SEF


Associazione di Volontariato
per i bambini autistici
danneggiati da vaccino
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24/12/2015

Medical Hypotheses (2001) **56**(4), 462–471

doi: 10.1054/mehy.2000.1281, available online at http://www.idealibrary.com on IDEAL®

Autism: a novel form of mercury poisoning

S. Bernard, A. Enayati, L. Redwood, H. Roger, T. Binstock

ARC Research, Cranford, New Jersey, USA

Early report

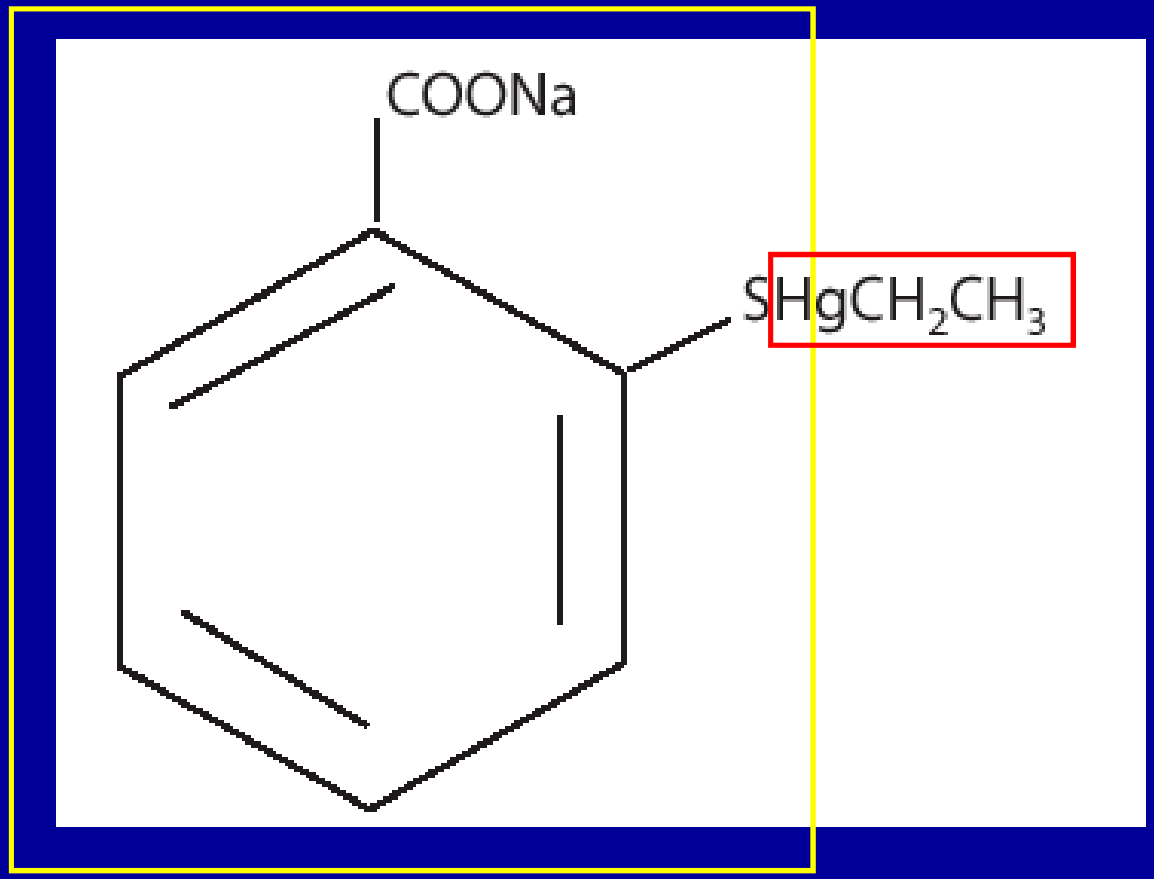
Lancet 1998; **351:** 637–41
See Commentary page

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Thimerosal o Tiomersale: struttura e funzione

Mobilizzazione del Ca^{2+} + danno enzimatico



Effetti ossidativi

Etilmercurio

Acido tiosalicilico

Solubilità in acqua

Tiomersale: effetti ossidativi

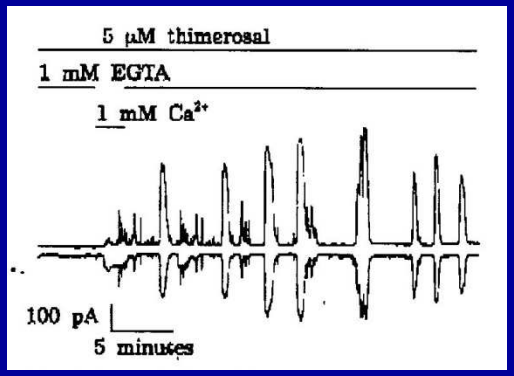
$$R\text{-}SH + Ar\text{-}S\text{-}Hg\text{-}C_2H_5 \longrightarrow R\text{-}S\text{-}Hg\text{-}C_2H_5 + Ar\text{-}SH$$

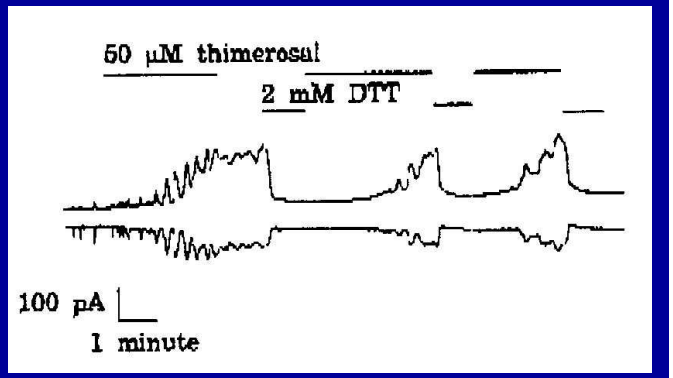
Enzima
Canale ionico
Pompa

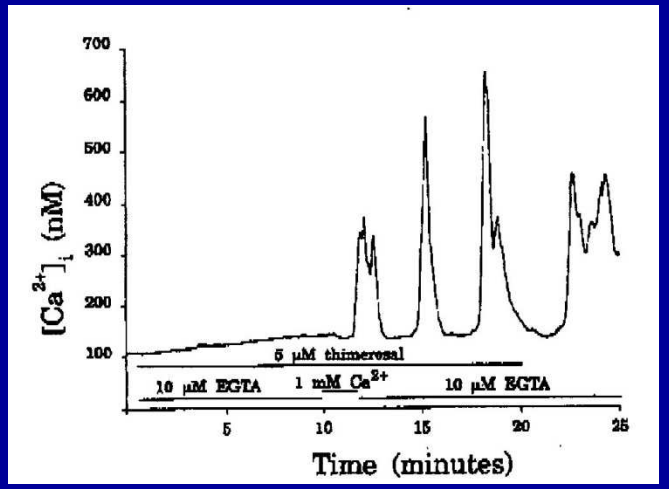
Enzim
Canal
Pompa

Agente antisettico & conservante in vaccini, immunoglobuline, cosmetici, soluzioni per la pulizia delle lenti a contatto, ecc

Tiomersale: mobilizzazione del Ca^{2+}







Thorn P et al, Eur J Physiol 422:173, 1992

- Rilascio intracellulare di Ca^{2+}
- Entrata di Ca^{2+} dall'ambiente extracellulare +
  Inibizione della pompa del Ca^{2+}

Metilmercurio ed etilmercurio NON sono la stessa cosa!

1) M-Hg passa la BEE ed è molto tossico per il cervello; l'E-Hg non passa altrettamento bene la BEE ed è più dannoso al rene

2) M-Hg – esposizione cronica
E-Hg – esposizione acuta e transitoria

Studi ecologici di confronto tra la prevalenza di autismo *prima* e *dopo* la rimozione del tiomersale dai vaccini

Nazione	*Referenze*	*Anni prima della rimozione*	*Anni dopo la rimozione*	*Esito*
Canada	Fombonne et al, 2006	1986-1995	1996-1998	negativo
Danimarca	Madsen et al, 2008 Stehr-Green et al, 2003	1971-1992 1981-1992	1993-2000 1993-2000	negativo negativo
Svezia	Stehr-Green et al, 2003	1980-1992	1993-2000	negativo
U.S.A.	Schechter & Grether, 2008	1989-2001	2002-2003	negativo

California: più tiomersale, più autismo

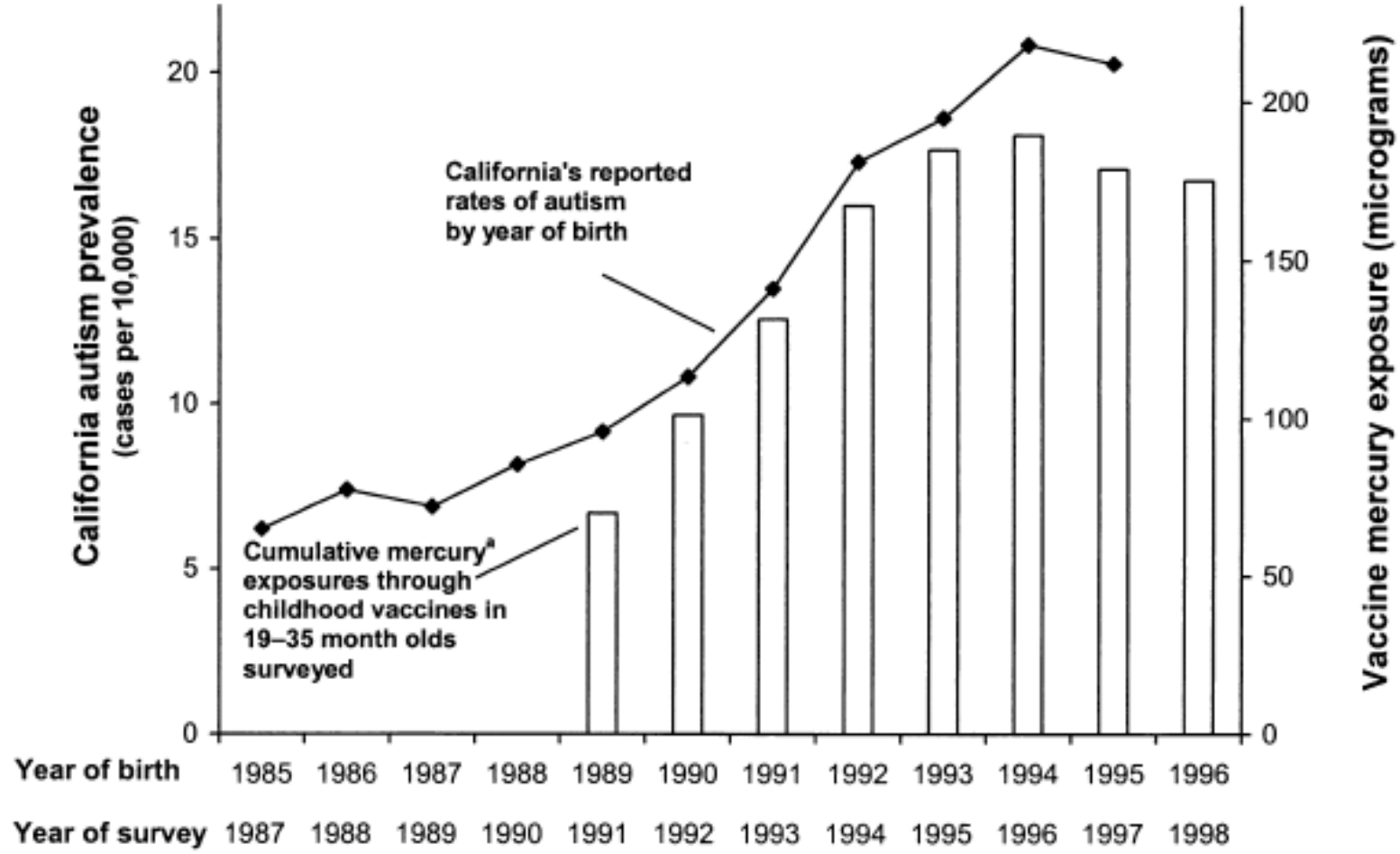


Figure 1. Graphical ecologic analysis presented by Blaxill[3] to the Institute of Medicine on July 16, 2001, comparing the estimated average cumulative dose of mercury exposure in the United States from vaccines, and the estimated prevalence (per 10,000 population) of children diagnosed with autism-like disorders seeking special education services for autism in California from 1987 to 1998, by birth-year cohort.
[a]Includes DPT, *Haemophilus influenza* B, and hepatitis B exposures weighted by survey year compliance.

Stehr-Green P et al, Am J Prev Med 25:101, 2003

Svezia e Danimarca: meno tiomersale, più autismo

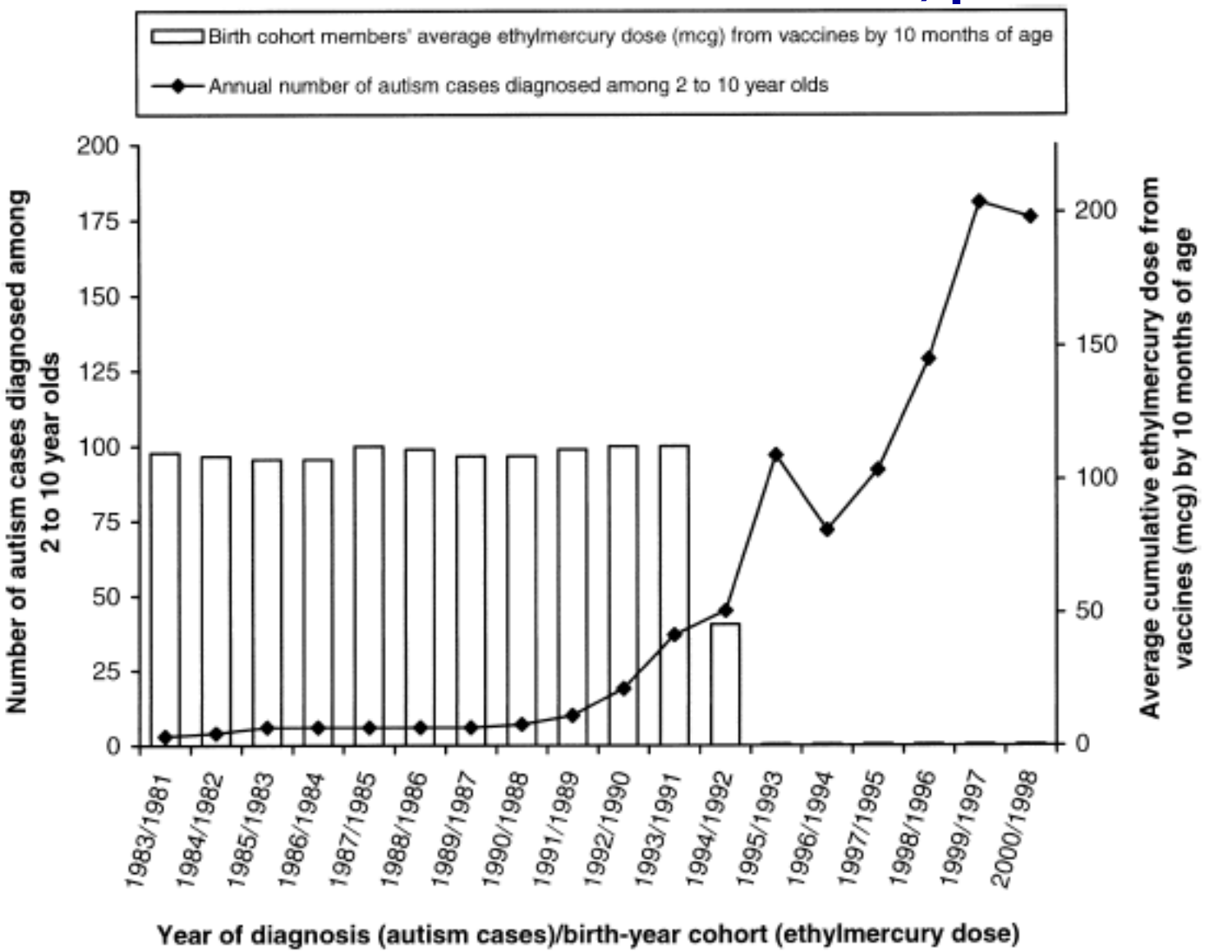


Figure 3. Graphical ecologic analysis comparing the average cumulative ethylmercury dose received from vaccines by birth-ye cohort from 1981 to 1998, and the annual number of incident cases of autism in children aged 2 to 10 years diagnosed Denmark from 1983 to 2000.

Stehr-Green P et al, Am J Prev Med 25:101, 2003

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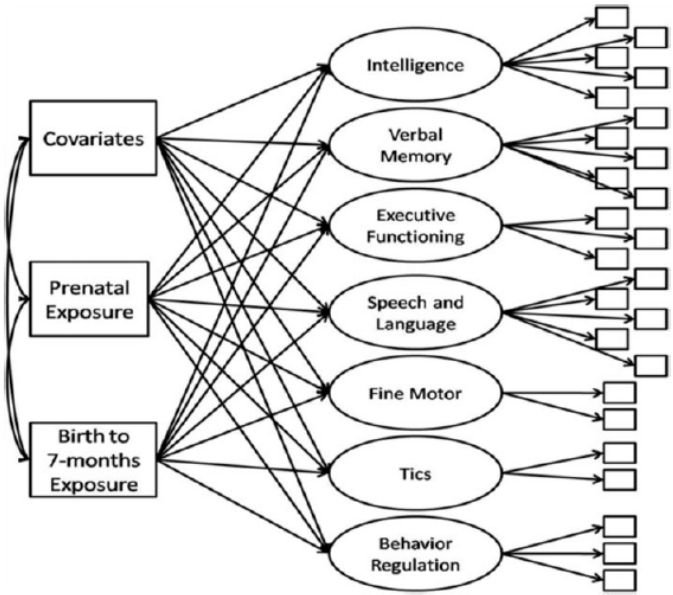
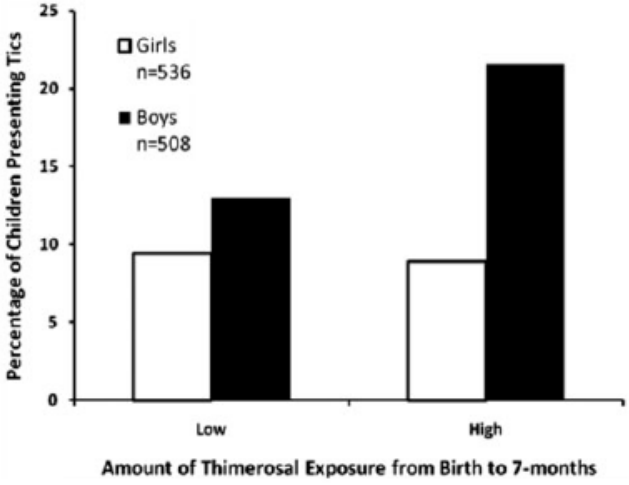
Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years

William W. Thompson, Ph.D., Cristofer Price, Sc.M., Barbara Goodson, Ph.D., David K. Shay, M.D., M.P.H., Patti Benson, M.P.H., Virginia L. Hinrichsen, M.S., M.P.H., Edwin Lewis, M.P.H., Eileen Eriksen, M.P.H., Paula Ray, M.P.H., S. Michael Marcy, M.D., John Dunn, M.D., M.P.H., Lisa A. Jackson, M.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Steve Black, M.D., Gerrie Stewart, M.A., Eric S. Weintraub, M.P.H., Robert L. Davis, M.D., M.P.H., and Frank DeStefano, M.D., M.P.H., for the Vaccine Safety Datalink Team





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A Two-Phase Case-Control Study of Autism Risk Among Children Born From the Late 1990s Through the Early 2000s in the United States

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Original Article

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Thimerosal-containing Hepatitis B Vaccine Exposure is Highly Associated with Childhood Obesity: A Case-control Study Using the Vaccine Safety Datalink

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Administration of thimerosal-containing vaccines to infant rhesus macaques does not result in autism-like behavior or neuropathology

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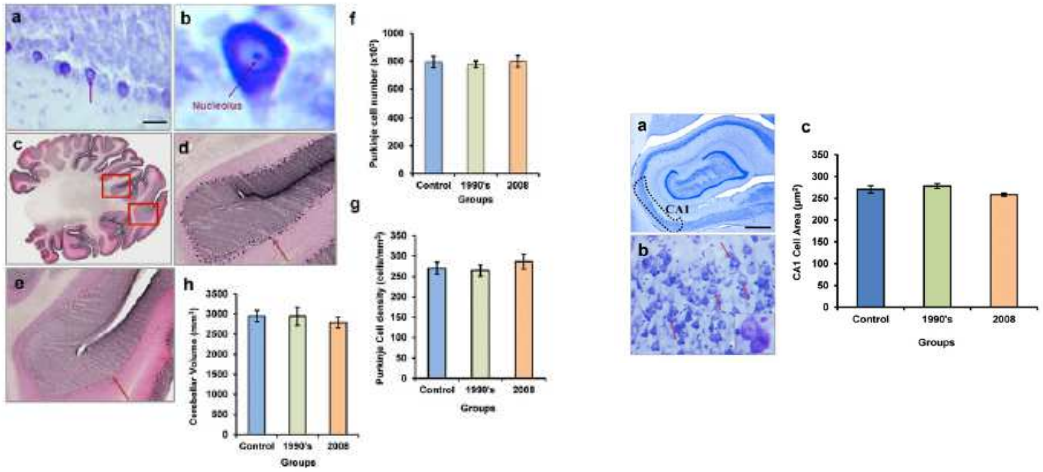
Table 1. Vaccination schedules used for the six groups of animals

Group	*N*	Vaccines administered
Control	16	None, all saline placebos
1990s Pediatric	12	Vaccine regimen as recommended in the 1990s
1990s Primate	12	Vaccine regimen as recommended in the 1990s accelerated fourfold
TCV's	12	All TCVs and saline placebo for MMR
MMR	15	MMR only, all others replaced with saline placebo
2008	12	Vaccine regimen recommended in 2008



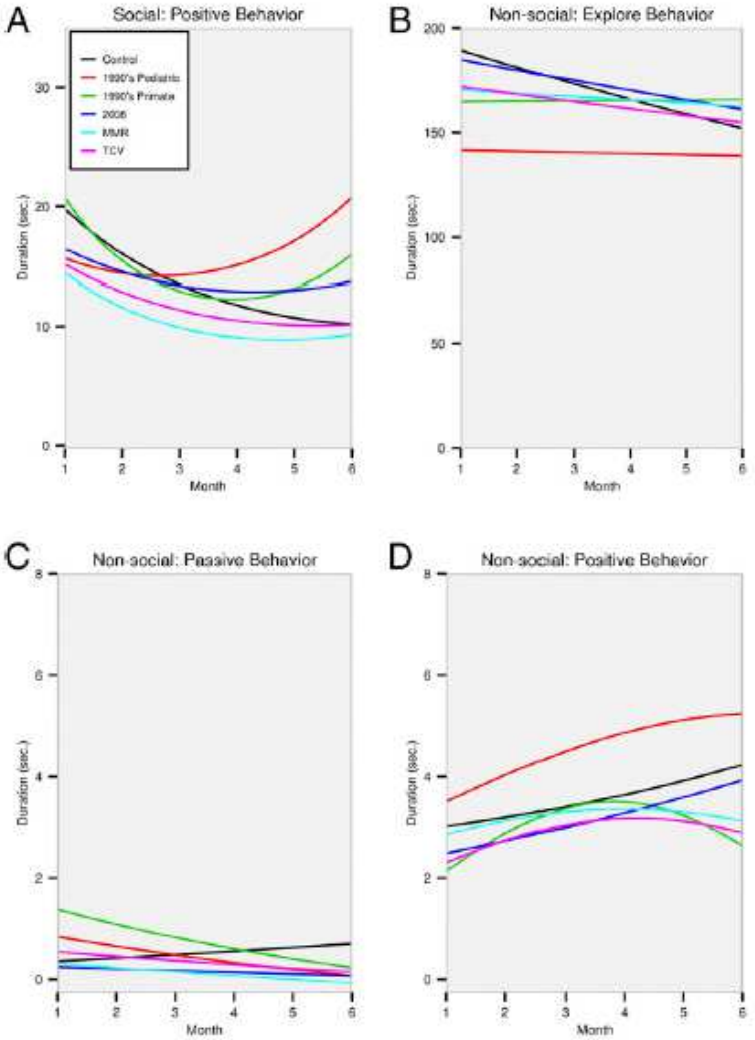


Fig. 1. Analysis of behavioral data. Fitted values from analytical models of social and nonsocial behavior for groups from age 12 to 18 mo, back-transformed with antilog. Durations of positive behaviors (play, sex, and aggression) were summed for each animal. Only behaviors that showed either a significant time main effect or a time × group interaction are shown: (*A*) Social: Positive Behavior, (*B*) Nonsocial: Explore Behavior, (*C*) Nonsocial: Passive Behavior, and (*D*) Nonsocial: Positive Behavior. Nonsocial: Explore Behavior demonstrated the only significant time × group effect, and this was only significant at the beginning of social living. Duration of behaviors is shown in seconds.

Research Article

Assessment of Hair Aluminum, Lead, and Mercury in a Sample of Autistic Egyptian Children: Environmental Risk Factors of Heavy Metals in Autism

Behavioural Neurology
Volume 2015, Article ID 545674, 9 pages
http://dx.doi.org/10.1155/2015/545674

Farida El Baz Mohamed,[1] Eman Ahmed Zaky,[1] Adel Bassuoni El-Sayed,[2] Reham Mohammed Elhossieny,[1] Sally Soliman Zahra,[1] Waleed Salah Eldin,[3] Walaa Yousef Youssef,[1] Rania Abdelmgeed Khaled,[1] and Azza Mohamed Youssef[1]

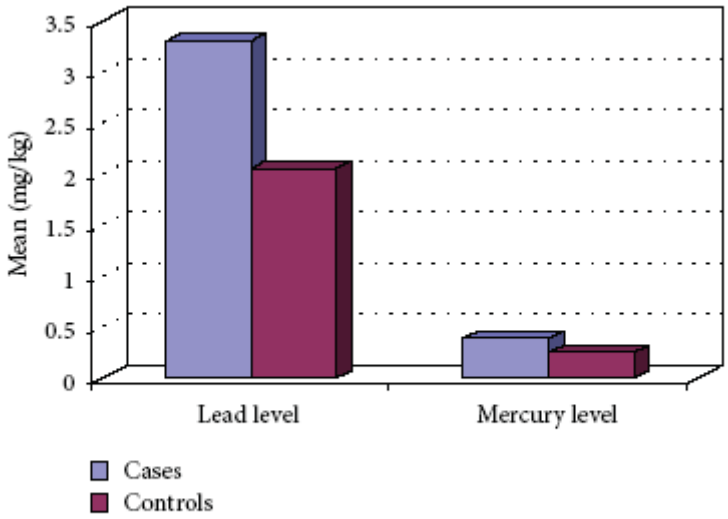


FIGURE 2: Mean lead and mercury levels in hair in both groups.

Copper and zinc levels in plasma and PBMCs of patients...with autism (?!?)

	patients	controls
Plasma zinc (µg/l)*	687 (467)	1024 (428)
PBMC zinc (µg/10^6 cells)†	135.2 (28.6)	98.4 (16.4)
Plasma copper (µg/l)‡	1646 (357)	946 (446)
PBMC copper (µg/10^6 cells)§	58.0 (43.2)	104.2 (8.5)

Nope!...it's rheumatoid arthritis!!!

Table 1 Copper and zinc levels in plasma and PBMCs of patients with RA. Results are given as mean (SD)

	Active RA	Inactive RA	Overall RA	Controls
Plasma zinc (µg/l)*	687 (467)	982 (264)	824 (386)	1024 (428)
PBMC zinc (µg/10^6 cells)†	135.2 (28.6)	108.3 (38.4)	121.4 (34.4)	98.4 (16.4)
Plasma copper (µg/l)‡	1646 (357)	1016 (296)	1426 (324)	946 (446)
PBMC copper (µg/10^6 cells)§	58.0 (43.2)	86.4 (33.2)	74.3 (38.2)	104.2 (8.5)

Wanchu A et al, Ann Rheum Dis 61: 88, 2002

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associ[ated] by the parents, with measles, mumps, and rub[ella] vaccination in eight of the 12 children, with measl[es] infection in one child, and otitis media in an[other]. All 11 children had intestinal abnormalities, rangi[ng] from lymphoid nodular hyperplasia to aph[thoid] ul[ceration]. Histology showed patchy chronic inflam[mation] in 11 children and reactive ileal lymphon[odular] hyperplasia in seven, but no granulomas. Be[havi]oural disor[ders] included autism (nine), disintegrative psych[osis] (one), a[nd] possible postviral or vaccinal encephalitis (one). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and a low serum IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351:** 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP,), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for 1 week, accompanied by their parents.

Clinical investigations

We took histories including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental data included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[2] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antiendomyseal antibodies and boys were screened for fragile-X if this had not been done

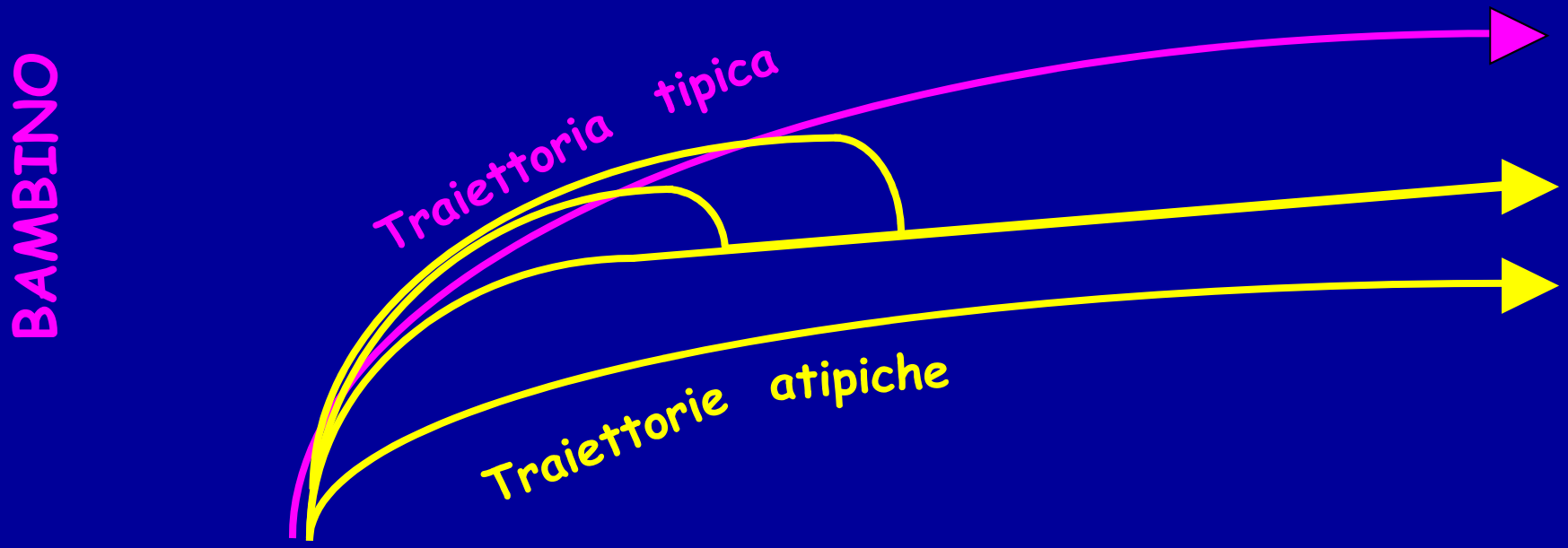
Following the judgment of the UK General Medical Council's Fitness to Practise Panel on Jan 28, 2010, it has become clear that several elements of the 1998 paper by Wakefield et al[1] are incorrect, contrary to the findings of an earlier investigation.[2] In particular, the claims in the original paper that children were "consecutively referred" and that investigations were "approved" by the local ethics committee have been proven to be false. Therefore we fully retract this paper from the published record.

[1]Wakefield, AJ, Murch, SH, Anthony, A et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998; 351: 637–641

[2]Hodgson, H. A statement by The Royal Free and University College Medical School and The Royal Free Hampstead NHS Trust. Lancet. 2004; 363: 824

Andrew Wakefield appearance at Trump inaugural ball triggers social media backlash (https://www.statnews.com)

Quattro traiettorie di sviluppo atipiche nell'autismo



1) Mancata acquisizione di nuove funzioni (linguaggio, gioco) tra i 9 ed i 24 mesi
2) Perdita di funzioni già acquisite tra i 18 ed i 24 mesi («Regressione»)
3) Perdita di funzioni già acquisite dopo i tre anni («Regressione tardiva»)
4) Ritardo globale di sviluppo fin dalla primissima infanzia

Traiettoria n.1:
Mancata acquisizione di nuove funzioni (linguaggio, gioco) tra i 9 ed i 24 mesi

Durante il primo anno di vita, tappe del neurosviluppo nella norma e nessun apparente campanello di allarme, ma durante il secondo anno di vita i genitori dicono:

- **Non ha ancora iniziato a parlare.**
- **Non si gira quando lo chiamo…sarà sordo?**
- **E' diventato un bambino molto serio, sorride poco, è irritabile, dorme male.**
- **Non mi guarda mai in faccia.**
- **E' sempre in movimento, ha un gioco molto meccanico e fisico, non come i suoi coetanei.**
- **Mette i giochi tutti in fila e guai a spostargli qualche cosa**

Traiettoria n.2:
Perdita di funzioni già acquisite tra i 18 ed i 24 mesi («Regressione»)

Durante il primo anno di vita, tappe del neurosviluppo nella norma e nessun apparente campanello di allarme, ma tra i 12 ed i 24 mesi i genitori descrivono gli stessi comportamenti anomali della traiettoria n.1, ma dicono che «E' successo tutto nell'arco di una settimana…»:

- **Dopo la somministrazione di un vaccino**
- **Quando il bambino ha iniziato a camminare**
- **Dopo un ricovero per un episodio infettivo importante**
- **Dopo una otite molto seria.**
- **Dopo una gastroenterite**
- **Dopo un incidente**

Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies

Luke E. Taylor, Amy L. Swerdfeger, Guy D. Eslick*

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Vaccine 32 (2014) 3623–3629

5 coorti (N=1.256.407) – UK, Danimarca, Giappone, USA

autismo	**O.R. 0,99; 95% CI: 0,92-1,06**
ASD	**O.R. 0,91; 95% CI: 0,68-1,20**
MMR	**O.R. 0,84; 95% CI: 0,70-1,01**
thimerosal	**O.R. 1,00; 95% CI: 0,77-1,31**
mercurio	**O.R. 1,00; 95% CI: 0,93-1,07**

5 studi caso-controllo (N=9.920) – USA, Giappone, Polonia, Inghilterra

patologia	**O.R. 0,90; 95% CI: 0,83-0,98; P=0.02**
esposizione	**O.R. 0,85; 95% CI: 0,76-0,95; p=0.01**

ISS 26 Marzo 2014, Vaccini e autismo, a cura di Stefania Salmaso, Direttore del Centro nazionale di epidemiologia, sorveglianza e promozione della salute dell'ISS

Anti-brain antibodies are associated with more severe cognitive and behavioral profiles in Italian children with Autism Spectrum Disorder

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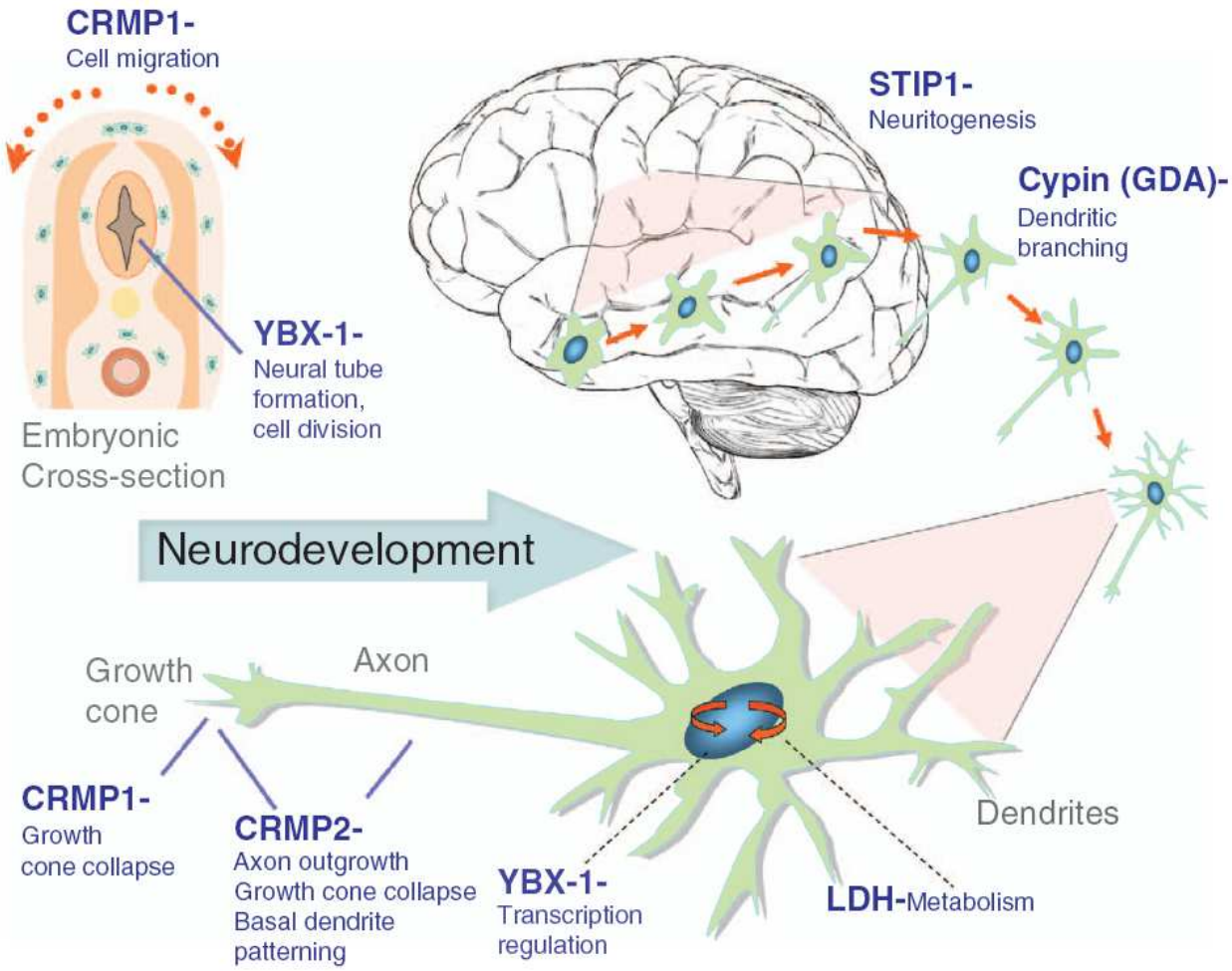
Brain Behav Immun 38:91-99, 2014

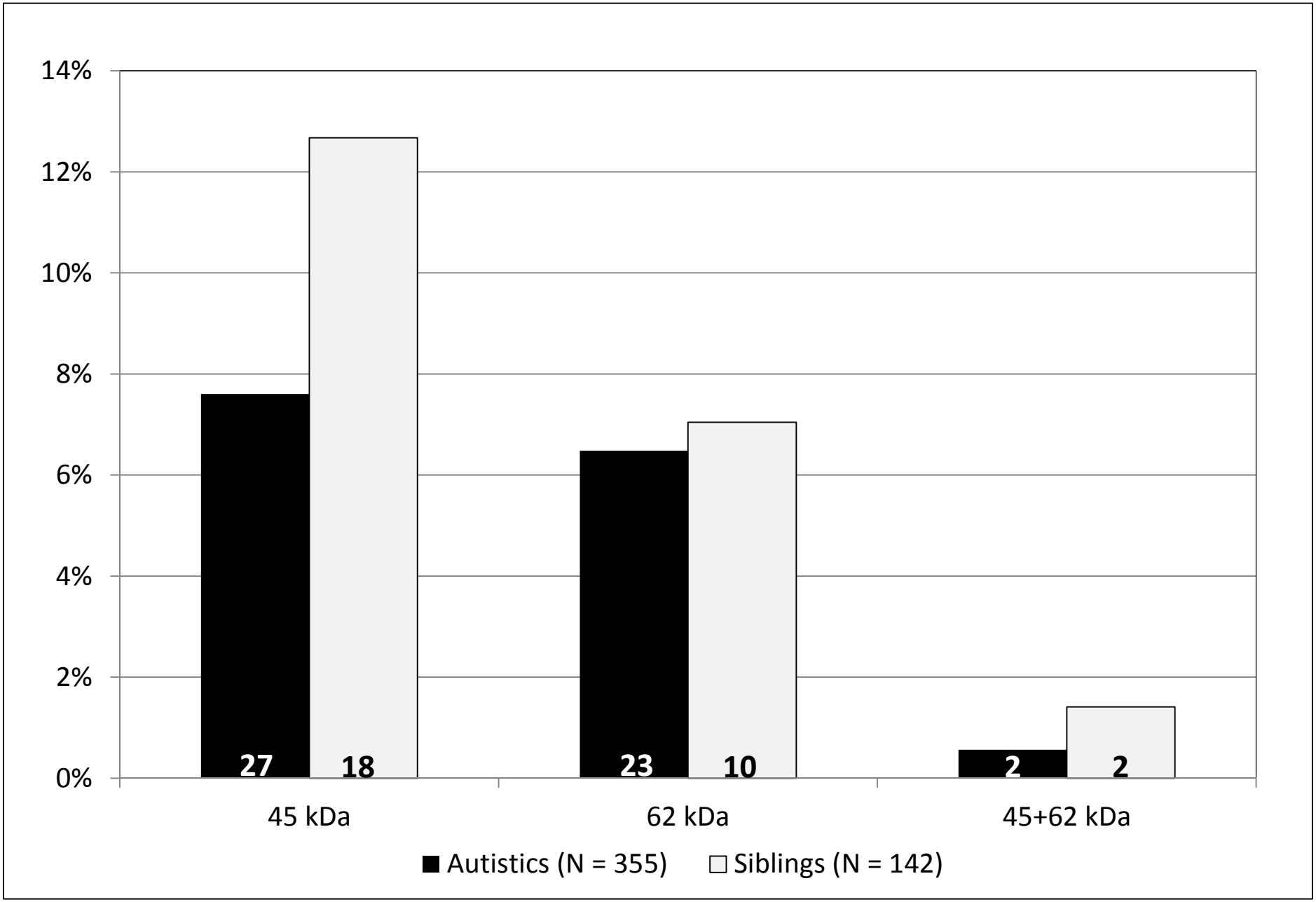
- **Autoanticorpi anticervelletto (45 e 62 kDa)**
  - **N=355 bambini autistici e 142 fratelli/sorelle non affetti**
- **Anticorpi materni anticervello (37, 39, 73 kDa)**
  - **N=333 madri di bambini autistici**

Anticorpi materni

CRMP – collapsin response mediator protein
STIP1 – stress-induced phosphoprotein 1
YBX1 – Y-box binding protein
LDH – lattico deidrogenasi



Braunschweigh et al., Transl Psychiatry 3:e277, 2013



Piras et al., Brain Behav Immun 38:91-99,2014

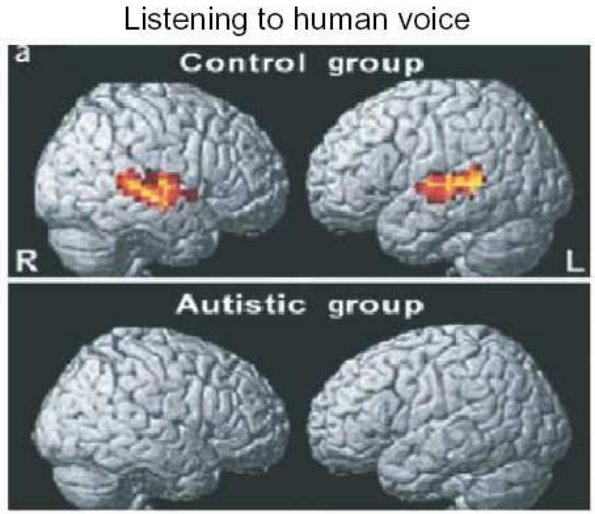
Table 2
Clinical characterization of autistic individuals carrying either the 45 or the 62 kDa antibrain autoantibodies (Ab+). Only categorical variables reaching a nominal $P < 0.05$ are listed. Data are reported as *N* (%).

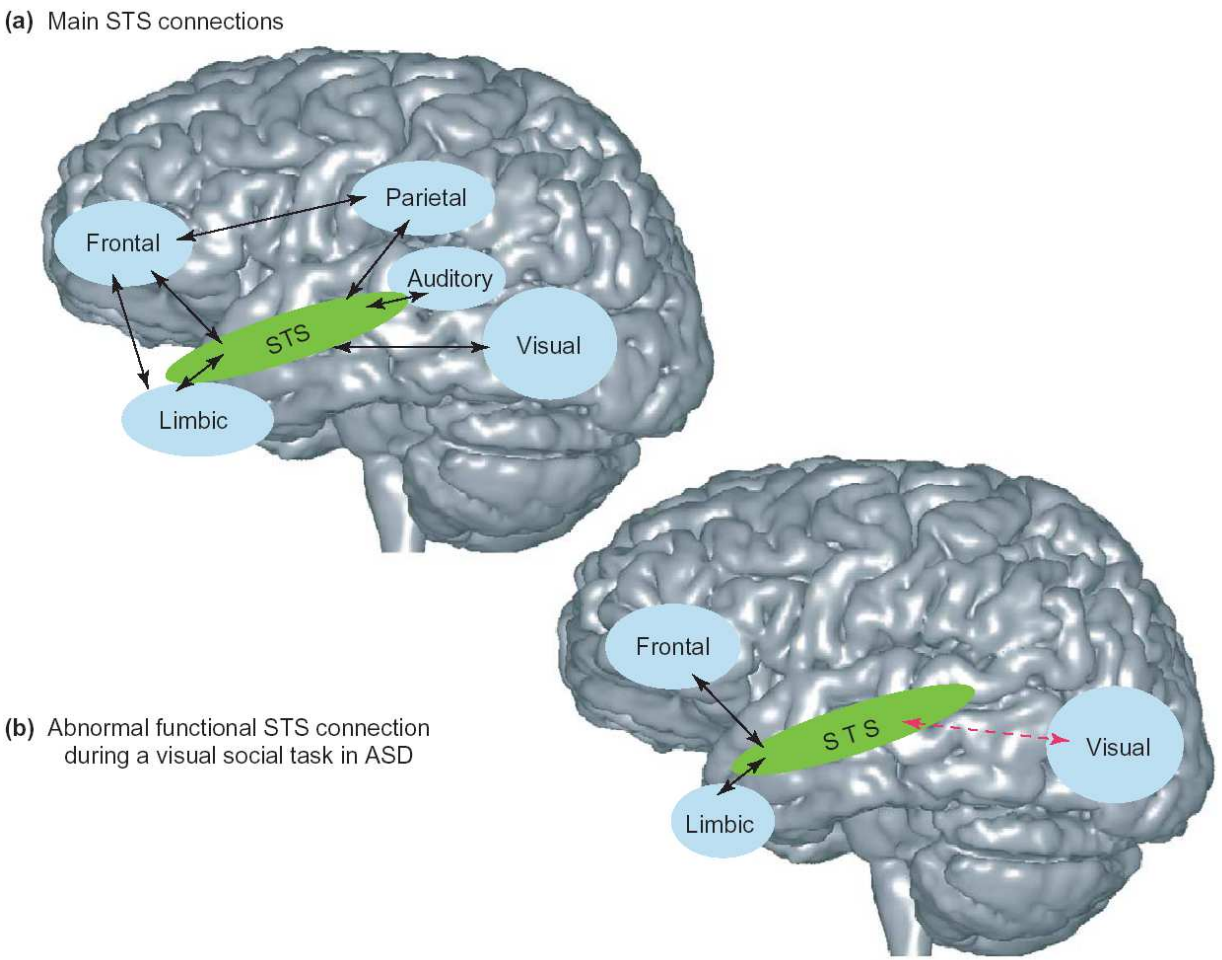
Autoantibody	Categorical variables		Total *N*	Ab+	Ab−	*P*
45 kDa	I.Q.	≤70	182	13 (100.0)	118 (69.8)	0.020
		>70		0 (0.0)	51 (30.2)	
	History of recurrent otitis at autism onset	Present	277	0 (0.0)	52 (20.2)	0.026
		Absent		20 (100.0)	205 (79.8)	
62 kDa	Motor stereotypies observed during the first visit	Present	258	17 (94.4)	170 (71.1)	0.032
		Absent		1 (5.6)	69 (28.9)	
Either 45 or 62 kDa or both	I.Q.	≤70	182	24 (92.3)	107 (68.6)	0.013
		>70		2 (7.7)	49 (31.4)	
	Motor stereotypies observed during the first visit	Present	257	33 (86.8)	154 (70.3)	0.035
		Absent		5 (13.2)	65 (29.7)	
	Sphincter control	Typical development	225	14 (43.8)	122 (63.2)	0.045
		Delayed		2 (6.3)	17 (8.8)	
		Never acquired		16 (50.0)	54 (28.0)	
	Self-injurious behavior observed during the first visit	Present	252	22 (64.7)	175 (80.3)	0.041
		Absent		12 (35.3)	43 (19.7)	

Table 3
Clinical characterization of autistic individuals carrying either the 45 or the 62 kDa antibrain autoantibodies (Ab+). Only continuous variables reaching a nominal $P < 0.05$ are listed.

Autoantibody	Continuous variables	Ab+		Ab−		*P*
		N	Mean ± SD	N	Mean ± SD	
45 kDa	Number of sisters	23	1.04 ± 1.02	268	0.53 ± 0.67	0.012
	VABS daily living	14	57.9 ± 31.7	128	79.0 ± 33.5	0.013
	VABS socialization	14	58.9 ± 18.2	128	75.9 ± 24.0	0.014
	VABS communication	14	59.6 ± 19.9	128	79.5 ± 32.0	0.016
	VABS adaptive behavior composite	11	52.0 ± 16.0	109	70.3 ± 28.9	0.028
	Principal component 2 "immune dysfunction"	12	−0.42 ± 0.980	126	0.11 ± 1.06	0.044
62 kDa	Order of birth	19	2.3 ± 1.4	271	1.6 ± 0.7	0.040
Either 45 or 62 kDa or both	ADI-R social interaction	12	26.4 ± 5.8	82	21.0 ± 7.1	0.023
	VABS communication	24	65.0 ± 22.4	116	79.9 ± 32.6	0.025
	Order of birth	39	2.1 ± 1.2	251	1.6 ± 0.7	0.031
	VABS socialization	24	64.2 ± 22.3	116	75.9 ± 23.9	0.031
	VABS daily living	24	63.8 ± 30.4	117	79.4 ± 34.0	0.032
	ADOS play and imagination	13	3.3 ± 1.0	100	2.4 ± 1.5	0.042

Solco temporale superiore e autismo



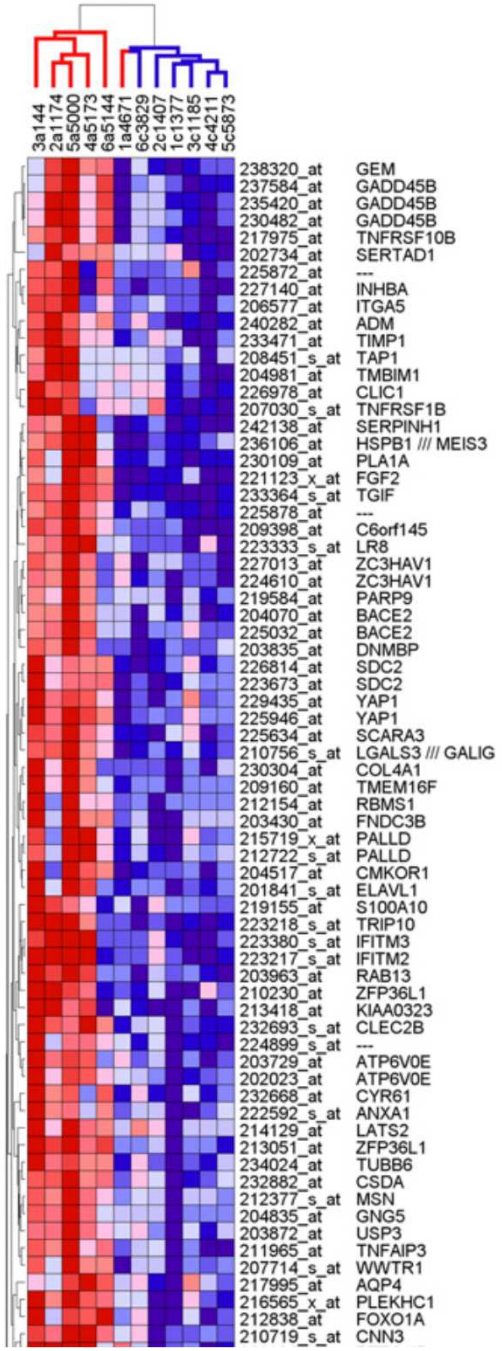


Zilbovicius M et al, Trends Neurosci 29:359-366, 2006

innate immune response

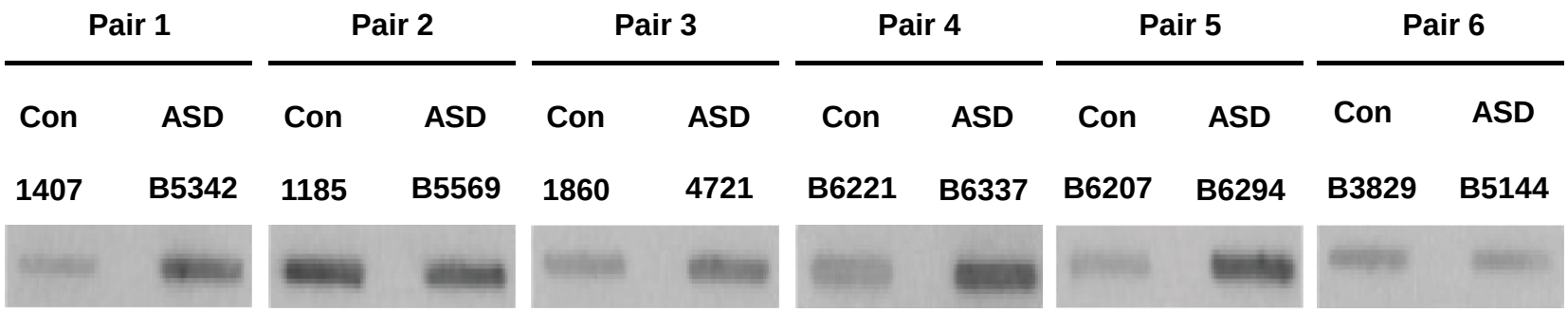
Gene Set	Genes	NES	*p-val*	*q-val*
NFKBPATHWAY	22	2.10	0.0000	**0.0000**
IL1RPATHWAY	30	2.05	0.0000	**0.0000**
TOLLPATHWAY	32	2.05	0.0000	**0.0000**
NKTPATHWAY	25	2.00	0.0000	**0.0000**
INFLAMPATHWAY	28	1.96	0.0000	**0.0000**
GSK3PATHWAY	25	1.91	0.0000	**0.0020**
TOB1PATHWAY	16	1.87	0.0000	**0.0040**
TNFR2PATHWAY	17	1.86	0.0000	**0.0040**
CARDIACEGFPATHWAY	16	1.86	0.0000	**0.0040**
P38MAPKPATHWAY	37	1.84	0.0030	**0.0050**
TIDPATHWAY	17	1.79	0.0000	**0.0120**
G1PATHWAY	24	1.76	0.0000	**0.0200**
HIVNEFPATHWAY	54	1.73	0.0010	**0.0290**
4-1BBPATHWAY	16	1.73	0.0020	**0.0270**
MCALPAINPATHWAY	23	1.70	0.0050	**0.0340**
P53HYPOXIAPATHWAY	18	1.69	0.0050	**0.0350**
METPATHWAY	36	1.68	0.0030	**0.0360**
DEATHPATHWAY	32	1.67	0.0060	**0.0370**
ATMPATHWAY	18	1.66	0.0160	**0.0390**
IL6PATHWAY	20	1.66	0.0130	**0.0400**
RELAPATHWAY	15	1.65	0.0060	**0.0400**
ALKPATHWAY	32	1.65	0.0060	**0.0380**
NTHIPATHWAY	20	1.65	0.0110	**0.0410**
CASPASEPATHWAY	21	1.65	0.0100	**0.0390**
DCPATHWAY	20	1.64	0.0140	**0.0400**
AKTPATHWAY	16	1.64	0.0070	**0.0400**
ECMPATHWAY	20	1.63	0.0130	**0.0400**
RACCYCDPATHWAY	21	1.63	0.0220	**0.0400**
IL2RBPATHWAY	33	1.61	0.0000	**0.0450**
TH1TH2PATHWAY	16	1.61	0.0110	**0.0450**
FASPATHWAY	26	1.60	0.0190	**0.0470**

acquired immune response



Garbett et al, Neurobiol Dis, 30:303-311, 2008

Oxyblot delle proteine mitocondriali in corteccia temporale



Palmieri et al, Mol Psychiatry, 15:38-52, 2010

Quanto spesso accade che i genitori riferiscano un esordio di autismo dopo vaccino o dopo un episodio infettivo?

	total N	assente	presents
gastroenterite	297	252	45 (15%)
otite	293	244	49 (17%)
altra patologia infettiva	205	192	13 (6.7%)
qualsiasi patologia infettiva	*345*	*253*	*92 (26.6%)*
regressione	278	170	108 (39%)
regressione post-vaccinica	*238*	*228*	*10 (3.6%)*

I 10 casi con regressione post-vaccinica

id. n.	gastroenterite	otite	altra patologia infettiva
1	no	no	no
2	no	no	no
3	no	yes	no
4	yes	yes	no
5	yes	no	yes
6	yes	yes	no
7	no	no	no
8	no	no	no
9	no	no	no
10	no	no	yes

Vaccini ed autismo

Nulla

Tutto

Correlazione temporale, ma non causale

Modulatore

Permissivo

Additivo

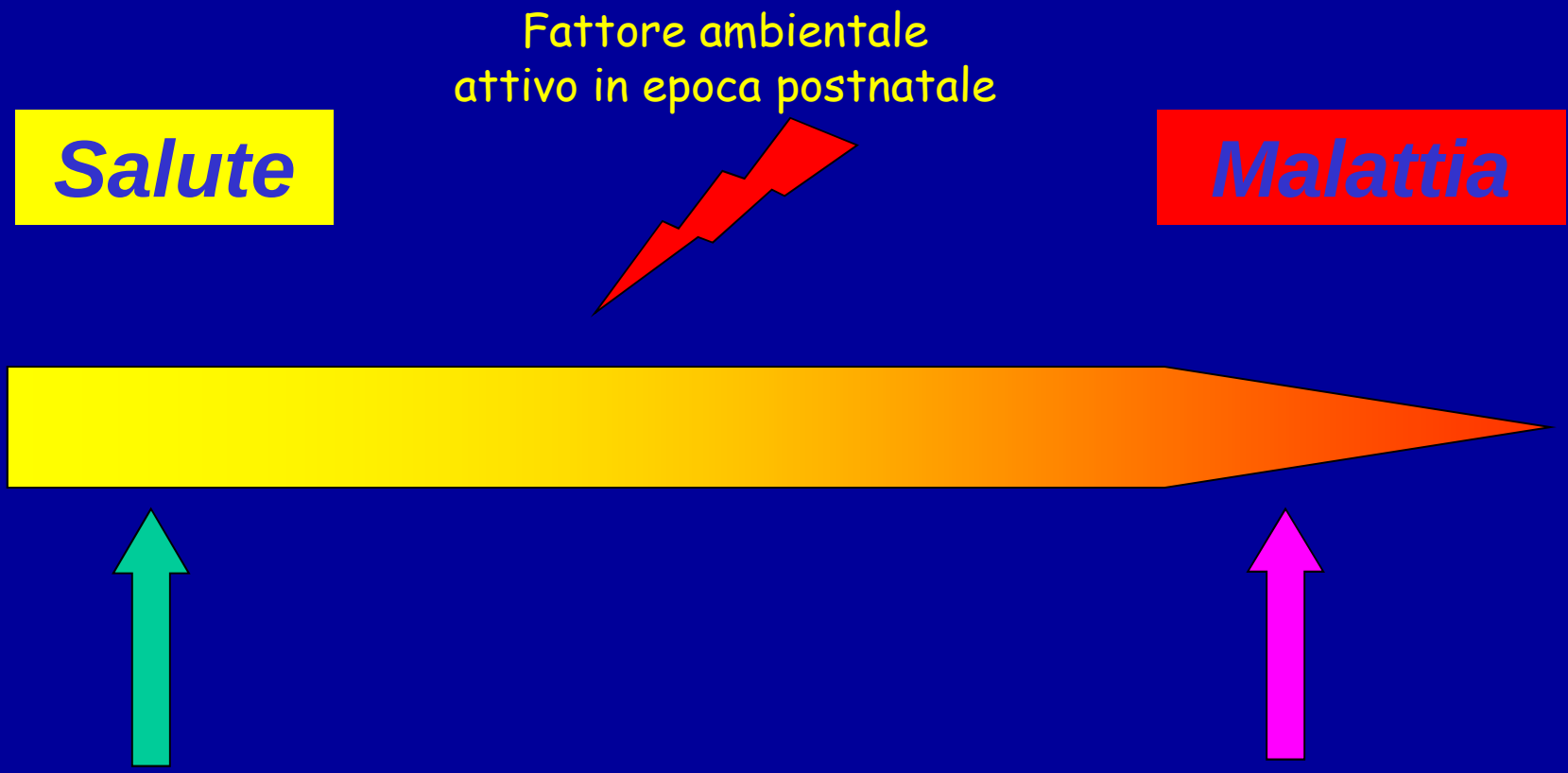
Sinergico

Causale

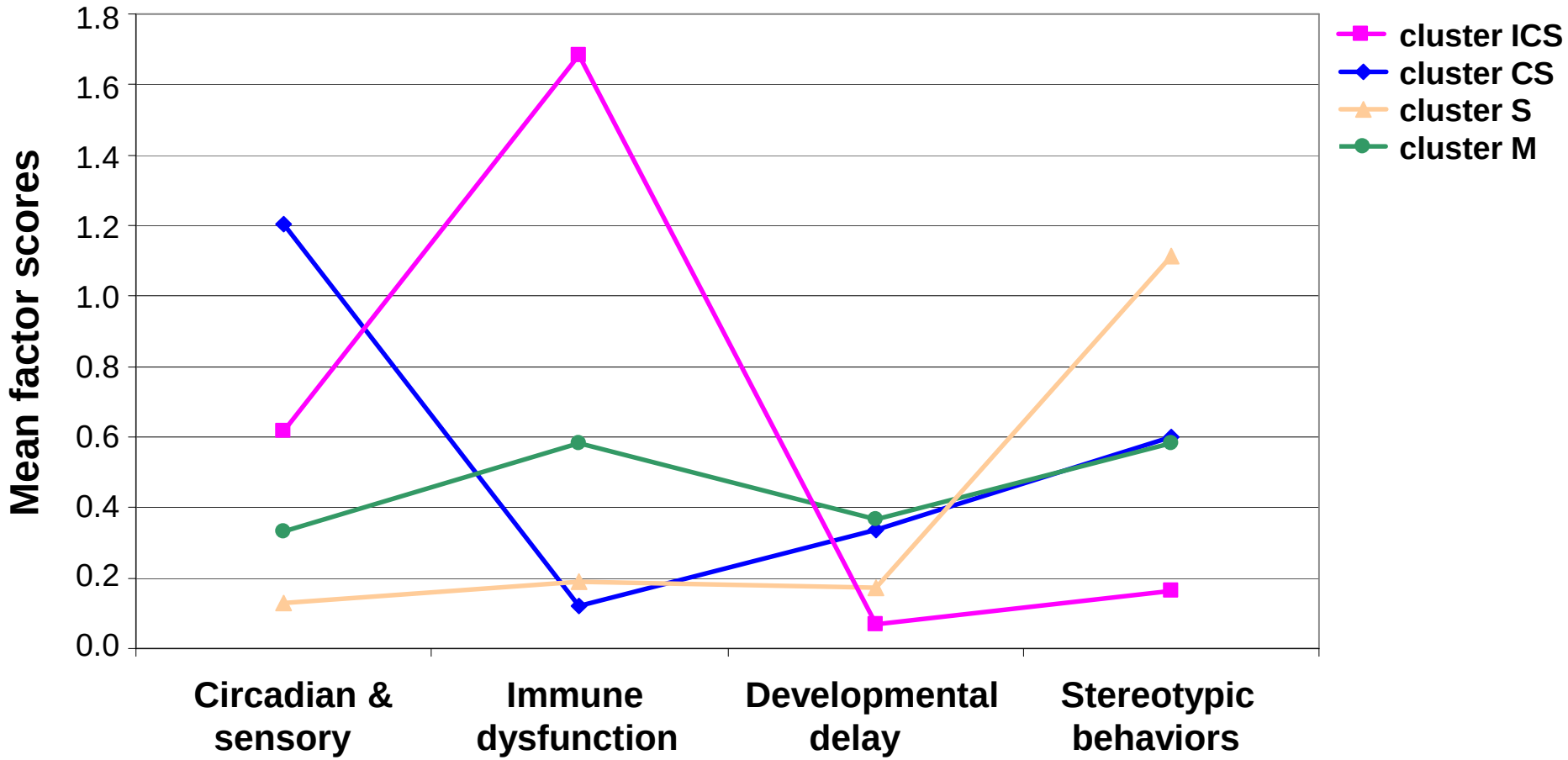
1) I vaccini ed il tiomersale NON causano autismo, anche in presenza di una correlazione temporale

2) In pochi casi, è plausibile, ma deve essere ancora conclusivamente dimostrato, che un'attivazione del sistema immunitario (per otite, influenza, vaccino, gastroenterite, ecc) attivi la neuroinfiammazione fornendo un contributo modulatore (ma anche in questo caso, il quadro autistico si sarebbe verificato comunque)

Spettro Autistico



Analisi di cluster dello spettro autistico basata su componenti principali



Sacco et al., Autism Res. 5:137-147, 2012

Pazienti autistici di cluster ICS

- Uno o più aborti spontanei precedenti o successivi alla gravidanza del paziente
- Complicanze durante la gravidanza (minacce d'aborto o di parto prematuro, preeclampsia, diabete gestazionale, infezioni oppure esordio di allergie gravi e atipiche durante il II trimestre di gravidanza).
- Parto prematuro o più spesso post-termine
- Frequenti patologie infettive durante il I e II anno di vita (otiti, raffreddori, bronchiti, gastroenteriti)
- Regressione durante il II o III anno di vita, molto spesso dopo un episodio infettivo o vaccino trivalente/esavalente
- Allergie nel paziente
- Allergie e/o patologie autoimmuni nei familiari di primo grado
- Scarsa o assente familiarità per patologie del neurosviluppo
- Spesso familiarità per sterilità di coppia, difficoltà al concepimento (inseminazioni artificiali) e poliabortività

Pazienti autistici di cluster ICS

- **Normali tappe di sviluppo durante il I anno di vita, ritardo o blocco a partire dal II anno di vita con il linguaggio espressivo, la comunicazione gestuale, la socializzazione ed il controllo sfinterico.**
- **Macrocefalia assoluta o almeno relativa generalmente a partire dal VI mese di vita in poi; spesso macrosomia.**

CARATTERI MENO COSTANTI E SPECIFICI:

- **Alterazioni del ritmo sonno-veglia (insonnia iniziale, più spesso intermedia, e/o tardiva)**
- **Autoaggressività**
- **Iperattività**
- **Ridotta sensibilità al dolore**

MOLTO FREQUENTE:

- **Array-CGH negativi**

Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies

Luke E. Taylor, Amy L. Swerdfeger, Guy D. Eslick*

The Whiteley-Martin Research Centre, Discipline of Surgery, The University of Sydney, Nepean Hospital, Level 3, Clinical Building, PO Box 63, Penrith 2751, NSW, Australia

5. Epilogue

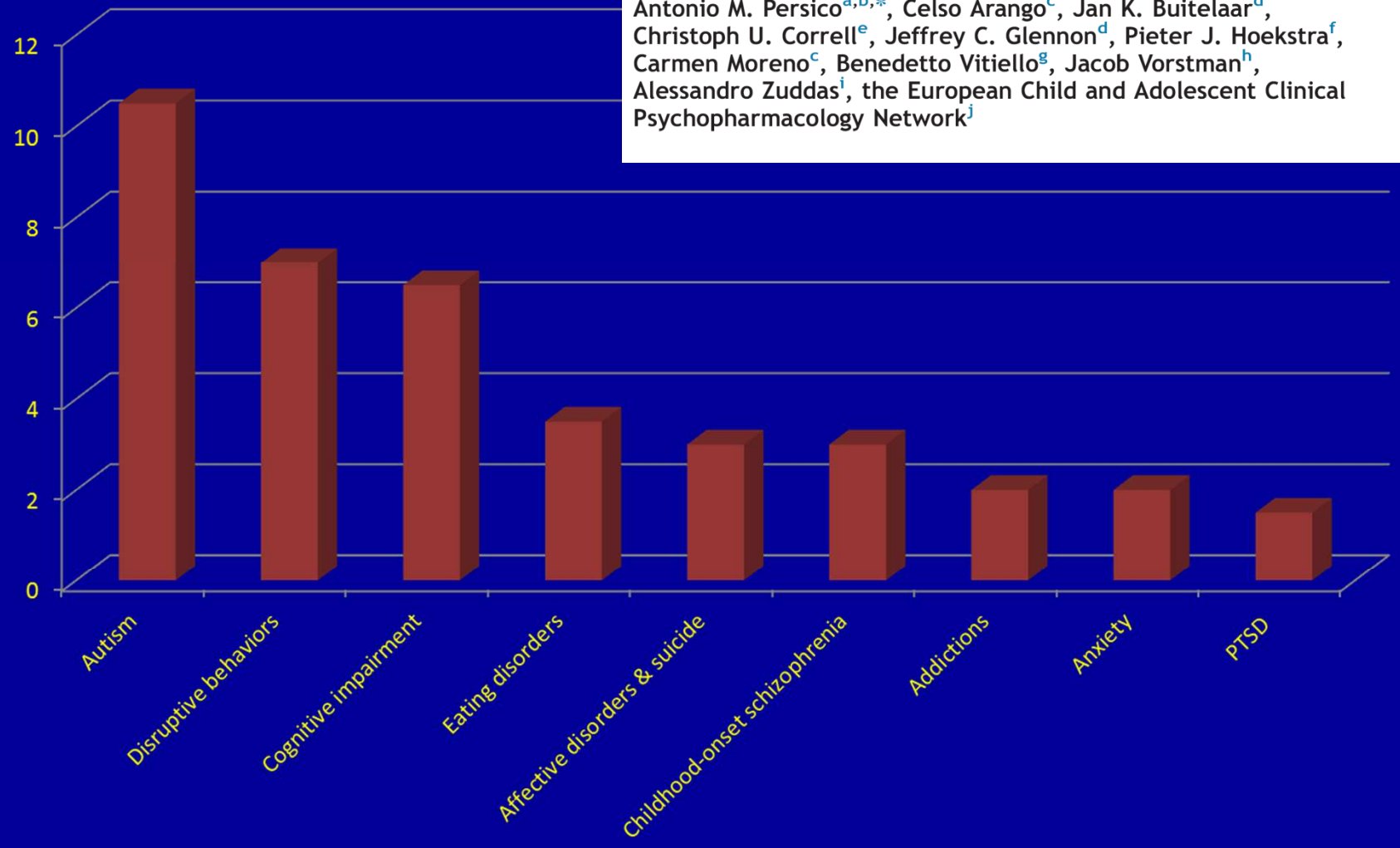
As an epidemiologist I believe the data that is presented in this meta-analysis. However, as a parent of three children I have some understanding of the fears associated with reactions and effects of vaccines. My first two children have had febrile seizures after routine vaccinations, one of them a serious event. These events did not stop me from vaccinating my third child, however, I did take some proactive measures to reduce the risk of similar adverse effects. I vaccinated my child in the morning so that we were aware if any early adverse reaction during the day and I also gave my child a dose of paracetamol 30 min before the vaccination was given to reduce any fever that might develop after the injection. As a parent I know my children better than anyone and I equate their seizures to the effects of the vaccination by increasing their body temperature. For parents who do notice a significant change in their child's cognitive function and behaviour after a vaccination I encourage you to report these events immediately to your family physician and to the 'Vaccine Adverse Event Reporting System'.

REVIEW

Eur. Neuropsychopharmacol 25:1513-31, 2015

Unmet needs in paediatric psychopharmacology: Present scenario and future perspectives

Antonio M. Persico[a,b,*], Celso Arango[c], Jan K. Buitelaar[d], Christoph U. Correll[e], Jeffrey C. Glennon[d], Pieter J. Hoekstra[f], Carmen Moreno[c], Benedetto Vitiello[g], Jacob Vorstman[h], Alessandro Zuddas[i], the European Child and Adolescent Clinical Psychopharmacology Network[j]



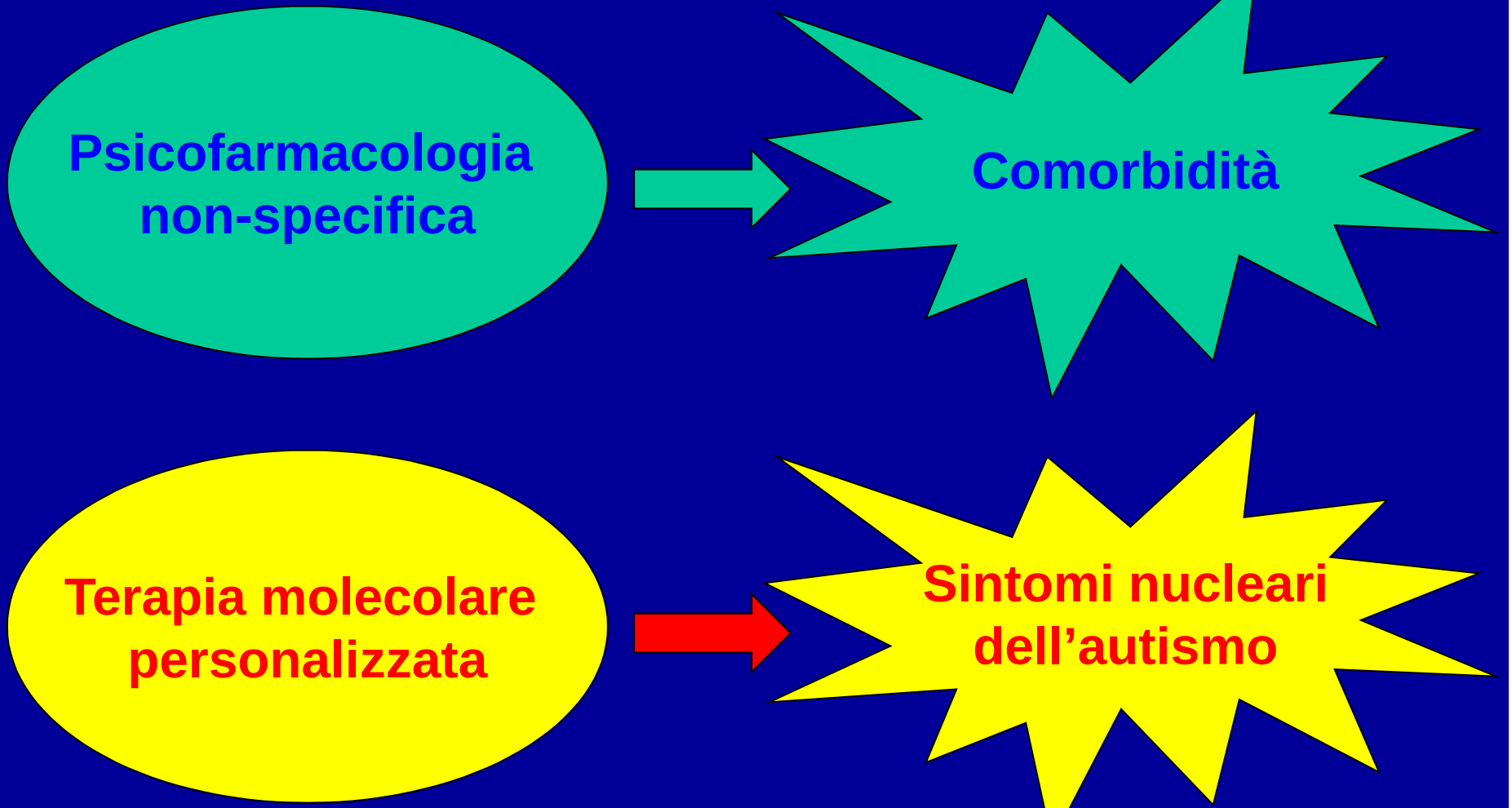
Priority list, TNM expert meeting, Child Psychopharmacology Network, ECNP 2013

Trattamento farmacologico delle co-morbidità nell'autismo

Possibili sintomi bersaglio:

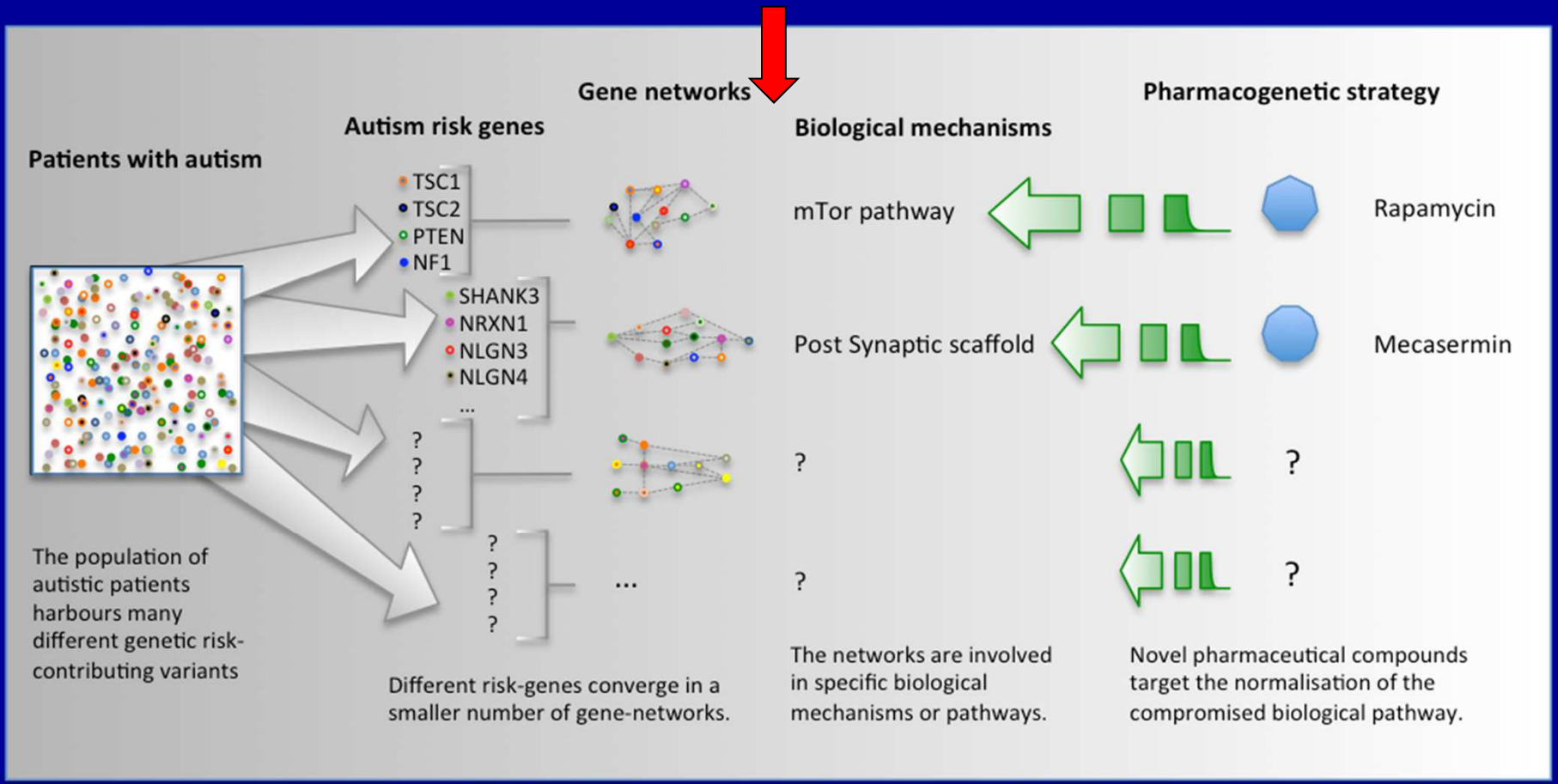
- **Auto- ed etero-aggressività, irritabilità**
- **Iperattività/impulsività**
- **Crisi di agitazione psicomotoria**
- **Comportamenti stereotipati e ripetitivi**
- **Insonnia**
- **Epilessia**

Psicofarmacologia dell'autismo: il presente, il futuro



AUTISMO: QUALE FARMACO PER QUALE PAZIENTE?

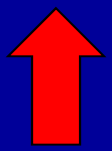
Pannello di biomarcatori



Vorstman et al, Psychopharmacol, 2013

Biomarker panels for targeted therapies

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36



Metabolomics

Proteomics

Transcriptomics (coding & non)

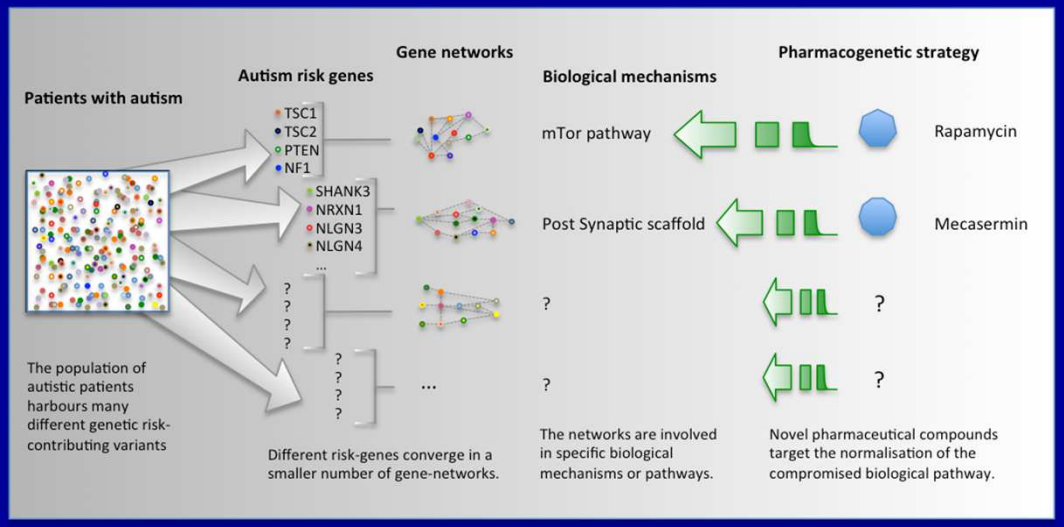
Methylomics

Genomics: CNVs, SNPs, repeats

Biological foundations of neurodevelopmental disorders

Ruggeri et al, Psychopharmacol, 231:1201-16, 2014

Two approaches to personalized psychopharmacology



Correct molecular damage downstream

Boost compensatory mechanisms

Direct approach

Indirect approach

Syndrome	Pathophysiology	Drug	Therapeutic target	Clinical trials by NCT n.
Rett syndrome [MeCP2]	Abnormal regulation of gene expression, impairing neuritic sprouting and synaptogenesis	(1-3) IGF1 [Mecasermin, Increlex]	Enhance neuritic sprouting and synaptogenesis	01253317, 01777542
22q13 deletion/Phelan-McDermid Syndrome [SHANK3]	Disrupted scaffolding of the post-synaptic elements, leading to reduced dendritic spines and synaptogenesis			01525901
Fragile X syndrome [FMR1]	Increased translation in dendritic spines	MPEP	mGLUR5 antagonism	None
		Fenobam		01806415
		STX107		01325740, 00965432
		AFQ056 [Mavoglurant]		01357239, 01253629, 01482143, 01348087, 01433354, 00718341
		RO4917523		01750957, 01015430, 01517698
		STX209 [Arbaclofen]	GABA-B receptor agonism	00788073, 01282268, 01555333 (terminated), 01325220
		CX516 [Ampalex]	Positive allosteric modulation of AMPA receptors	00054730
Fragile X syndrome and idiopathic autism [neuroinflammation].	Microglial activation	Minocycline	Microglial inhibition	00409747
	Increased expression and activity of MMP9		MMP9 inhibition	01053156, 0858689
Tuberous Sclerosis [TSC1/TSC2]	Disinhibition of the mTOR pathway	Rapamycin [Sirolimus]	mTOR inhibition	00457808
		Everolimus [RAD001, Afinitor]		01289912, 01070316, 01730209, 01713946
Autism with macrocephaly (PTEN)				None
Neurofibromatosis (NF1)	Disinhibition of RAS activity & mTOR pathway	Lovastatin	Ras activity inhibition	00352599

Vorstman et al, Psychopharmacol, 231:1063-78, 2014

Drug	Company	Mode of action	Age, Gender	ASD indication	Study design, phase, trial n.	Results
CM-AT	Curemark LLC	Protease stimulant	3-8, M/F	Behavior	RCT, III, NCT00881452	Completed
			9- 12, M/F	Behavior	Open Label Ext., III, NCT00912691	Ongoing
Lurasidone	Sunovion	5-HT2A, 5-HT7, D2 antag.	6–17, M/F	Irritability	RCT, III, NCT01911442	Completed, no effect
			6–17, M/F	Safety, Irritability	Open-label ext., III, NCT01914393	Recruiting
RG7314	Hoffmann-La Roche	V1A Vasopressin rec. antag.	18-45, M	Social deficits	RCT, I-IV, NCT01793441	Recruiting
Vincerinone (EPI-743)	Edison	NADPH quinone oxidoreductase 1 modulator	3-14, M/F	Behavior	Open Label, II, NCT02226458	Halted prior to enrolling
Bumetanide	Univ. Hosp. Brest (FR)	Chloride diuretic	3-10, M/F	Behavioral and Social responses	RCT, III, NCT01078714	Significant improvement
	NeuroClin02		2-18, M/F	Safety	Dose ranging study, II, 2013-003259-39	Completed
Trichuris Suis Ova (CNDO-201)	Hadassah Medical Org.	Immunomodulator	6-17, M/F	Behavior, safety	RCT, II, NCT01734941	Well tolerated but no efficacy
	Coronado Bio-sciences, Inc.				RCT, II, NCT02140112	
Dextro-methorphan (Nuedexta)	Sutter Health	Non-competitive NMDA rec. antag., sigma-1 agonist, NA- and 5-HT-reuptake inhibitor	18-60, M/F	Irritability	RCT, II, NCT01630811	Ongoing
UC-MSC	Translational Biosciences	IV infusion of Umbilical Cord Tissue Mesenchymal Stem Cells (UC-MSC)	6-16, M/F	Safety	Open Label, I-II, NCT02192749	Ongoing
Intranasal oxytocin	OptiNose AS	Oxytocin rec. agonist	18-35, M	brain activity, eye tracking, heart rate, social cognition test.	RCT, I, NCT01983514	Completed
Sulforaphane	Rutgers Univ.	Antioxidant, immunomodulator, antinflammatory	13-30, M	ASD symptoms	RCT, II, NCT02677051	Recruiting
Memantine	Evdokia Anagnostou	NMDA Antag.	6-23, M/F	Memory, motor, expressive language	RCT, II, NCT01372449	Ongoing, not recruiting
	Forest Laboratories		6-12, M/F	Unspecified	RCT, II, NCT01592747	Completed
Docosa Hexanoic Acid	Rutgers Univ	Production of natural antioxidants	5-17, M/F	ASD baheviors	12 wk RCT, X, NCT01260961	Ongoing, not recruiting

Brogna C & Persico AM, in preparation

Pardo *et al. Journal of Neurodevelopmental Disorders* 2013, **5**:9
http://www.jneurodevdisorders.com/content/5/1/9

RESEARCH Open Access

A pilot open-label trial of minocycline in patients with autism and regressive features

Carlos A Pardo[1*], Ashura Buckley[2], Audrey Thurm[2], Li-Ching Lee[3], Arun Azhagiri[1], David M Neville[2] and Susan E Swedo[2]

CNS Drugs (2015) 29:715–724
DOI 10.1007/s40263-015-0279-2

LEADING ARTICLE

Maternal Anti-Fetal Brain IgG Autoantibodies and Autism Spectrum Disorder: Current Knowledge and its Implications for Potential Therapeutics

Elizabeth Fox-Edmiston[1,2] · Judy Van de Water[1,2,3]

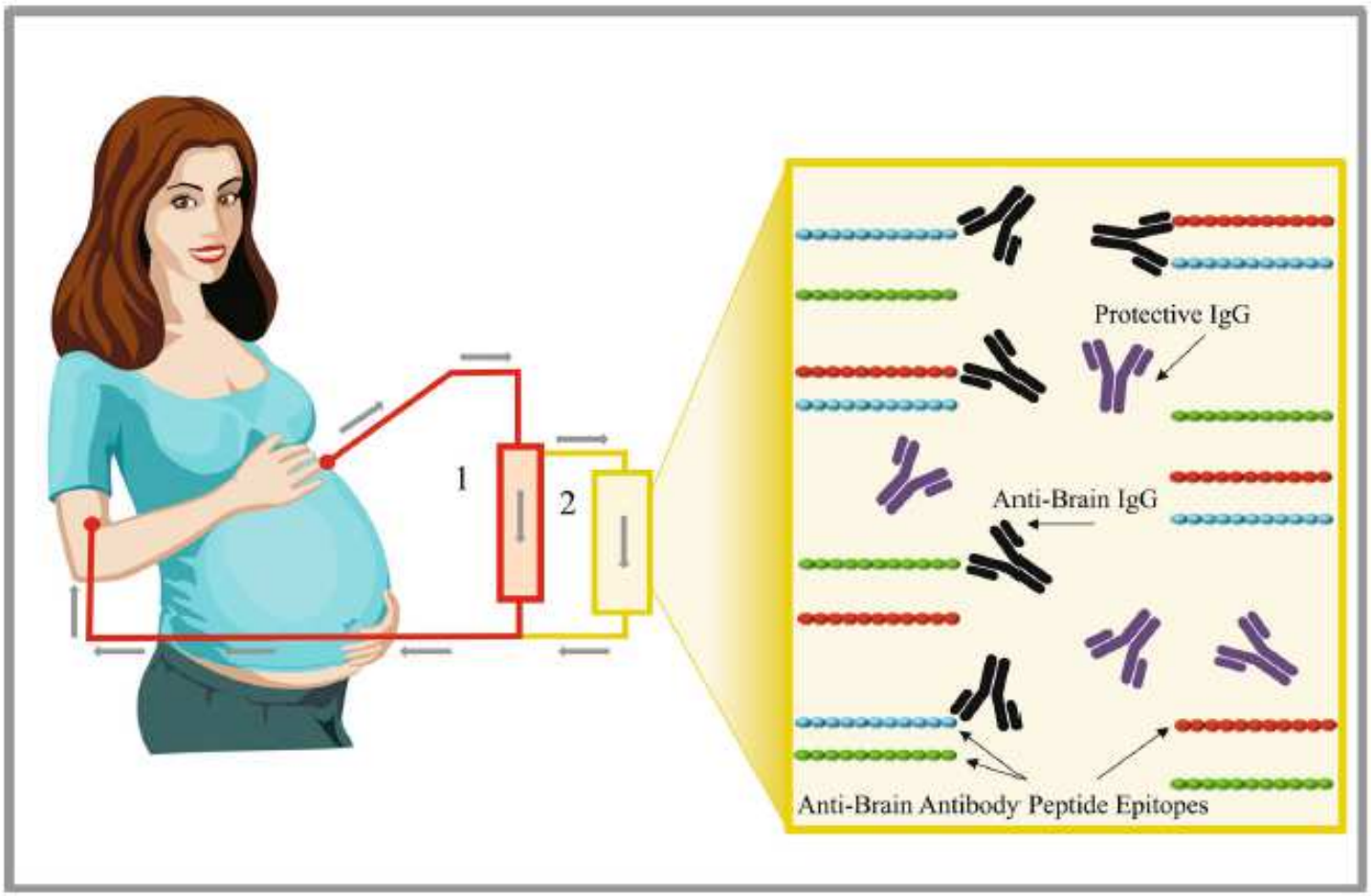
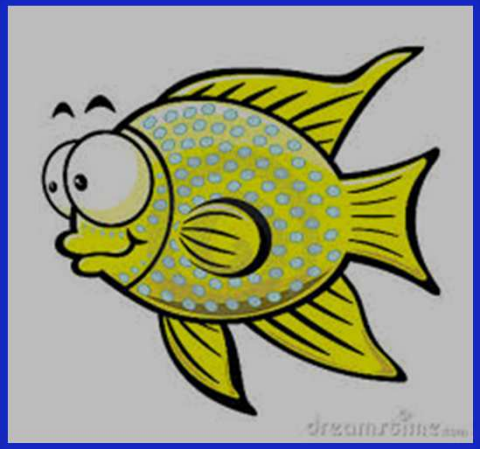


Fig. 1 Ex vivo maternal anti-brain autoantibody removal. The identification of the specific peptide epitopes targeted by maternal anti-brain autoantibodies enables the specific removal of these antibodies using plasmapheresis. First (*1*), the blood cells are separated from the blood plasma and returned to the maternal blood stream. Subsequently (*2*), the plasma is filtered using affinity chromatography. In this procedure, the anti-brain autoantibodies are selectively removed from the maternal blood stream by filtering the plasma through a peptide-bound column. Autoantibodies with reactivity to the peptide epitopes will bind to the column and are removed from circulation, while the remaining, unbound antibodies are returned to the maternal blood stream. *IgG* immunoglobulin G

Fox-Edmiston E. & Van de Water J, CNS Drugs 29:715-724, 2015



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