Antonio M. Persico

Cattedra di Neuropsichiatria Infantile & dell'Adolescenza

Programma Interdipartimentale «Autismo 0-90»

Università degli Studi di Messina

&

Centro Mafalda Luce per i Disturbi Pervasivi dello Sviluppo, Milano

Approcci innovativi evidence-based alla terapia della sindrome di Phelan-McDermid

Assemblea Ordinaria Annuale 2017 AISPHEM Onlus
Bologna, 25 Marzo, 2017

Dichiarazione di conflitto di interessi

L'autore non ha conflitti di interessi

Queste ricerche sono state finanziate dal Ministero della Salute e dall'IMI (consorzio europeo EU-AIMS)

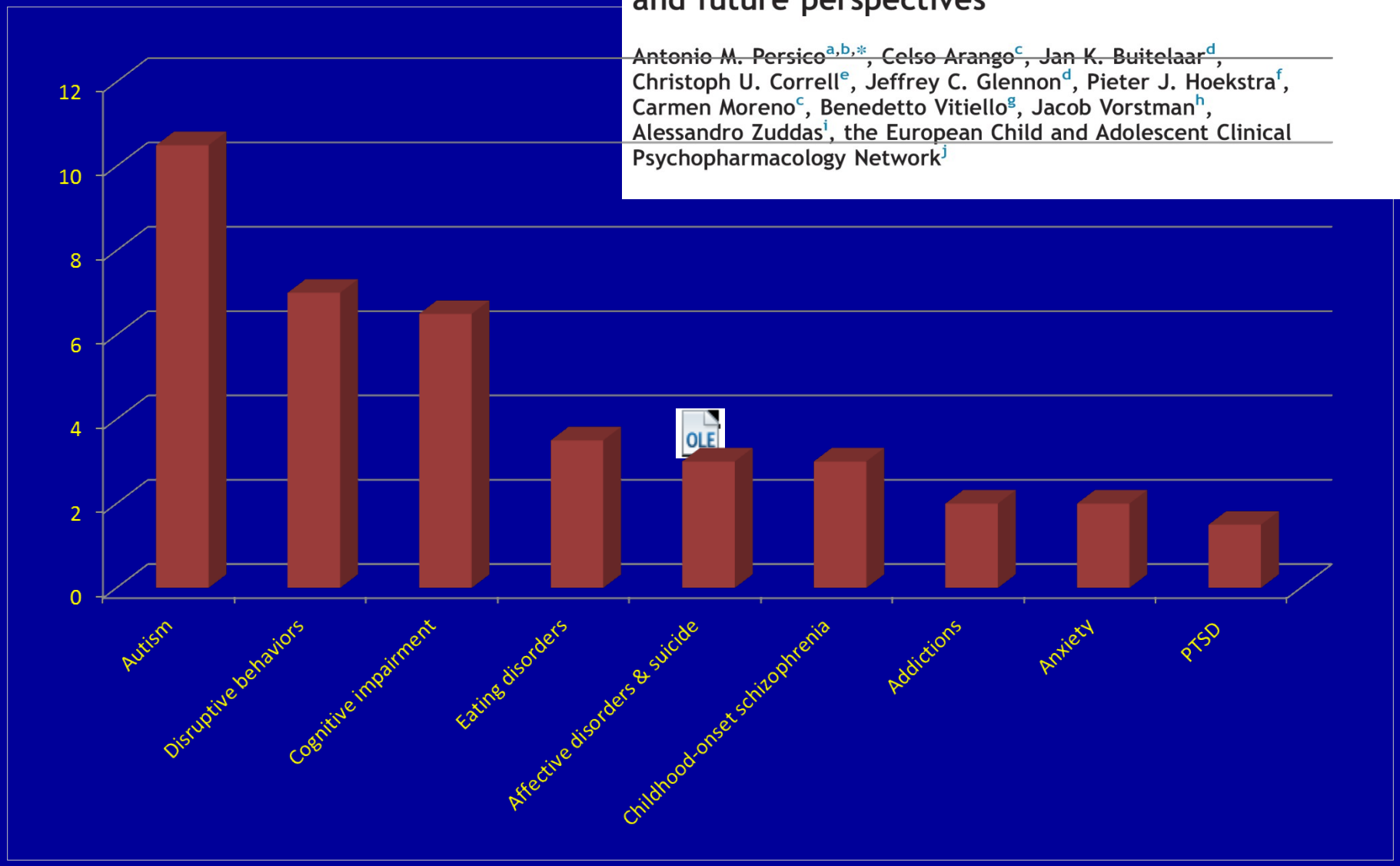
EU-AIMS
Autism Research in Europe

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

Psicofarmacologia molecolare personalizzata: una rivoluzione”silenziosa” in atto

Psicofarmacologia non-specifica

Comorbidità

Terapia molecolare personalizzata

ntomi nucleari dell’autismo

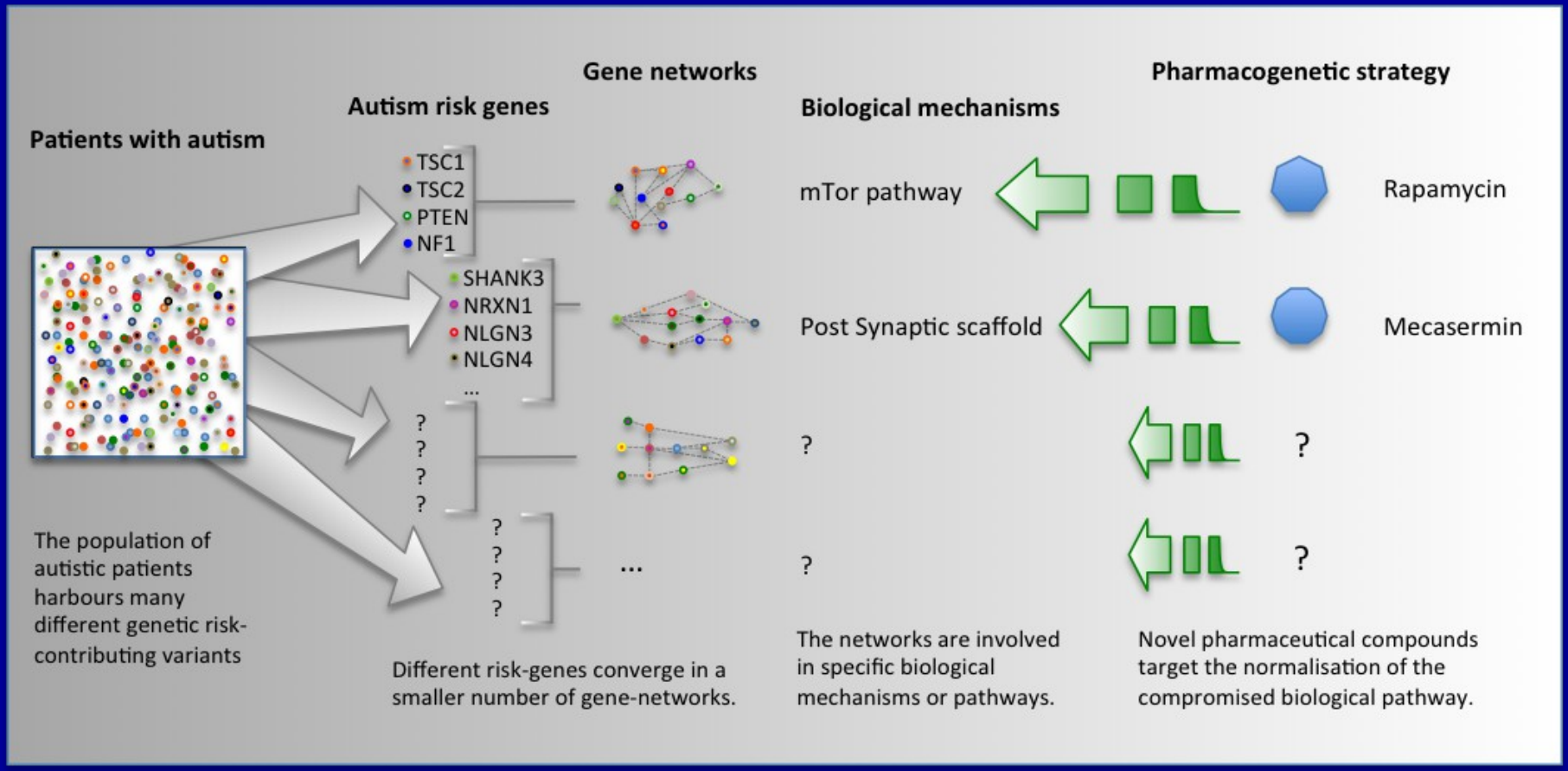
Syndrome	Pathophysiology	Drug	Therapeutic target	Clinical trials by NCT n.
Rett syndrome [MeCP2]	Abnormal regulation of gene expression, impairing neuritic sprouting and synaptogenesis	(1-3) IGF1 [Mecasermin, Increlex]	Enhance neuritic sprouting and synaptogenesis	01253317, 01777542
22q13 deletion/Phelan-McDermid 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

La Sindrome di Phelan-McDermid come paradigma di Disturbo dello Spettro Autistico a patogenesi nota

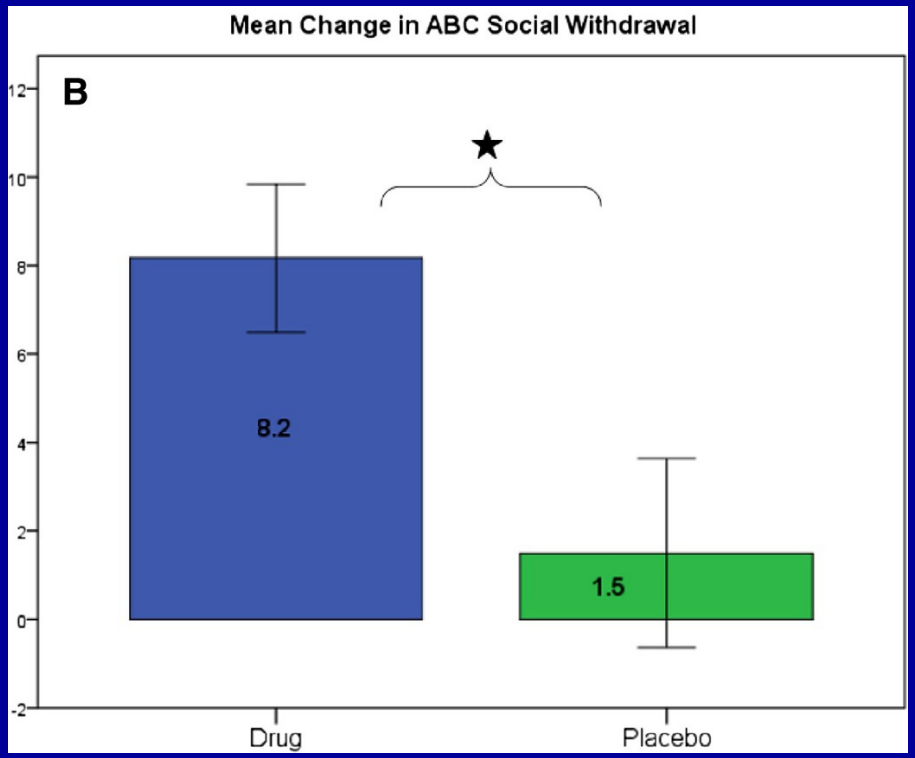


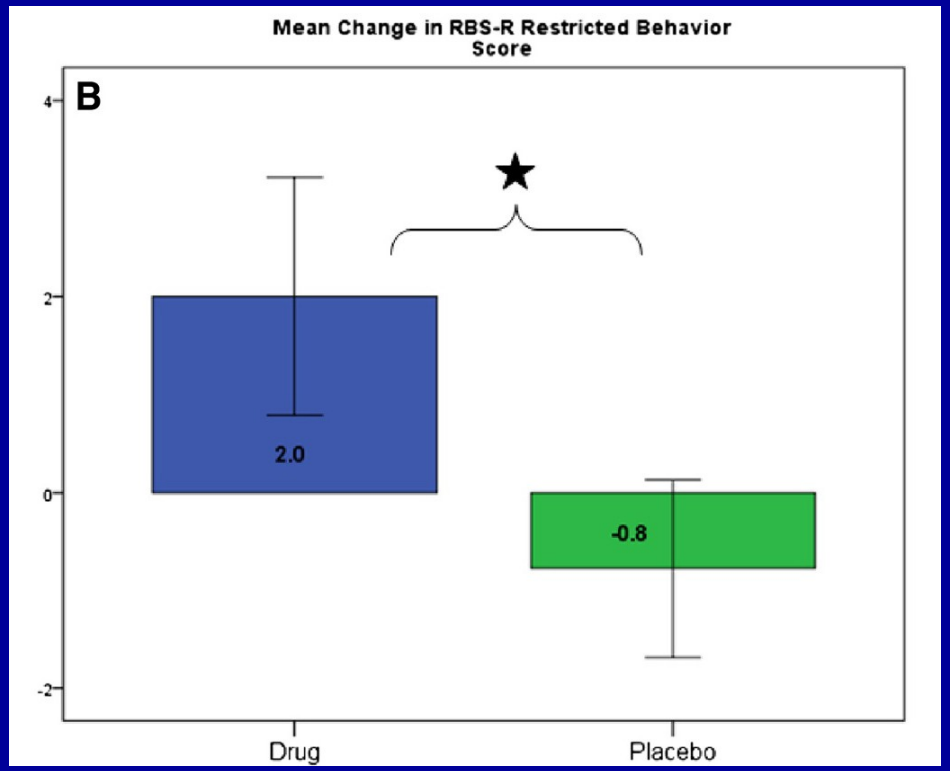
Vorstman et al, Psychopharmacol, 231:1063-78, 2014

RESEARCH Open Access

A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

Alexander Kolevzon[1,2,3,4,5,10*], Lauren Bush[1,4,10], A Ting Wang[1,2,4,6,10], Danielle Halpern[1,4,10], Yitzchak Frank[1,4,5,7,10], David Grodberg[1,4,10], Robert Rapaport[5,9,10], Teresa Tavassoli[1,4,10], William Chaplin[11], Latha Soorya[12] and Joseph D Buxbaum[1,2,3,4,6,8,10]





Kolevzon et al., Mol. Autism 5:54, 2014

Case Report – L.F.

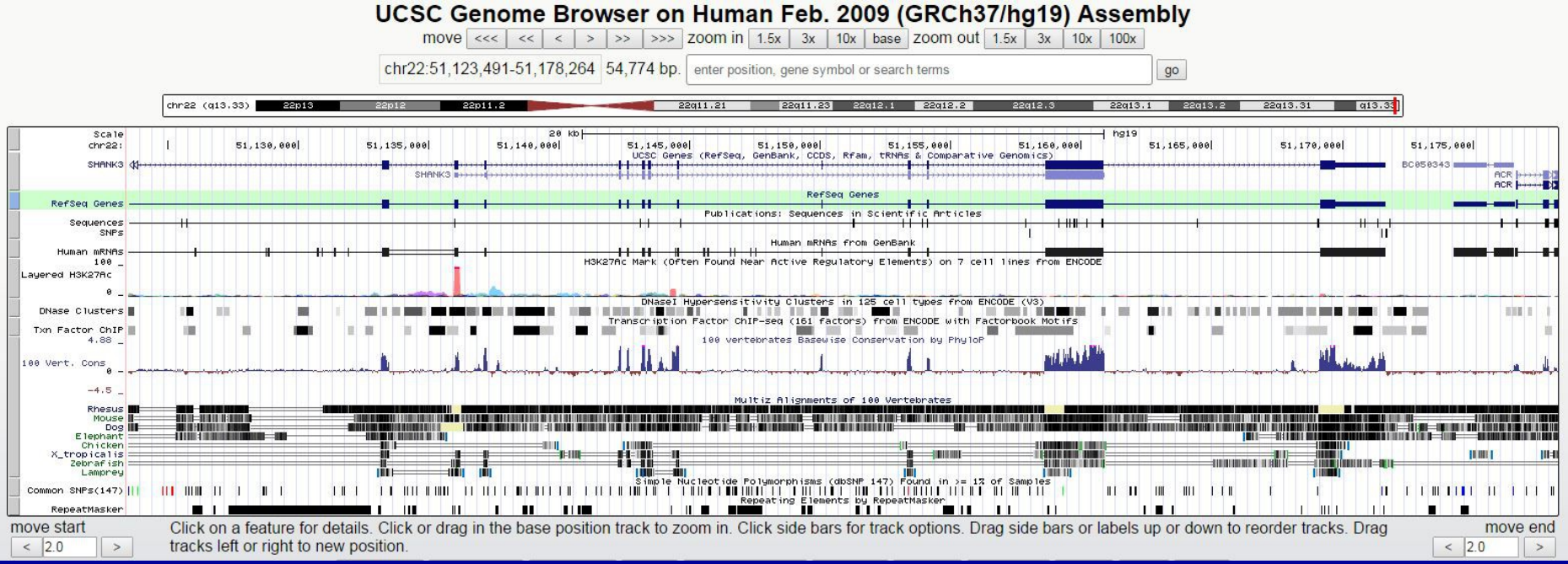
33 anni, F, diagnosi di «Disturbo generalizzato dello sviluppo con ritardo mentale» (IRCCS Stella Maris):

- **Ritardo di acquisizione delle competenze motorie e del linguaggio**
- **Disturbi del sonno tra 1 e 5 anni**
- **Deficit nell'interazione reciproca (isolamento a scuola, carente contatto di sguardo, ecc)**
- **Forte regressione dai 12 anni in poi (da 100 parole contestualizzate e piccole frasi di 2-3 parole a 50 parole decontestualizzate; comparsa di stereotipie di sfarfallamento e delle mani; perdita delle autonomie acquisite)**

Età: 32 Anni | Data accettazione: 25/09/2015

Risultato: **arr 22q13.33(51,123,491-51,178,264)x1 dn**

Interpretazione: L'analisi condotta ad una risoluzione media di circa 100Kb ha evidenziato una microdelezione de novo di circa 55 Kb su un cromosoma 22. Nella regione deleta sono presenti i gene SHANK3 ed ACR. L'analisi ai genitori e' stata limitata alla regione dello sbilancio genomico. Si consiglia consulenza genetica.



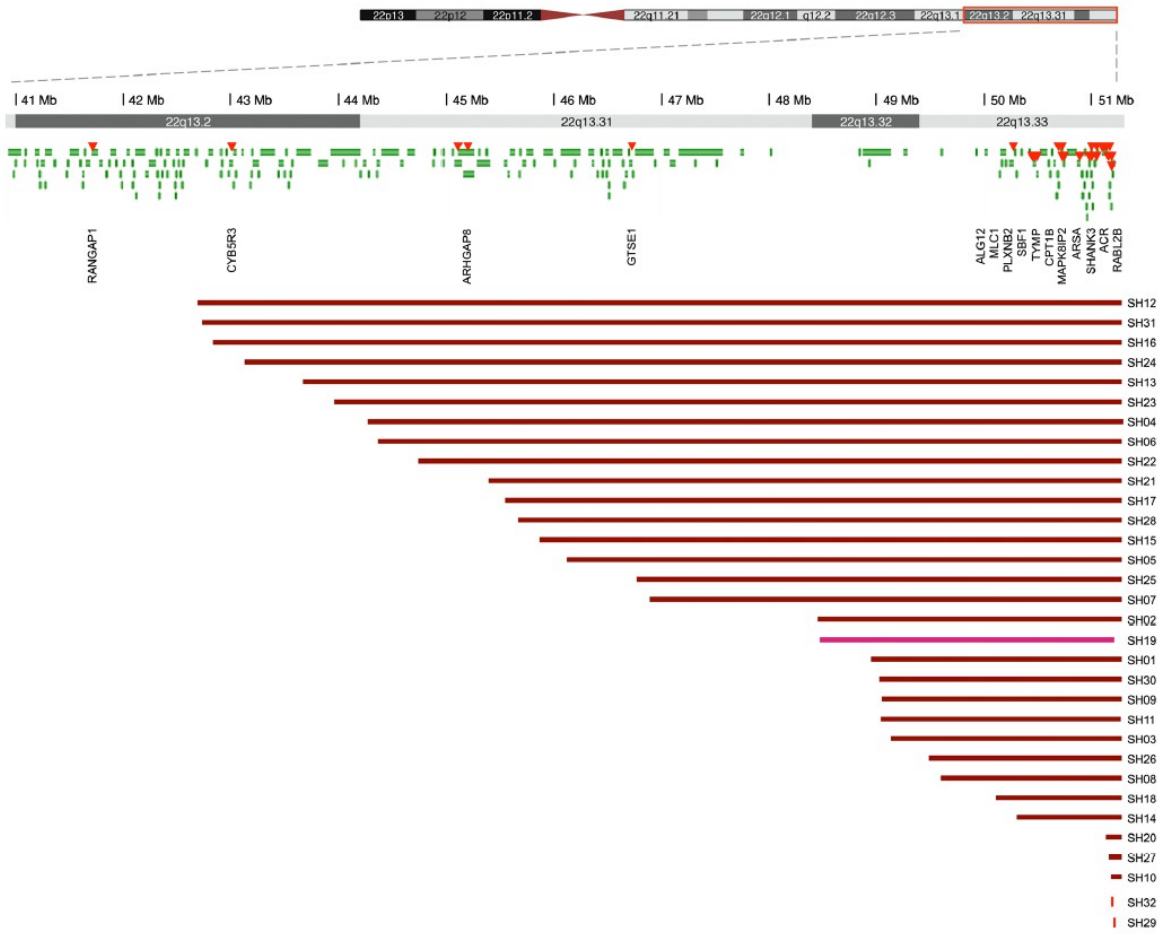
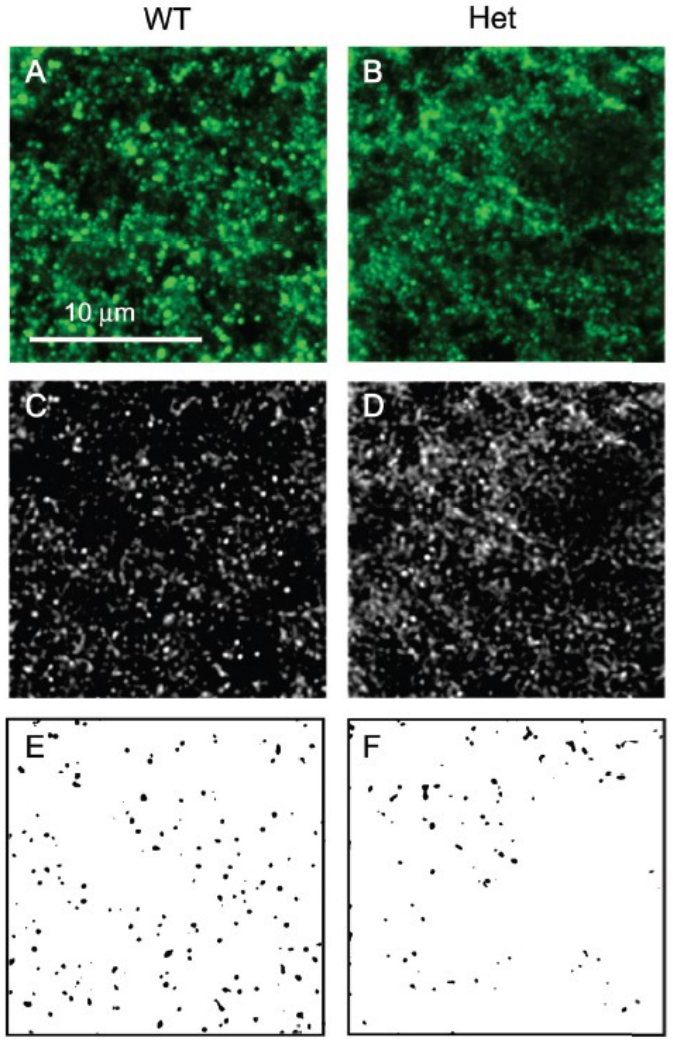
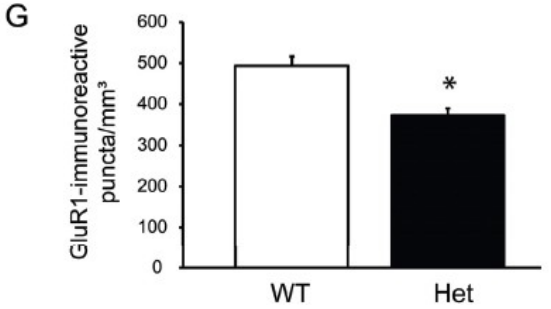


Figure 1 Deletion sizes at 22q13.2-11q13.3 in 32 patients. Genes are indicated across the top in green, the red triangles represent MLPA probes. The two patients with *SHANK3* mutations are shown in red and the patient with an interstitial deletion is shown in pink. Genomic coordinates correspond to the hg19 genome assembly (Build 37).

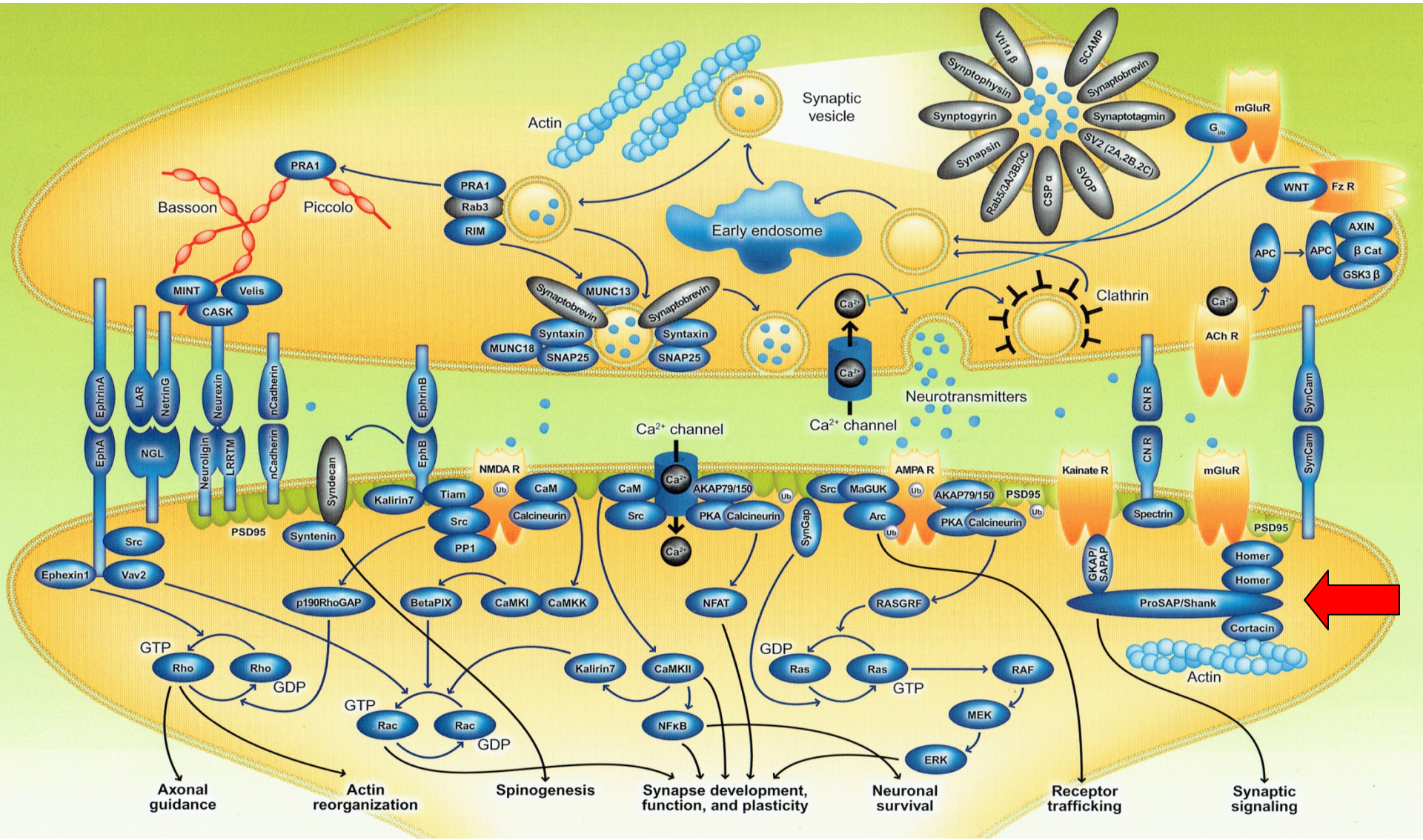
Soorya *et al. Molecular Autism* 2013, **4**:18



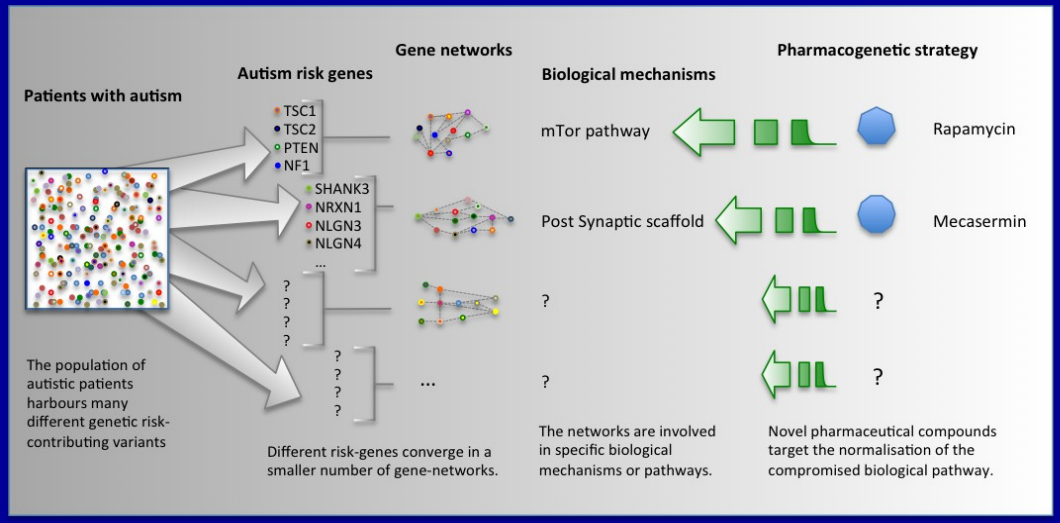


Bozdagi *et al. Molecular Autism* 2010, **1**:15

La sinapsi glutammatergica

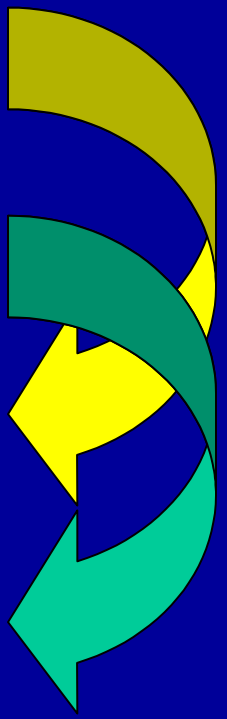


Due approcci diversi e complementari alla psicofarmacologia personalizzata



Correggere il danno molecolare a valle

Potenziare i meccanismi di compenso



Approccio diretto

Approccio indiretto

Tre livelli di intervento per L.F.

1) **Potenziare il trasporto assonale e la funzionalità delle sinapsi stimolando la produzione di energia a livello mitocondriale:**
   - **Q10 ubiquinolo (2 mg/kg/die b.i.d.)**
   - **Vit. E, 200-400 mg/die**
   - **B50 vitamin complex, 1 caps/die**

2) **Come sopra, ma con maggiore potenza**
   - **Idebenone, 150-300 mg/die t.i.d.**

3) **Correggere anomalie nel funzionamento dei recettori glutammatergici NMDA e AMPA, al contempo aumentando il numero di spine dendritiche e bottoni sinaptici:**
   - **IGF-1 s.c., 4 sett. con dose crescente (40-120 mg/kg b.i.d.) e proseguimento per tre mesi alla dose massima tollerata.**

Molecular Psychiatry (2008) 0, 1–15

www.nature.com/mp

ORIGINAL ARTICLE

Altered calcium homeostasis in autism-spectrum disorders: evidence from biochemical and genetic studies of the mitochondrial aspartate/glutamate carrier AGC1

L Palmieri[1,2], V Papaleo[3,4,16], V Porcelli[1,16], P Scarcia[1], L Gaita[3,4], R Sacco[3,4], J Hager[5], F Rousseau[5], P Curatolo[6], B Manzi[6], R Militerni[7], C Bravaccio[7], S Trillo[8], C Schneider[9], R Melmed[10], M Elia[11], C Lenti[12], M Saccani[12], T Pascucci[13,14], S Puglisi-Allegra[13,14], K-L Reichelt[15] and AM Persico[3,4]

[1]*Laboratory of Biochemistry and Molecular Biology, Department of Pharmaco-Biology, University of Bari, Bari, Italy;* [2]*Consiglio Nazionale delle Ricerche, Institute of Biomembranes and Bioenergetics, Bari, Italy;* [3]*Laboratory of Molecular Psychiatry and Neurogenetics, University 'Campus Bio-Medico', Rome, Italy;* [4]*Laboratory of Molecular Psychiatry and Psychiatric Genetics, Department of Experimental Neurosciences, I.R.C.C.S. 'Fondazione Santa Lucia', Rome, Italy;* [5]*IntegraGen SA. Genopole, Evry, France;* [6]*Department of Child Neuropsychiatry, University 'Tor Vergata', Rome, Italy;* [7]*Department of Child Neuropsychiatry, University of Naples Federico II, Naples, Italy;* [8]*ASL RM/B, Rome, Italy;* [9]*Center for Autism Research and Education, Phoenix, AZ, USA;* [10]*Southwest Autism Research and Resource Center, Phoenix, AZ, USA;* [11]*Unit of Neurology and Clinical Neurophysiopathology, I.R.C.C.S. 'Oasi Maria S.S.', Enna, Italy;* [12]*Department of Child Neuropsychiatry, University of Milan, Milan, Italy;* [13]*Department of Psychology, University 'La Sapienza', Rome, Italy;* [14]*Laboratory of Behavioral Neurobiology, Department of Experimental Neurosciences, I.R.C.C.S. 'Fondazione Santa Lucia', Rome, Italy and* [15]*Department of Pediatric Research, Rikshospitalet, University of Oslo, Oslo, Norway*

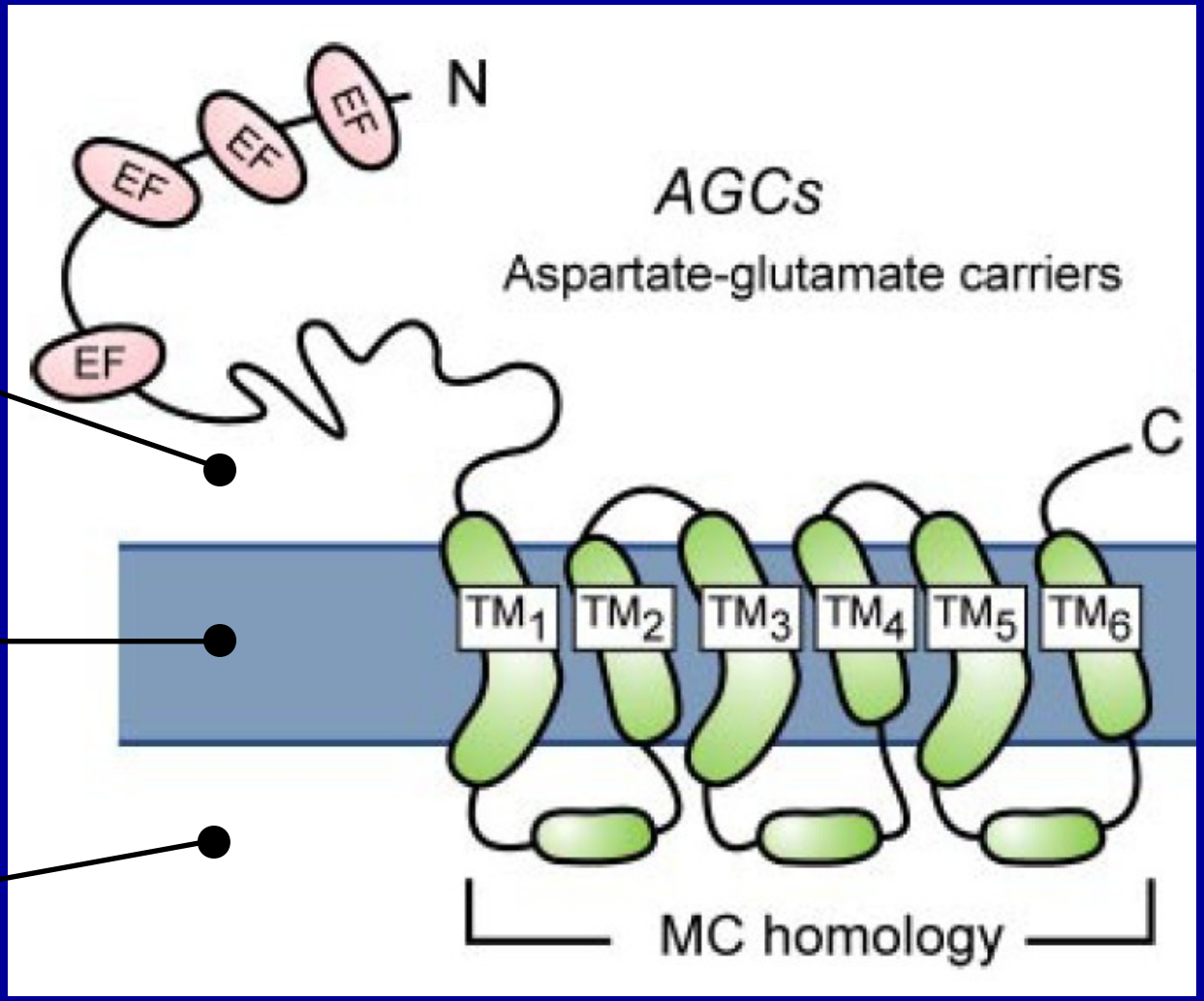
L. Palmieri et al., Mol Psychiatry 15:38-52, 2010

Trasportatore mitocondriale aspartato/glutamato *AGC1*

spazio intermembrana

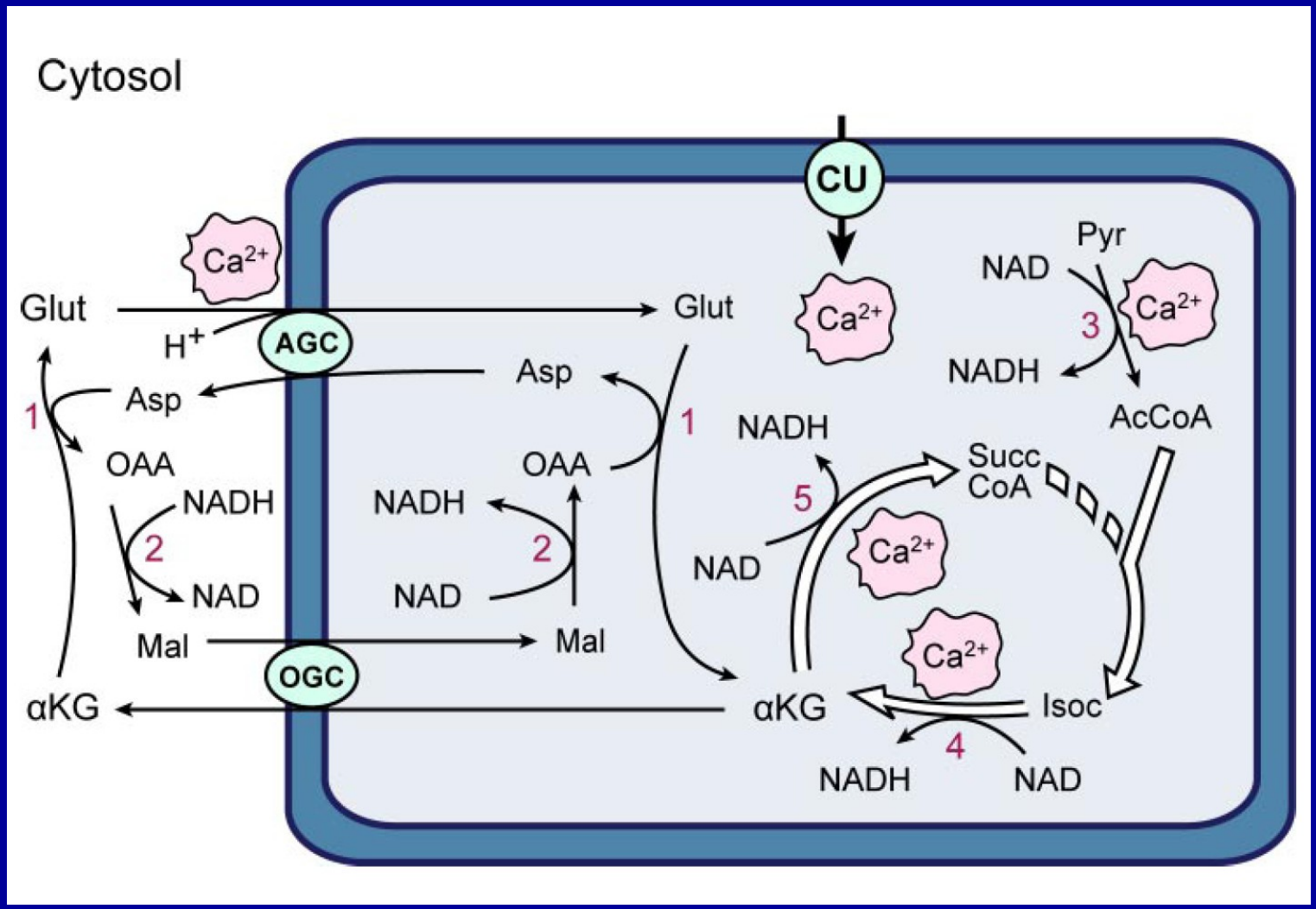
membrana mitocondriale interna

matrice



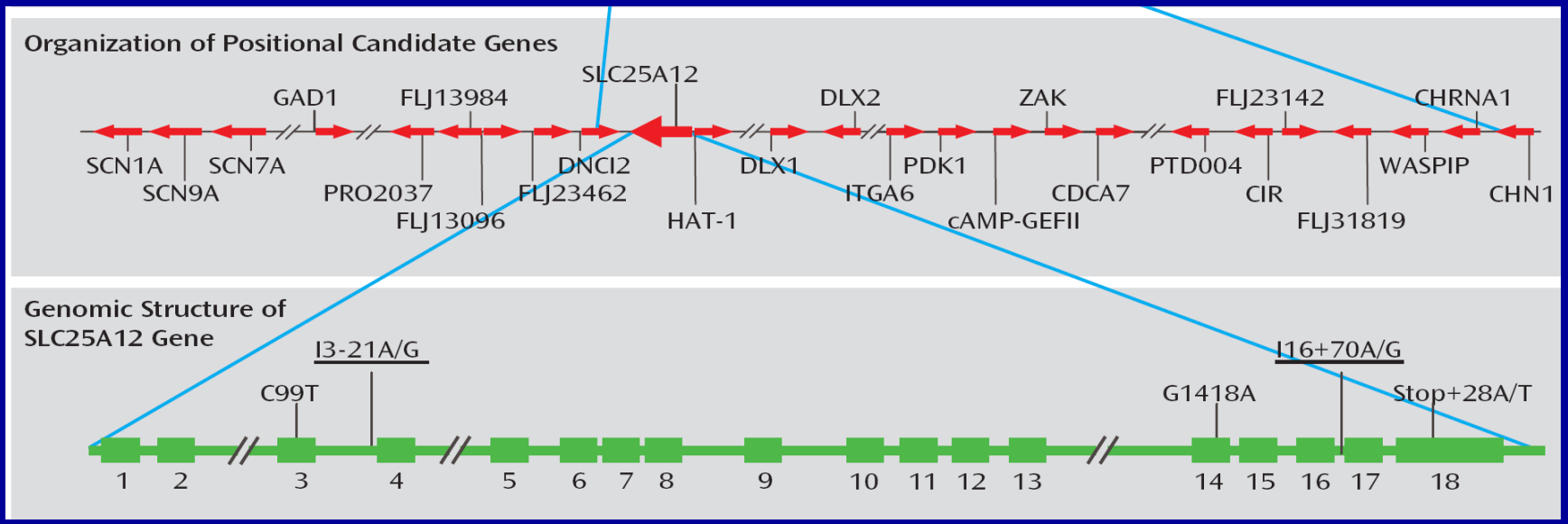
Satrùstegui J et al, *Physiol Rev* 87:29, 2007

AGC1 nello shuttle malato-aspartato



Satrùstegui J et al, *Physiol Rev* 87:29, 2007

Autismo e gene SLC25A12 (ch 2q31)



SNP or Haplotype	At Least One Parent Heterozygous: Number of Children: With Transmission	At Least One Parent Heterozygous: Number of Children: Without Transmission	At Least One Parent Heterozygous: Analysis: χ^2	At Least One Parent Heterozygous: Analysis: p	Mother Heterozygous: Number of Children: With Transmission	Mother Heterozygous: Number of Children: Without Transmission	Mother Heterozygous: Analysis: χ^2	Mother Heterozygous: Analysis: p
SNPs								
rs2056202	116	71	10.83	0.001	53	30	6.37	0.01
rs2292813	72	45	6.23	0.01	40	19	7.47	0.006
Haplotypes								
G*G	102	45	22.10	3×10^{-6}	54	19	66.52	3×10^{-16}
G*A	8	9	0.06	0.81	3	8	2.9	0.09
A*G	21	47	9.94	0.002	11	23	7.11	0.008
A*A	26	56	10.98	0.001	12	30	13.76	0.0002

[a] Selected SNPs were those with evidence of divergent distribution between affected and nonaffected subjects. For the individual SNPs, data are for the G allele.

Ramoz N et al, *Am J Psychiatry* 161:662, 2004

LD nel locus SLC25A12