Contemporary etiology concepts

Maria Luisa Scattoni

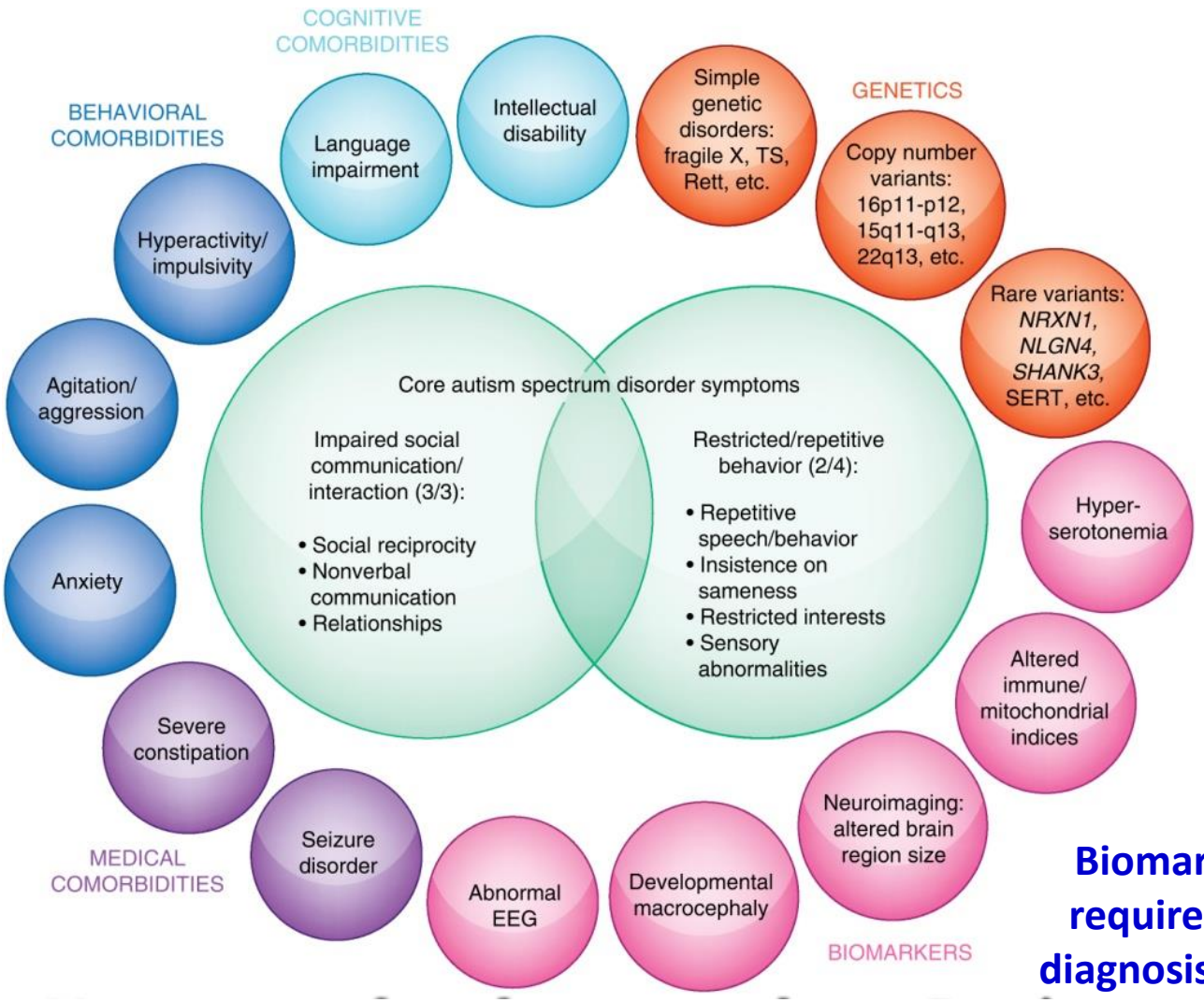
Coordinator of the

Italian Network for early detection of ASD

Italian ASD Registry

Istituto Superiore di Sanità

Autism Spectrum Disorders



Biomarkers are not required for an ASD diagnosis but are more common in ASD than in the general populations

Neuropsychopharmacology Reviews (2012) **37,** 196-212

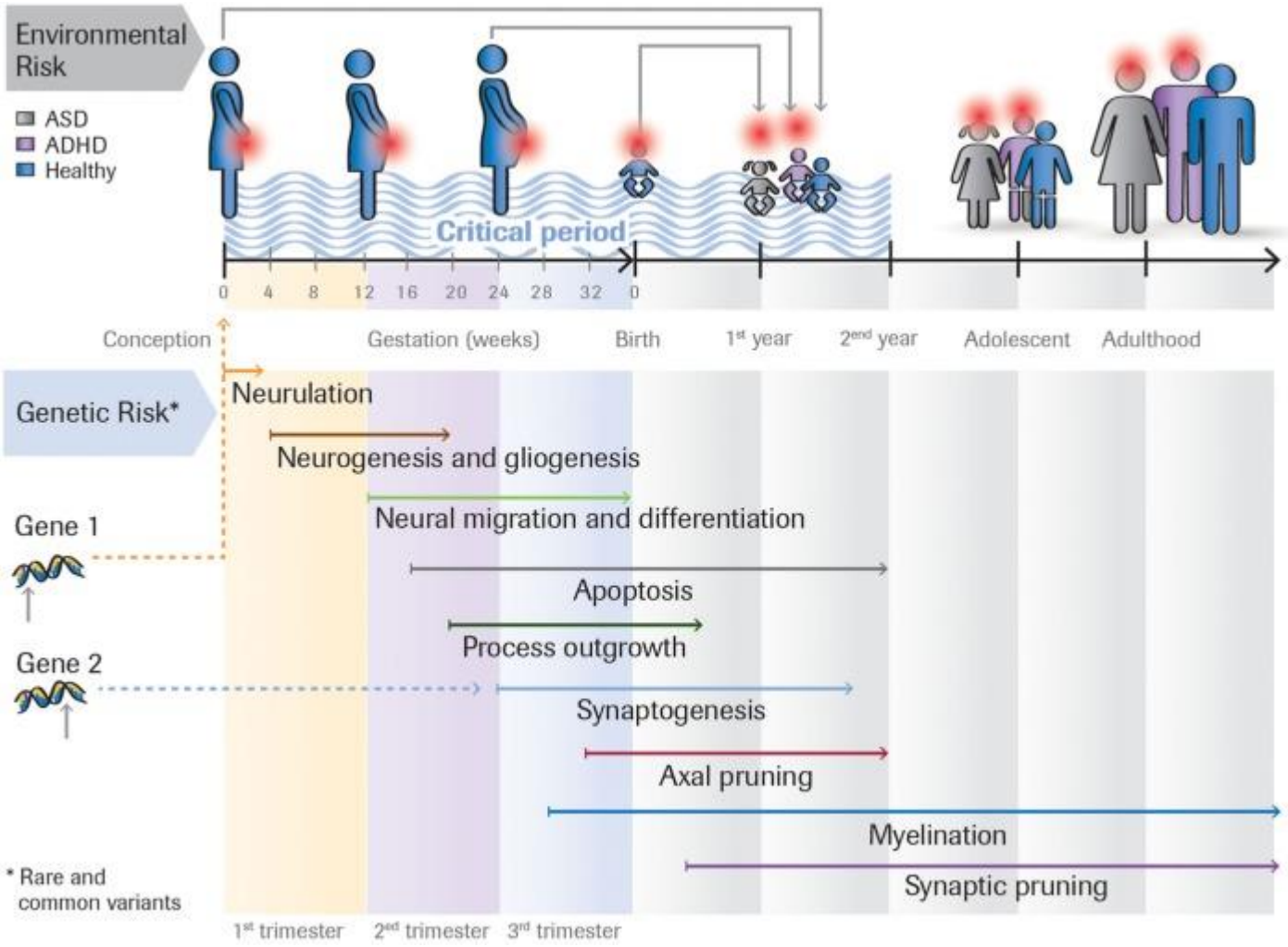
SHANK3
NLG4
CNTNAP2
…

AUTISM SPECTRUM DISORDERS

Residential proximity to freeways
Parental Occupational Exposures
…

AUTISM SPECTRUM DISORDERS

AUTISM SPECTRUM DISORDERS


Environmental Risk
ASD
ADHD
Healthy
Critical period
0 4 8 12 16 20 24 28 32 0
Conception
Gestation (weeks)
Birth
1st year
2end year
Adolescent
Adulthood
Genetic Risk*
Neurulation
Neurogenesis and gliogenesis
Neural migration and differentiation
Gene 1
Apoptosis
Process outgrowth
Gene 2
Synaptogenesis
Axal pruning
Myelination
Synaptic pruning
* Rare and common variants
1st trimester
2ed trimester
3rd trimester

1 ENVIRONMENTAL FACTORS:

1. Advanced age of parents (Sanders et al., Nature 2012; Reichenberg et al., Arch Gen Psychiatry 2006)

1. Low body weight at birth (Eaton 2001)

2. Multiple pregnancies (distance between the pregnancies lower of 12 months; Cheslack-Postava et al, 2011)

3. Maternal infection during gestation (rubella virus, flu and cytomegalovirus)

4. Chemical contaminants to which the mother and/or the baby is exposed [ethanol, valproic acid, thalidomide; organophosphates]

be in
CHARGE
CHildhood Autism Risks from Genetics and the Environment

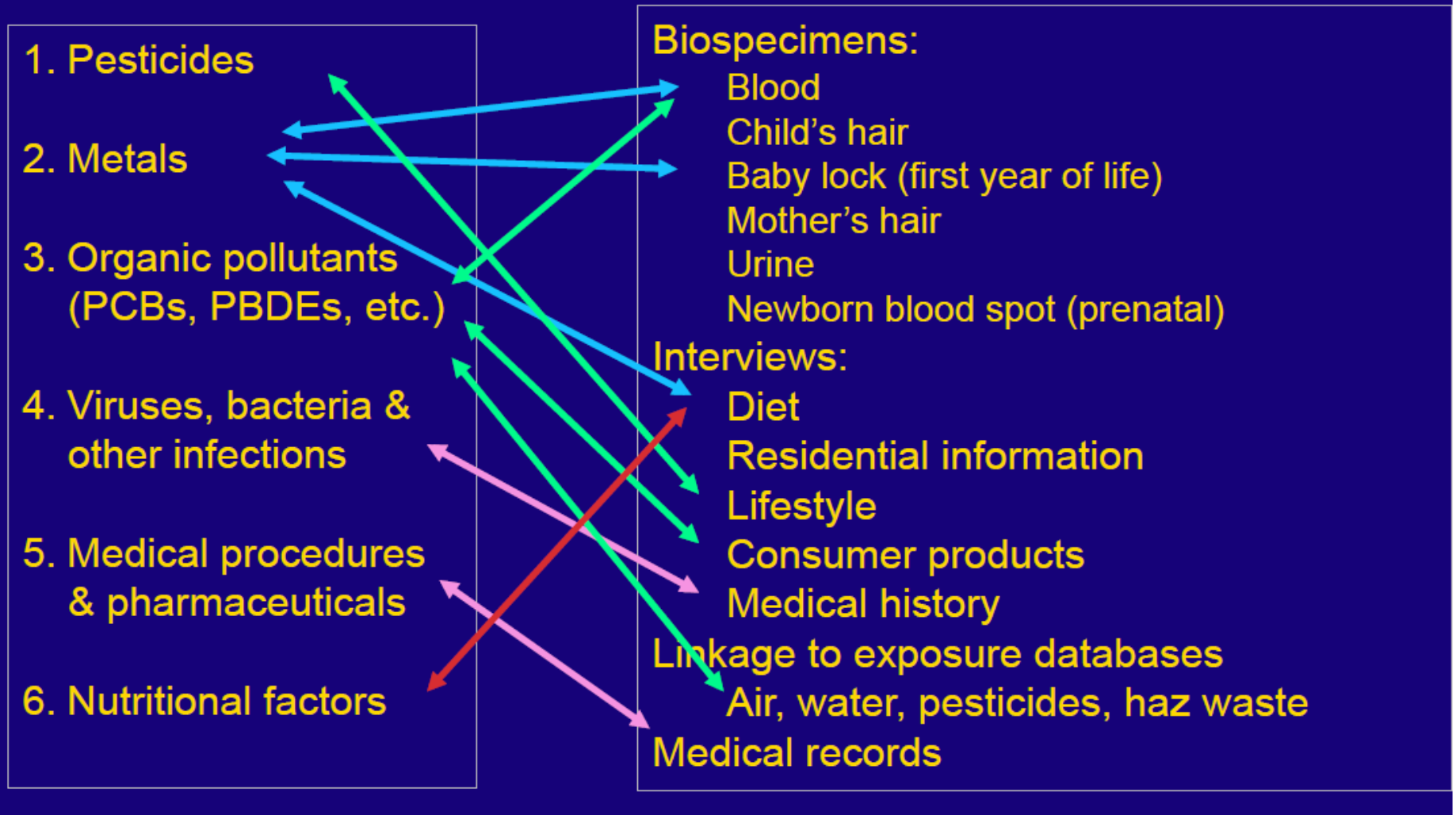
CHARGE (**Childhood Autism Risks from Genetics and the Environment**) was launched in 2003 as a study of 1,000 to 2,000 children with differing patterns of development. The goal is to better understand the causes and contributing factors for autism or developmental delay. Three groups of children are being enrolled in the CHARGE study: **children with autism**, **children with developmental delay who do not have autism** and **children from the general population**. All of them are evaluated for a broad array of exposures and susceptibilities.

The participants

Children enrolled in the study must:

- Be between 24 and 60 months of age
- Have been born in California
- Have parents who speak either English or Spanish
- Live with at least one biological parent

Environmental Exposures & Ways to Assess



SEED

Under the auspices of CDC, began recruiting about 2700 children aged two to five

The study includes developmental evaluations, questionnaries, a review of medical records and analysis of blood, cheek-cell and hair-samples to examine genetic make-up exposures to environmental chemicals

EARLI

Funded by NIH is enrolling up to 1200 families that have a child with autism and are preparing to have another baby

The study intends to look for any interplay between environmental factors and genetic susceptibility that might contribute to autism risk in their next child

2

Causes of Autism Spectrum Disorders: strongest evidence is genetic

- Concordance of 60-80% in monozygotic twins
- Concordance of 20-30% in dizygotic twins
- 4:1 frequency ratio boys:girls (8:1 in AS and 1:1 when IQ <50)

Linkage and associations studies indicate many genes underlying Autism Spectrum Disorders: *GABA-β3*, *5-HTT*, *MET, PTEN*, *En2*, *UBE3a*, *CNTNAP2,* neurexins, neuroligins, shanks and genes for comorbid neurodevelopmental disorders including *FMR1, MECP2, TSC*

HIGH RISK INFANTS

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

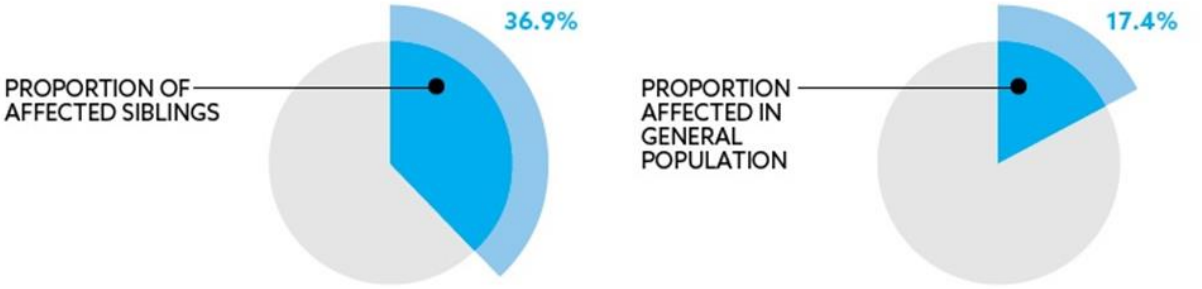
Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study

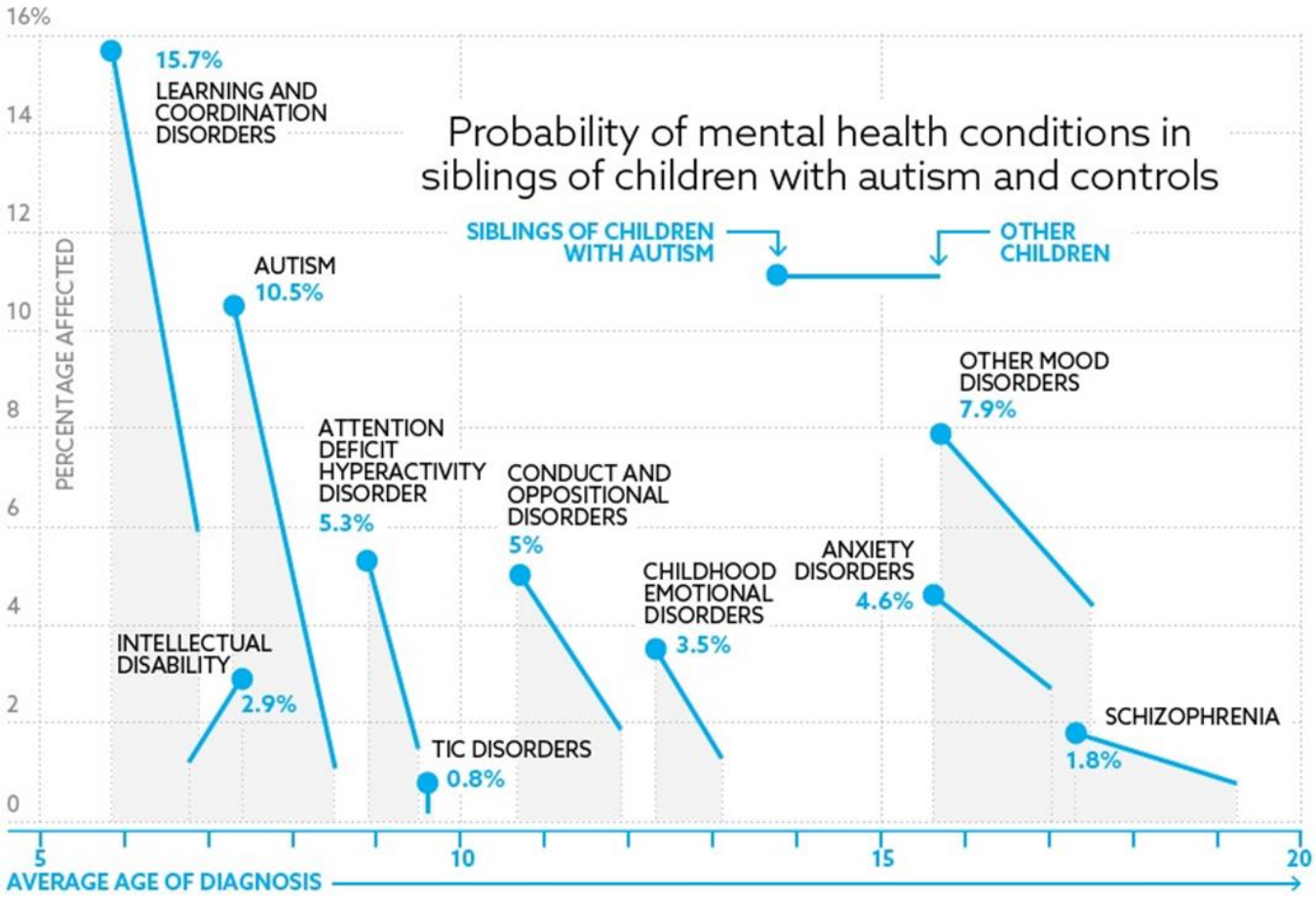
Sally Ozonoff, Gregory S. Young, Alice Carter, Daniel Messinger, Nurit Yirmiya, Lonnie Zwaigenbaum, Susan Bryson, Leslie J. Carver, John N. Constantino, Karen Dobkins, Ted Hutman, Jana M. Iverson, Rebecca Landa, Sally J. Rogers, Marian Sigman and Wendy L. Stone

Pediatrics; originally published online August 15, 2011;
DOI: 10.1542/peds.2010-2825

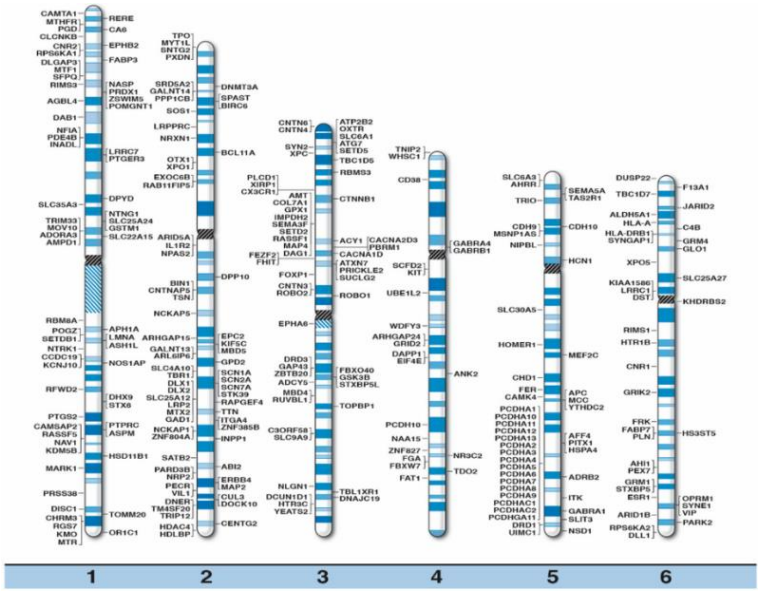
Recurrence risk of 18%
(25.9% in males and 9.6% in females)

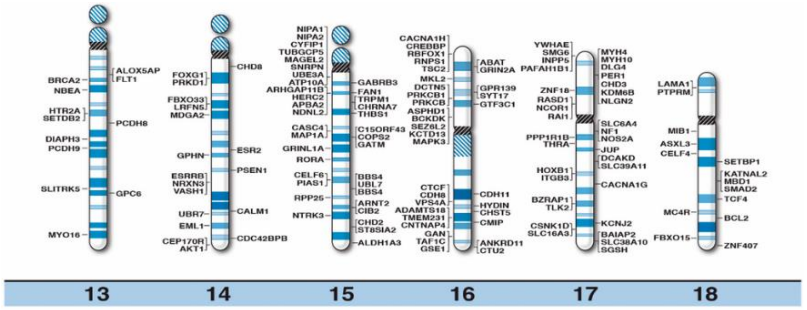
Likelihood of psychiatric conditions in siblings of children with autism

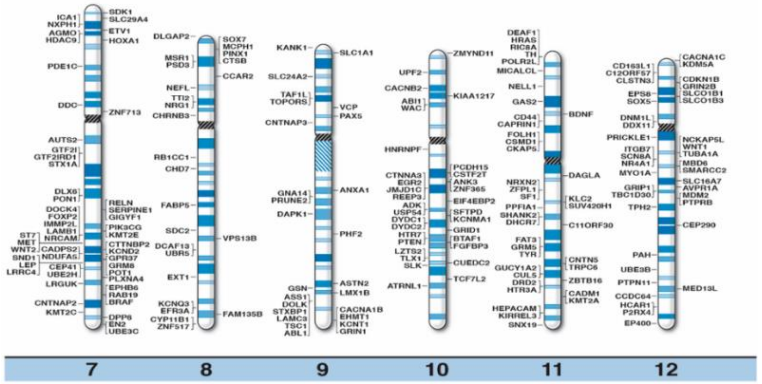


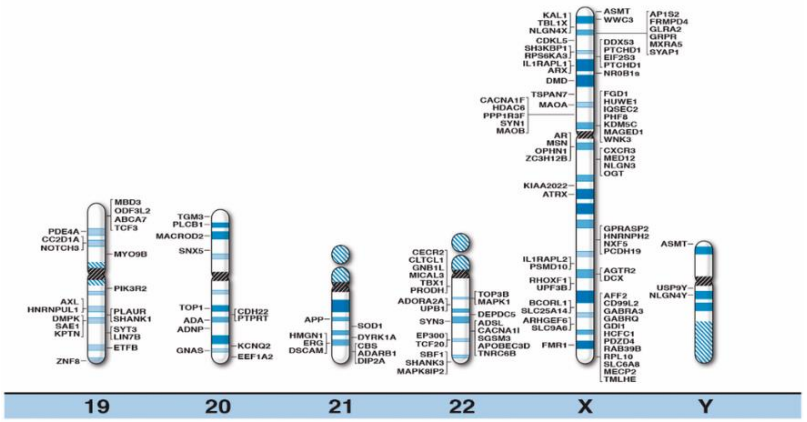


GENETIC COMPLEXITY: 2193 genes (99 syndromic autism related genes and 2135 non-syndromic autism related genes), 4617 Copy Number Variations (CNVs) and 158 linkage regions associated with ASD









Mendelian Syndromes

12p13.33 (CACNA1C) Timothy Syndrome
15q11.2 (UBE3A) Angelman Syndrome
Xq27.3 (FMR1) Fragile X Syndrome
9q34.13 (TSC1) Tuberous Sclerosis type 1

Rare variants: 1% of cases

2p16.3 (NRXN1) ASD, ID, language delay, SCZ
3p13 (FOXP1) ID, ASD
22q13.33 (SHANK3) ASD
Xp22.32-p22.31 (NLGN4X) ASD, ID, TS, ADHD
Xq13.1 (NLGN3) ASD

Common Alleles

1q42.2 (DISC1)
7q22.1 (RELN)
7q36.3 (EN2)

SnapShot: Genetics of Autism

Neuron

Kimberly A. Aldinger, Jasmine T. Plummer, Shenfeng Qiu, and Pat Levitt
Keck School of Medicine of USC, Los Angeles, CA, 90089, USA

	CHR GENE	PROTEIN FUNCTION	HUMAN PHENOTYPE (MUTANT MOUSE PHENOTYPES)
Mendelian Syndromes[1]	6q23.3 (AHI1*)	Jouberin; interacts with β-catenin in cilia	**Joubert syndrome.** (Reduced brain and body size. Cerebellar, retinal, and kidney defects. Most die by P10. Neuron-specific loss leads to depressive-like phenotypes.)
	7q35-q36.1 (CNTNAP2*)	Caspr2, a neurexin family member; clusters voltage-gated K+ channels	**Recessive EPI syndrome, ASD, ADHD, TS, OCD.** (Neuronal migration defects. Reduced GABAergic neurons and decreased cortical synchrony. Seizures. Deficits in social, repetitive behaviors, and USV.)
	9q34.13 (TSC1)	Hamartin, a growth inhibitory protein that negatively regulates the mTOR pathway	**Tuberous Sclerosis type I.** (Liver and neural tube defects. Die by E12. Abnormal kidney and liver growth in heterozygotes. Variable brain structure, function and behavior abnormalities in conditional mutants. Die at various postnatal ages. Neuron-specific loss causes abnormal spine morphology and cortical excitability. Loss of LTD.)
	10q23.31 (PTEN)	Protein tyrosine phosphatase; negatively regulates the mTOR pathway	**Cowden disease.** (Placenta and germ cell defects. Die by E9.5. Neuron-specific loss alters synaptic physiology. Heterozygotes have prostate, skin and colon defects, and spontaneous tumors. Macrocephaly, neuronal hypertrophy, abnormal social interaction, and increased survival in conditional mutants.)
	11q13.4 (DHCR7)	Final enzyme in cholesterol biosynthetic pathway	**Smith-Lemli-Opitz syndrome.** (Craniofacial and lung abnormalities. Die by P1. Abnormal cholesterol regulation and enlarged bladders. Hypomorphic mutants are viable and fertile. Compound mutants have fused toes, enlarged ventricles, and 25% embryonic lethality.)
	12p13.33 (CACNA1C)	α-1 subunit of a voltage-dependent Ca2+ channel	**Timothy syndrome.** (Die embryonically. Impaired pancreatic function. Motor defects and antidepressant-like behavior in heterozygotes; anxiety-like deficits in females. Neuron-specific loss, impaired cognition and LTP.)
	15q11.2 (UBE3A)	Ubiquitination ligase; targets protein degradation system	**Angelman syndrome.** (Small brain, seizure susceptibility, motor and learning deficits. Reduced spine density and impaired LTP. Impaired synapse maturation and plasticity.)
	16p13.3 (TSC2)	Tuberin; which negatively regulates the mTOR pathway	**Tuberous Sclerosis type II.** (Heart, neural tube, and motor defects. Purkinje cell death. Die by E12. Various tumors and axon guidance defects in heterozygotes. Dominant-negative mutant has enhanced anxiety-like behaviors; motor, learning, social behavior deficits.)
	17q11.2 (NF1)	Neurofibromin; a GTPase activator and negative regulator of RAS signaling	**Neurofibromatosis.** (Macrocephaly, small eyes, and heart defects. Delayed organ development. Embryonic lethal. Increased astrocytes and tumor susceptibility. LTP and learning and memory deficits in heterozygotes.)
	Xp21.2 (DMD)	Dystrophin; cytoskeletal protein bridging ECM	**Duchenne muscular dystrophy.** (Muscle and heart defects in hemizygous males and homozygous females. Reduced fertility. Abnormal retinal electrophysiology and synapse organization, density, and maturation.)
	Xp21.3 (ARX)	Aristaless-related homeobox protein TF	**LIS, XLID, EPI, ASD.** (Hemizygous males die perinatally. Decreased inhibitory synaptic transmission. Males hemizygous for point mutations or triple repeat expansions have seizures. Defects in behavior and GABAergic neuron generation and migration.)
	Xq27.3 (FMR1)	Fragile X mental retardation protein; an RNA-binding protein that traffics mRNA	**Fragile X syndrome.** (Seizures. Enlarged testes in males. Learning and social behavior defects. Dendritic spine abnormalities. Enhanced LTD and impaired LTP. Altered cortical drive and E/I neuronal cortical networks.)
	Xq28 (MECP2)	MeCP2; involved in transcriptional regulation and chromatin organization	**Rett syndrome.** (Brain, breathing, and motor defects in hemizygous males. Mild cognitive and anxiety-like phenotypes in heterozygous females. Various conditional loss and postnatal reduction mimic null phenotypes in adult hemizygous males. Impaired excitatory synapses and spine morphology. Increased neuronal connectivity.)
Rare Variants	2p16.3 (NRXN1)	A neurexin; forms intracellular junctions through neuroligin binding	**ASD, ID, language delay, SCZ.** (Reduced startle and PPI. Enhanced anxiety-like behavior and motor learning. Impaired spatial memory. Defective LTP. Defects in excitatory synaptic strength and diminished NMDA/AMPA receptor current.)
	3p13 (FOXP1)	A forkhead box TF	**ID, ASD, SLI.** (Cardiovascular defects. Die embryonically.)
	6q16.3 (GRIK2*)	A postsynaptic glutamate receptor subunit	**Recessive ID.** (Increased sensitivity to drug-induced seizures. Elevated startle and pain threshold. Impaired synaptic plasticity and inhibitory transmission.)
	7q31.1 (FOXP2)	A forkhead box TF	**SLI.** (Growth retardation, reduced USV, cerebellar, motor and neurological defects. Perinatal death. Impaired LTD and plasticity.)
	15q11-q13		**ASD, EPI, ID.** (Cleft palate in deletion mutants; die by P3; motor, and cognitive defects. Seizures. Increased newborn USV in maternal heterozygotes. Reduced activity, social interactions, and USV; increased anxiety-like behavior in duplications.)
	16p11.2		**ASD, ADHD, ID, EPI, SCZ.** (Mild structual brain defects and gene dose-dependent behavioral phenotypes.)
	17q11.2 (SLC6A4)	5-HT transporter	**ASD, OCD.** (Heart defects. Hyperactive, aggressive, anxiety-like behaviors, and learning deficits.)
	22q11.21		**DiGeorge syndrome, SCZ, ASD, ID.** (Sensorimotor, learning, and memory deficits. Hyperactivity. Increased anxiety-like behavior.)
	22q13.33 (SHANK3)	A PSD scaffold protein	**ASD.** (Variable phenotypes including excessive grooming, anxiety-like behavior, and disrupted social interactions. Abnormal dendritic spines. Reduced synaptic transmission, LTP, LTD, and NMDAR-dependent responses.)
	Xp22.32-p22.31 (NLGN4X)	A neuroligin; ligand for β-neurexins	**ASD, ID, TS, ADHD.** (Reduced brain size. Social interaction and USV deficits.)
	Xq13.1 (NLGN3*)	A neuroligin; ligand for β-neurexins	**ASD.** (Reduced brain size. Abnormal learning, social behavior, USV, and olfaction. Hyperactivity, altered E/I balance shift caused by increased inhibitory synaptic transmission.)
Common Alleles	1q42.2 (DISC1)	Large transmembrane protein involved in neurite outgrowth and brain development	(Region-specific changes in neuronal morphology. Homozygote and heterozygote learning and memory deficits. Reduced neurogenesis and altered neuron distribution. Abnormal dendritic spines. Reduced short-term plasticity.)
	2q31.1 (SLC25A12)	Mitochondrial Ca2+-binding carrier	(Growth retardation. Tremors, myelination and motor defects. Die E18–P15.)
	3p25.3 (OXTR)	GPCR for oxytocin	(Abnormal maternal behavior. Hypoactivity, increased aggression and USV in males. Social memory defects. Fewer GABAergic synapses.)
	7q31.2 (MET)	Receptor tyrosine kinase	(Muscle, axon guidance, placenta, and liver defects. Die by E14. Abnormal cortical dendrites/spines and hyperconnectivity of local circuits in conditional mutant.)
	7q22.1 (RELN)	Large secreted ECM protein involved in cell-cell interactions	(Reduced body size and premature death in some mutants. Retinal, olfactory, and fertility defects. Various neuron structural, functional, and localization abnormalities. Impaired PPI and LTP and reduced inhibitory tone in heterozygotes.)
	7q36.3 (EN2)	Homeobox TF critical for hindbrain patterning	(Deficits in cerebellar development. Altered DA neuron generation and degeneration. Hyperactivity. Motor, learning, and grooming impairments.)
	12q14.2 (AVPR1A)	GPCR for arginine vasopression	(Impaired spatial memory and reduced PPI. Social deficits in females. Reduced anxiety-like behaviors in males.)
	17q21.32 (ITGB3)	Mediates platelet cell adhesion and cell-surface signaling	(Platelet defects, anemia, internal bleeding, increased bone mass, hypocalcemia, and premature death. 50% die embryonically from placental defects. Altered social and repetitive behaviors.)

"Many-to-one" relationship

The number of genes predicted to carry risk for ASD has steadily increased (now reaching well into hundreds) with no single locus accounting for more than 1% of cases

"One-to-many" phenomenon

Identical highly penetrant variants in different individuals carry large effects but for a wide range of outcomes, including ASD, epilepsy, intellectual disability and schizophrenia

Family with a mutation in the Neuroligin 4 gene

Stuart, the older but smaller of the two brothers, can speak. But he's still very limited in how he communicates.

Timmy is non-verbal and tends to wander the house searching for things to "get into".

European Journal of Human Genetics (2008) **16,** 614–618; doi:10.1038/sj.ejhg.5202006; published online 30 January 2008

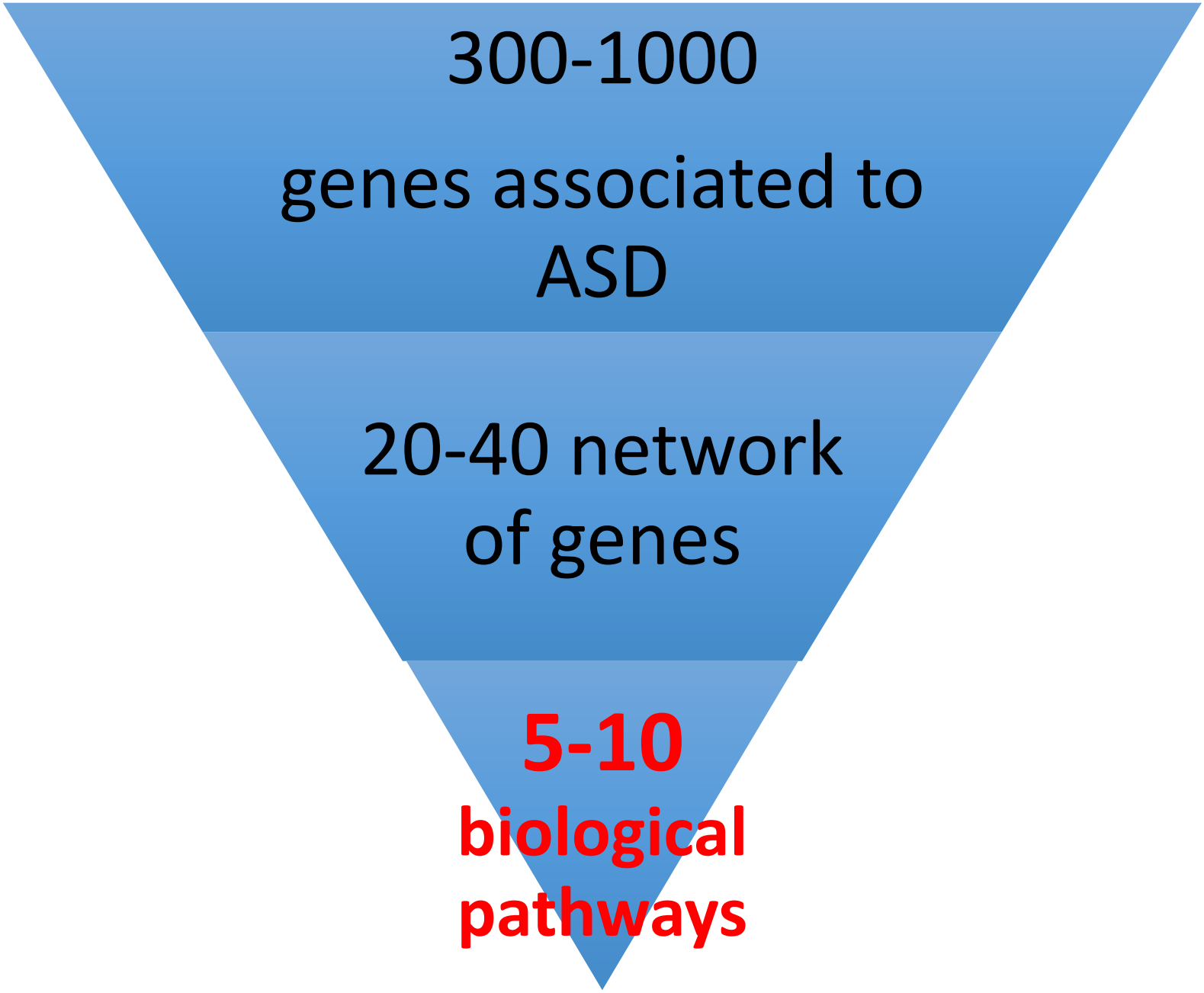
Familial deletion within NLGN4 associated with autism and Tourette syndrome

Amy Lawson-Yuen[1], Juan-Sebastian Saldivar[2], Steve Sommer[2] and Jonathan Picker[1]

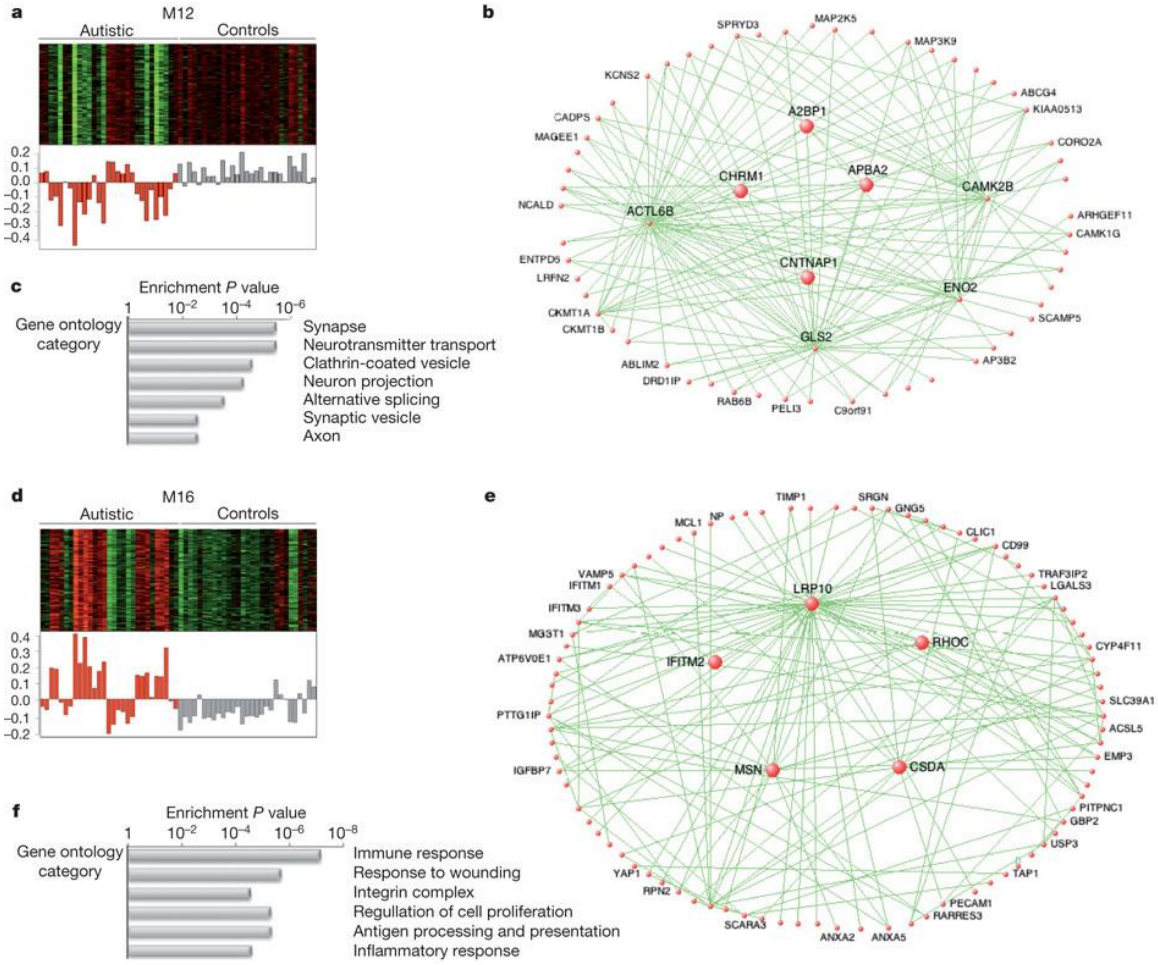
Abstract

Top

Neuroligin 4 (NLGN4) is a member of a cell adhesion protein family that appears to play a role in the maturation and function of neuronal synapses. Mutations in the X-linked *NLGN4* gene are a potential cause of autistic spectrum disorders, and mutations have been reported in several patients with autism, Asperger syndrome, and mental retardation. We describe here a family with a wide variation in neuropsychiatric illness associated with a deletion of exons 4, 5, and 6 of *NLGN4*. The proband is an autistic boy with a motor tic. His brother has Tourette syndrome and attention deficit hyperactivity disorder. Their mother, a carrier, has a learning disorder, anxiety, and depression. This family demonstrates that *NLGN4* mutations can be associated with a wide spectrum of neuropsychiatric conditions and that carriers may be affected with milder symptoms.


300-1000
genes associated to ASD
20-40 network of genes
5-10
biological pathways

TRANSCRIPTOMIC



Gene ontology category	p-value
Down-regulated genes (N=209)	
Synapse	4.48E-08
Axon	5.07E-07
Neuropeptide hormone activity	2.62E-06
Synaptic transmission	9.96E-07
Synaptic vesicle	2.98E-04
Up-regulated genes (N=235)	
Immune response	5.59E-09
Regulation of cell proliferation	6.96E-08
Cell adhesion	3.34E-06
Negative regulation of cell death	6.86E-06
Inflammatory response	7.73E-06
Immunoglobulin domain	4.12E-04

Voineagu I *et al. Nature*, 1-5 (2011)

706 Cell 147, October 28, 2011 ©2011 Elsevier Inc. DOI 10.1016/j.cell.2011.10.015

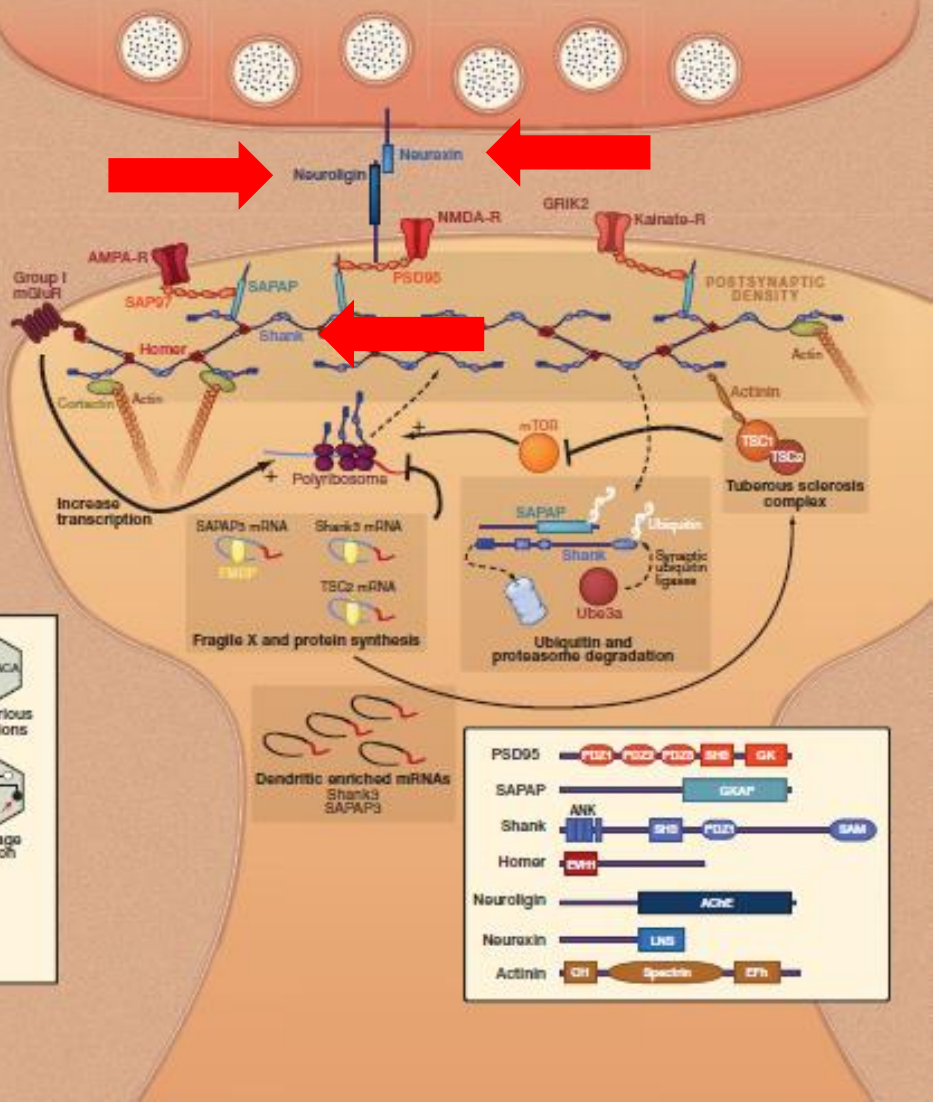
SnapShot: Autism and the Synapse

João Peça,[1] Jonathan Ting,[1] and Guoping Feng[1]
[1]McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Cell

Gene/Protein	Locus	Evidence
PROSAP2/ Shank3 Phelan-McDermid syndrome	22q13	Schizophrenia
PROSAP1/ Shank2	11q13	
DLG1/SAP97 3q29 deletion syndrome	3q29	Autism and schizophrenia + Schizophrenia
DLG4/ PSD95	17p13	Schizophrenia
DLGAP2/ SAPAP2	8p23	Schizophrenia
DLGAP3/ SAPAP3	1p34	OC-Spectrum disorders
GRIK2/ GluR6	6q16	Intellectual disability
NRXN1/ Neurexin1	2p16	Schizophrenia
NRXN2/ Neurexin2	11q13	
NLGN1/ Neuroligin1	3q26	
NLGN3/ Neuroligin3	Xq13	
NLGN4X/ Neuroligin4	Xp22	
TSC1/harmartin tuberous sclerosis complex	9q34	
TSC2/tuberin tuberous sclerosis complex	16p13	
FMR1/FMRP fragile X syndrome	Xq27	
UBE3A/E6AP Angelman syndrome	15q11	

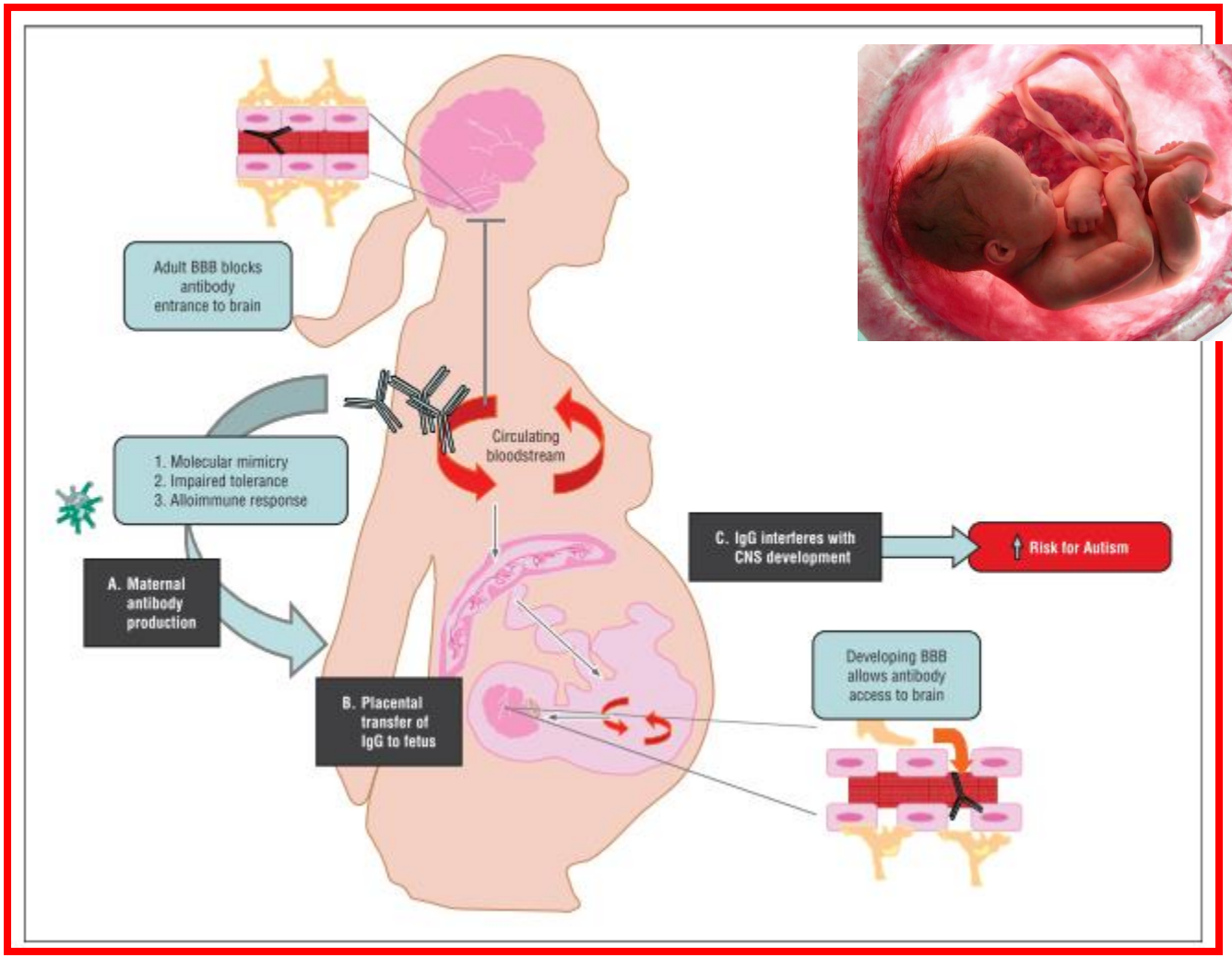
Genetic syndrome
Deleterious mutations
Copy number variations
Linkage region
SNP association



See online version for legend and references.

2

Immune dysfunction in ASD



Maternal inflammation during early pregnancy (viral or bacterial infections)

Elevated levels of circulating pro-inflammatory cytokines

Table 1
Cytokines in autism spectrum disorders. A variety of independent clinical studies have linked cytokines to ASD. This table presents detailed findings for each individual cytokine. Often multiple cytokines were associated with ASD in a single study, which is noted in parentheses.

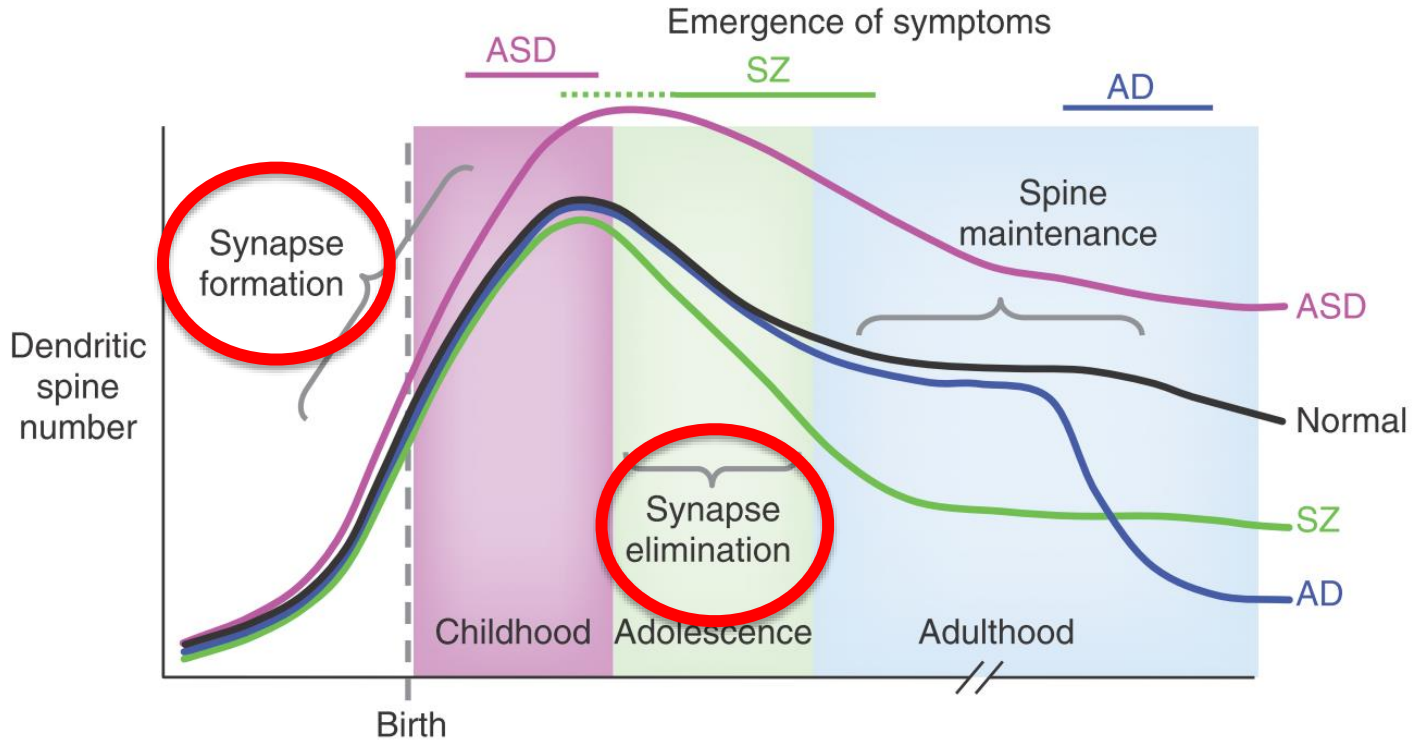
Cytokine	Findings in autism	Reference
IL-1B	Elevated plasma levels in children with ASD, correlated with regressive onset. (IL-6, IL-8 and IL-12p40 also elevated)	(Ashwood et al., 2011a, 2011b)
	Elevated plasma levels in high functioning children with ASD. (IL-1RA, IL-5, IL-8, IL-12p70, IL-13, IL-17 and GRO-α also elevated)	(Suzuki et al., 2011)
	Elevated plasma levels in adults with severe ASD. (IL-6 and endotoxin levels also elevated)	(Emanuele et al., 2010)
	Peripheral blood cells from ASD subjects produce higher baseline levels. (Similar trends for IL-6 and TNF-α)	(Jyonouchi et al., 2001)
	Peripheral blood cells from ASD subjects produce higher levels with TLR2 or TLR4 stimulation, and lower levels with TLR-9 stimulation. (Similar trends for IL-6 and TNFα)	(Enstrom et al., 2010)
IL-6	Elevated plasma levels in children with ASD, correlated with regressive onset. (IL-1B, IL-8, and IL-12p40 also elevated)	(Ashwood et al., 2011a, 2011b)
	Elevated plasma levels in adults with severe autism. (IL-B and endotoxin levels also elevated)	(Emanuele et al., 2010)
	Peripheral blood cells from ASD subjects produce higher baseline levels. (Similar trends for IL-1B and TNF-α)	(Jyonouchi et al., 2001)
	Peripheral blood cells from children with ASD produce higher levels with TLR2 or TLR4 stimulation, and lower levels with TLR-9 stimulation. (Similar trends for IL-6 and TNFα	(Enstrom et al., 2010)
	Lymphoblasts from ASD subjects produce more IL-6. (Also TNF-α)	(Malik et al., 2011)
	Increased IL-6 staining in postmortem cerebellar sections from ASD subjects	(Wei et al., 2011)
	Increased IL-6 in postmortem brain specimens (various regions) from ASD subjects. (Also increased TGF-B and inflammatory chemokines).	(Vargas et al., 2005)
	Increased IL-6 in postmortem brain tissue from ASD subjects. (Also increased TNF-α, IFN-γ, GM-CSF, and IL-8)	(Li et al., 2009)
IL-4	Increased IL-4 in mid-gestational serum samples from mothers giving birth to a child with ASD. (Also IL-5 and IFN-γ)	(Goines et al., 2011b)
	Increased IL-4 in amniotic fluid samples from mothers giving birth to a child with ASD (Also IL-10, TNF-α and TNF-B)	(Abdallah et al., 2011)
	Peripheral blood cells from ASD subjects stimulated with PMA-ionomycin were more likely to be IL-4$^+$ (And less likely to be IFN-γ$^+$)	(Gupta et al., 1998)
IFN-γ	Increased IFN-γ in mid-gestational serum samples from mothers giving birth to a child with ASD. (Also IL-4 and IL-5)	(Goines et al., 2011b)
	Increased plasma levels in individuals with ASD. (Also IL-12)	(Singh, 1996)
	Peripheral blood cells stimulated with PMA-ionomycin are less likely to be IFN-γ$^+$ (And more likely to be IL-4$^+$)	(Gupta et al., 1998)
	Unstimulated whole blood from ASD subjects produced significantly more IFN-γ compared to controls. (Also increased IL-1RA, IL-6, and TNF-α)	(Croonenberghs et al., 2002)
	NK cells from children with ASD produced higher IFN-γ under resting conditions, and lower levels after stimulation. (Also observed with perforin and granzyme B)	(Enstrom et al., 2009a)
	Increased IFN-γ in post mortem brain specimens from ASD subjects. (Also increased TNF-α, IL-6, GM-CSF, and IL-8)	(Li et al., 2009)
TGF-B	Decreased plasma TGF-B in children with ASD. Lower levels correlated with more severe behavioral scores.	(Ashwood et al., 2008)
	Decreased serum TGF-B in adults with ASD.	(Okada et al., 2007)
	Increased TGF-B levels in postmortem brain specimens (various regions) from ASD subjects. (Also IL-6 and inflammatory chemokines)	(Vargas et al., 2005)

Goines PE, Ashwood P, Cytokine dysregulation in autism spectrum disorders (ASD): Possible role of the environment, Neurotoxicol Teratol (2012)

Species	Significant Outcomes	Administration Route; Gestational Age; Amount per Injection; Serum or IgG	Maternal IgG Population
Animal Behavioral Studies			
Rat[31]	Decreased exploration Impaired motor control IHC Purkinje/neuroblastoma staining Decreased choline and creatinine levels	Intraperitoneal; embryonic day (for rodents) 10-17; 0.5 mL; serum	AU = 1; TD = 4 (all multiplex)
Rhesus macaque[32]	Reduced peer contact Increased nonsocial activity Hyperactivity Whole-body stereotypies	Intravenous; gestational day (for primates) 27, 41, and 55; 15-20 mg; IgG	AU = 12; TD = 7 (all multiplex)
Mouse[24]	Hyperactivity Increased anxiety Reduced social interaction Embryonic day 18 microglial activation Increased brain BDNF levels	Intraperitoneal; embryonic day 13-18; 1.25-1.4 mg; IgG	AU = 63; TD = 63 (mixed parity)

3

Dendritic spine pathology in neuropsychiatric disorders

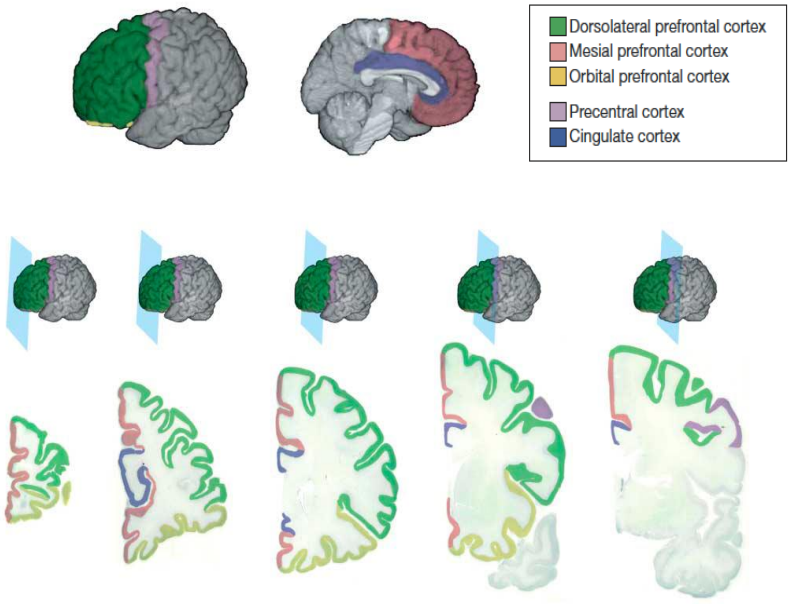


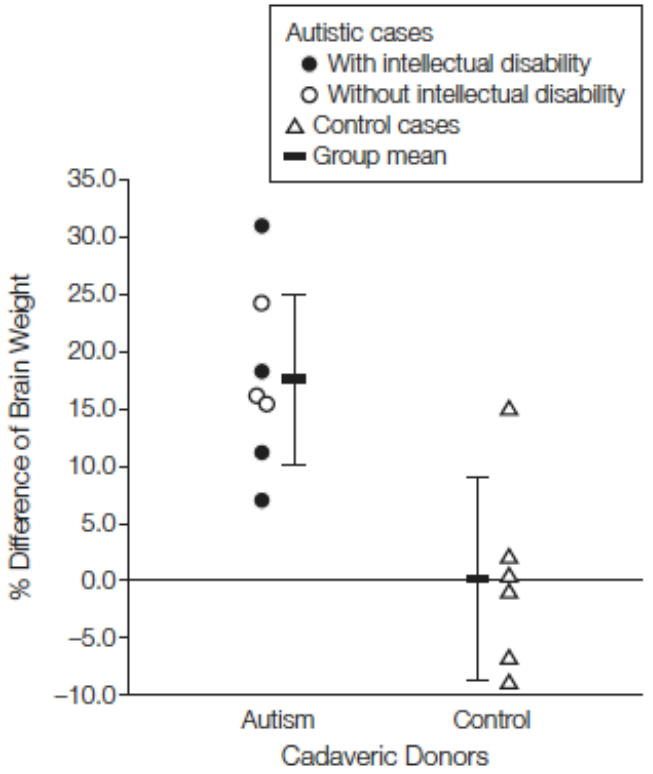
Penzes et al., Nat Neuroscience 2011

Variations in the number of neurons

Brain weight is heavier in autistic children

Prefrontal cortex:





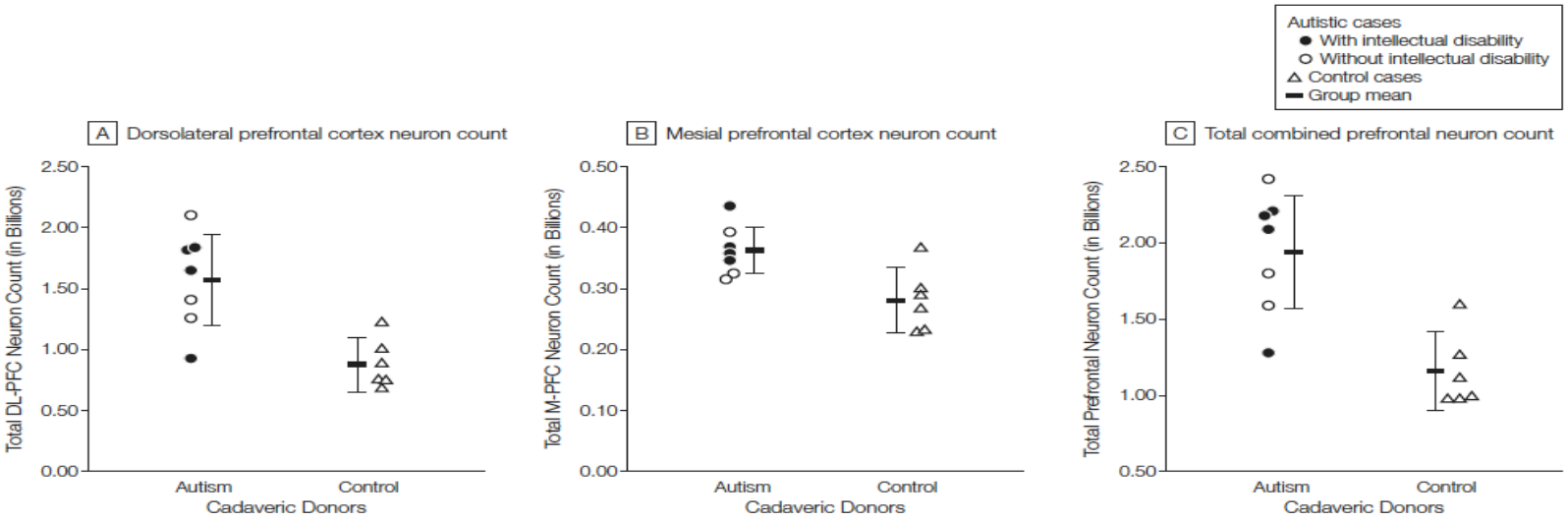
n = 7 n = 6

between 2 and 16 years

Courchense E. et al, Jama, 2011

Variations in the number of neurons

In the prefrontal cortex is observed a greater number of neurons



Reasons of the greater number of neurons should be searched at the prenatal level:

Uncontrolled proliferation?

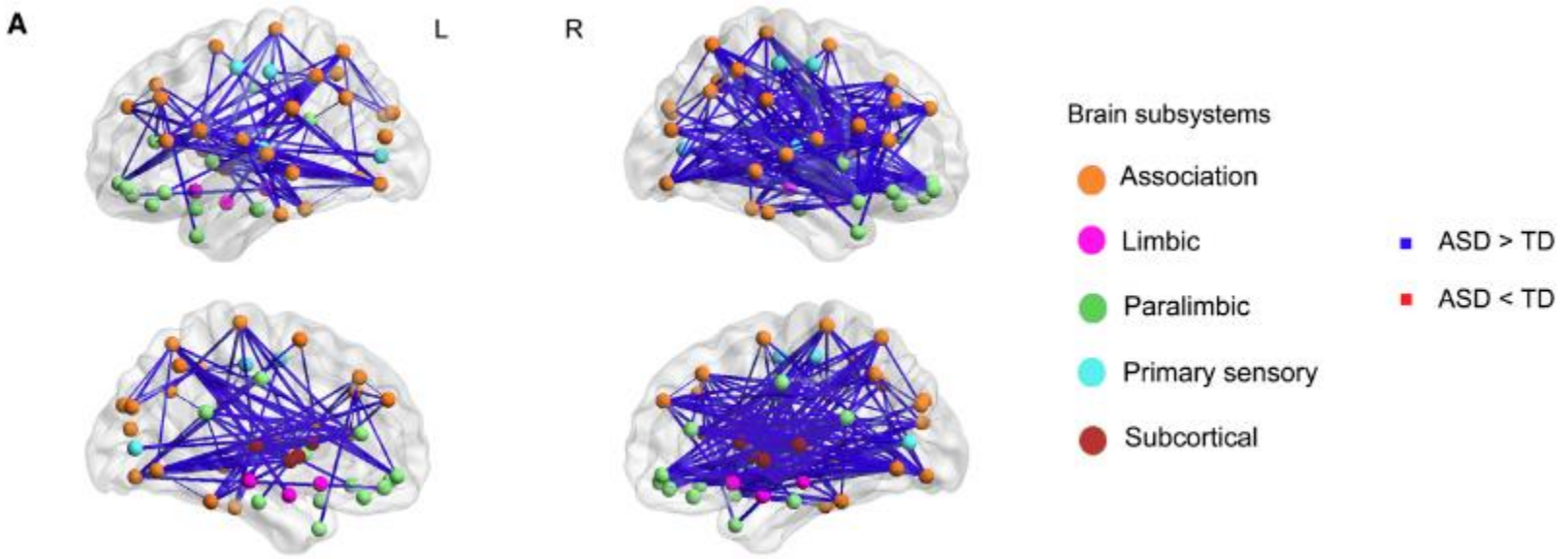
A reduced apoptosis? Or both?

Courchense E. et al, Jama, 2011

What are the consequences of this neuronal overload?

HYPERCONNECTIVITY in children with ASD

Controls **ASD**

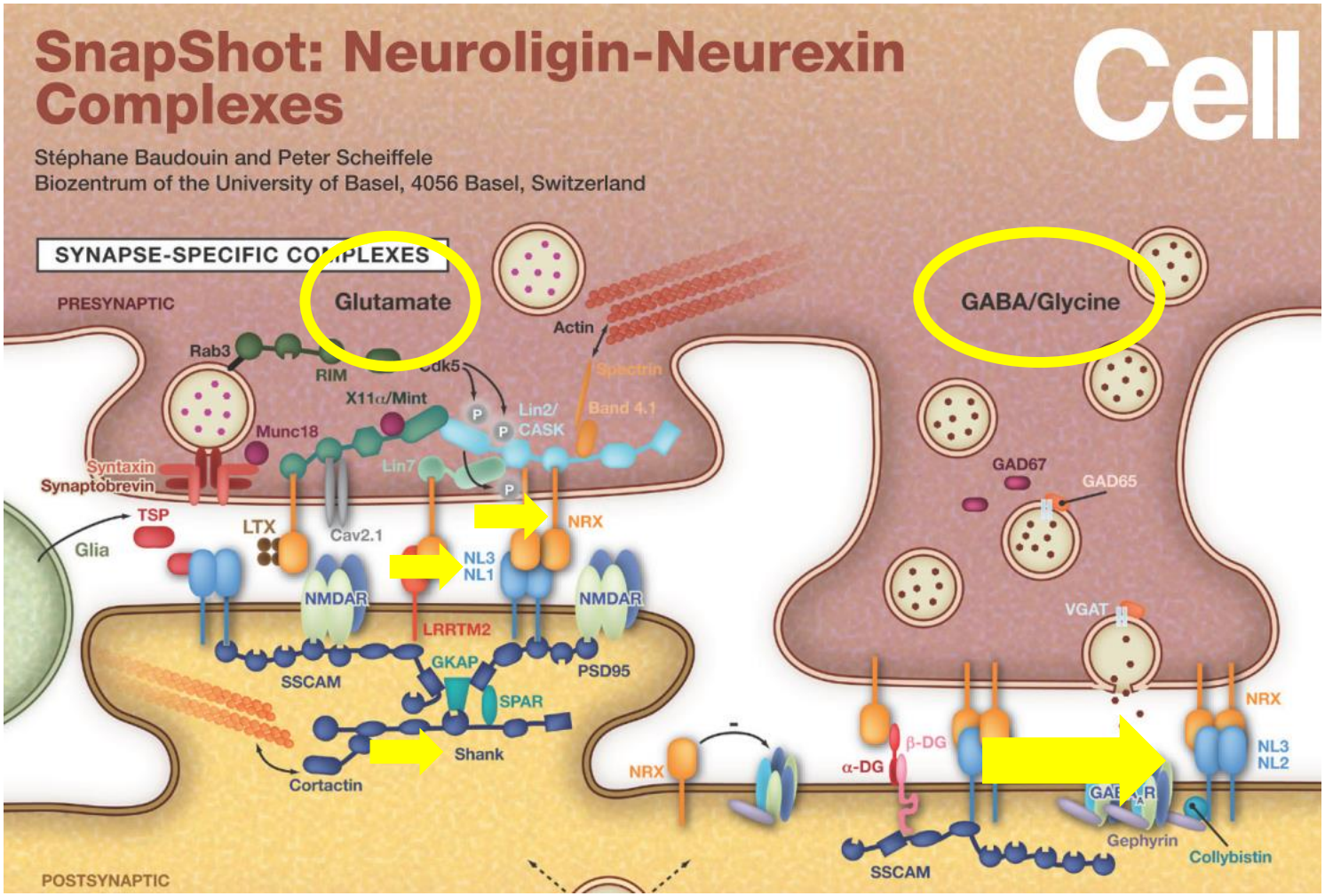


Hyperconnectivity is predictive of autistic symptoms: children with hyperconnectivity have more severe deficits in the social domain

Supekar K et al., Cell Rep. 2013 Nov 14; 5(3): 738–747

4

Excitatory/Inhibitory Imbalance

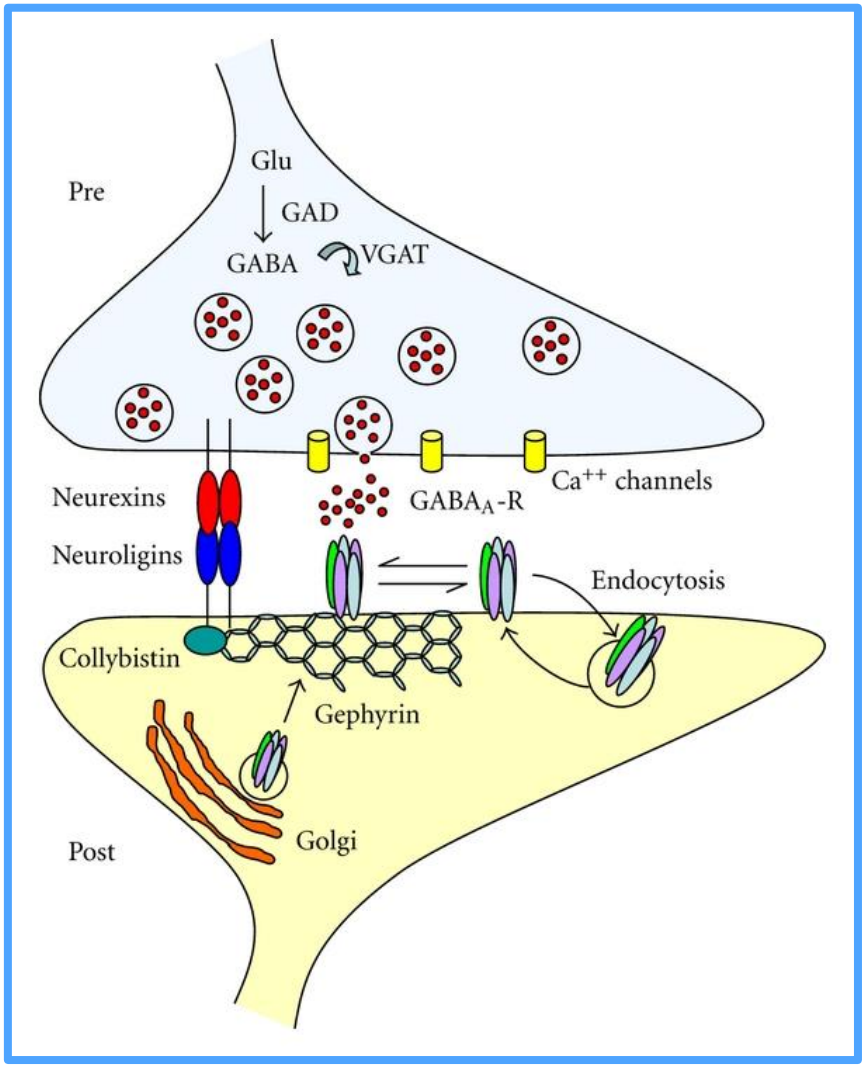


GABA

- during the embrional and perinatal phases: this neurotransmitter depolarizes targeted cells and triggers calcium influx
- in the **mature brain** GABA acts as an inhibitory transmitter

GABA regulates many processes during development:

Cell proliferation
Migration
Differentiation
Synaptic maturation
Apoptosis



Animal models in which was found an alteration of the balance E/I

Mouse model	Alterations in GABAergic signaling
Mecp 2-KO (Rett syndrome)	Reduced levels of GAD65 and GAD67 (*Viaat-Mecp2*$^{-/y}$)
	Reduced inhibitory quantal size in layer 2/3 pyramidal neurons of the somatosensory cortex
	The E/I balance is shifted to favor inhibition over excitation in cortical networks (*Mecp2*$^{2lox/x}$, *Nestin-Cre*)
	Reduced frequency of IPSC-based spontaneous rhythmic field potentials in the hippocampus (*Mecp2*$^{tm1.1Bird}$)
Fmr 1-KO (X fragile)	Down regulation of GABAA-mediated tonic inhibition in the subiculum
	Reduced expression of α5 and δ GABAA receptor subunits in the subiculum
	Increased frequency of sIPSCs and mIPSCs in the striatum
	Reduction in amplitude and frequency of sIPSCs and mIPSCs
	Reduced GABAA-mediated tonic inhibition
	Reduced GABAergic innervation in the amygdala
	Reduced expression of GABAA receptor subunits
Gabrb 3 KO	The E/I balance is shifted to favor excitation over inhibition in cortical networks (EEG recordings)
Dlx1/Dlx2 KO	Abnormal cell migration
	Reduction in the number of GABAergic interneurons in the cortex, olfactory bulb and hippocampus
Reln-KO	Reduced level of GAD67
	Decreased GABA turnover
En2-KO	Reduced expression of parvalbumin- and somatostatin-
	positive GABAergic interneurons in the hippocampus
	Increased susceptibility to seizures
Nlg3 R451C KI	Increased frequency of mIPSC
	Increased level of VGAT and gephyrin
	Asymmetric reduction of PV positive basket cells across cortical hemispheres
valproic acid	The E/I balance is shifted to favor excitation over inhibition in the lateral amygdala (multi electrode arrays)
	Asymmetric reduction of PV positive basket cells across cortical hemispheres

Despite these observations, there are no biological markers for autism because:

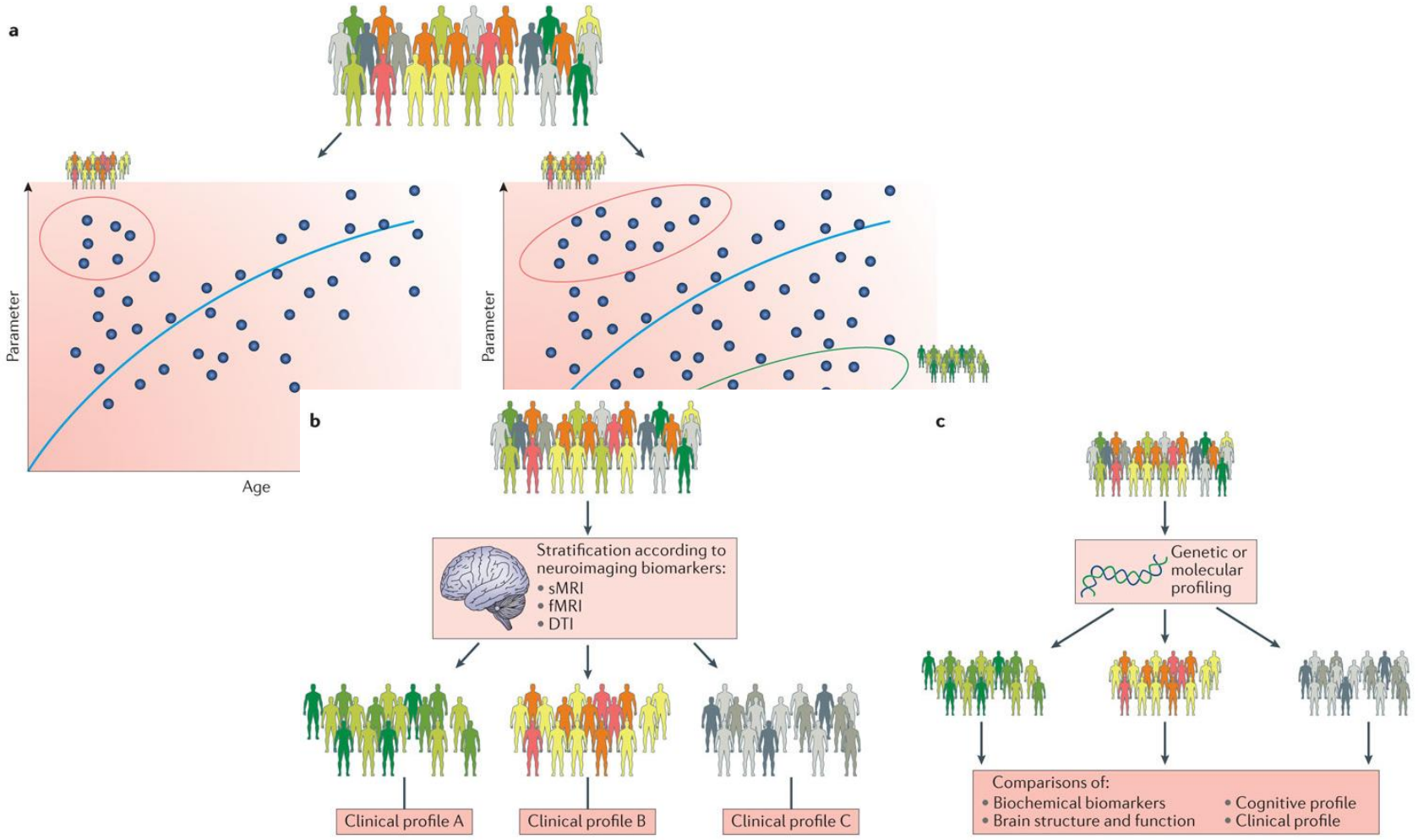
- **The few candidate biomarkers were not detected in ALL autistic patients**

- **Biomarkers found are often associated with other neurodevelopmental disorders**

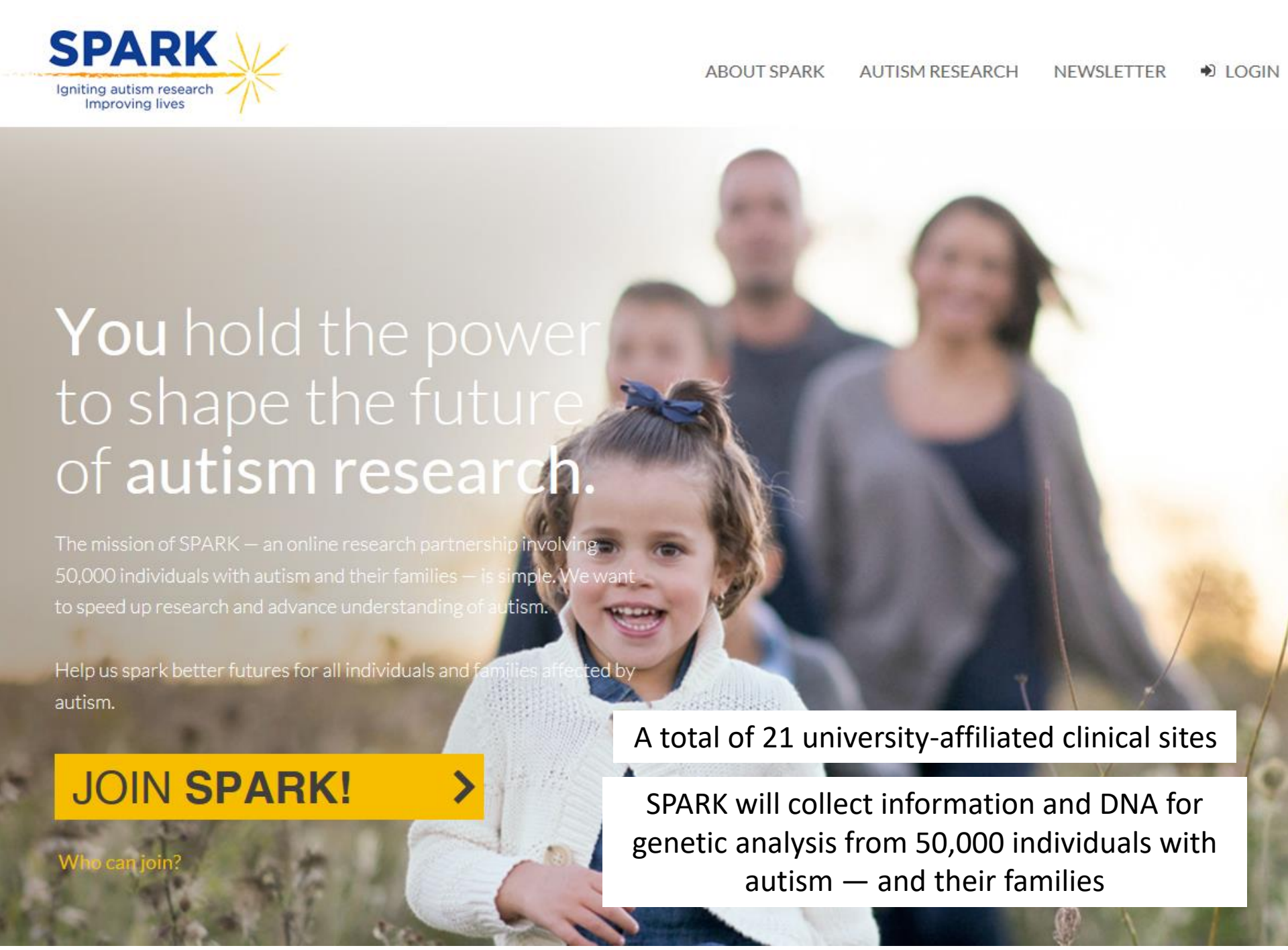
Biomarker type	Sample/measure
Gene expression profile	Blood samples
Proteomic profile	Serum samples
Metabolomic profile	Urine samples
Head size	Head circumference trajectory
Brain size and structure	MRI, DTI
Brain function	Functional MRI, EEG, ERPs
Eye movement	Looking measures, saccadic reaction time

DTI, diffusion tensor imaging; EEG, electroencephalography; ERPs, event-related potentials.

PRECISION MEDICINE: the need of subtyping



Nature Reviews | Drug Discovery


SPARK
Igniting autism research
Improving lives
ABOUT SPARK
AUTISM RESEARCH
NEWSLETTER
LOGIN
You hold the power to shape the future of autism research.
The mission of SPARK — an online research partnership involving 50,000 individuals with autism and their families — is simple. We want to speed up research and advance understanding of autism.
Help us spark better futures for all individuals and families affected by autism.
JOIN SPARK!
Who can join?
A total of 21 university-affiliated clinical sites
SPARK will collect information and DNA for genetic analysis from 50,000 individuals with autism — and their families

A PROJECT BY AUTISM SPEAKS®

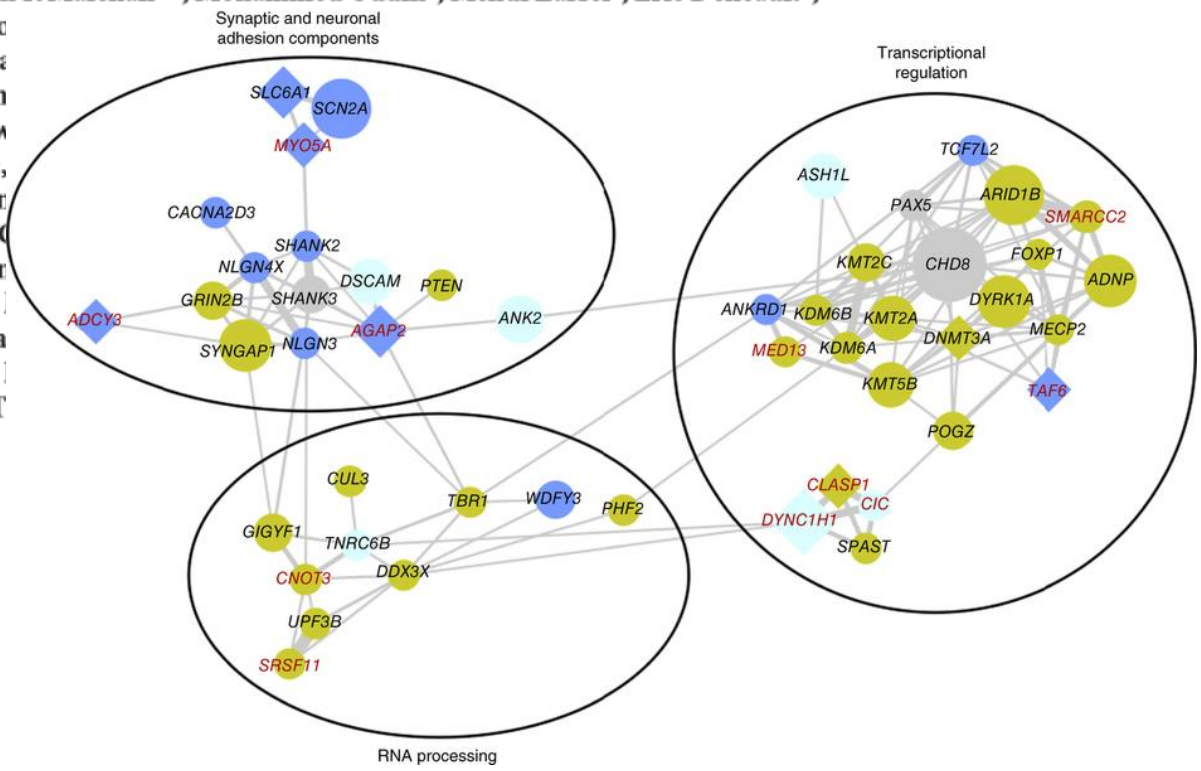
MSSNG is a groundbreaking collaboration between Autism Speaks, Google and the research community to create the world's largest genomic database on autism. MSSNG's goal is to provide the best resources to enable the identification of many subtypes of autism, which may lead to better diagnostics, as well as personalized and more accurate treatments

RESOURCE

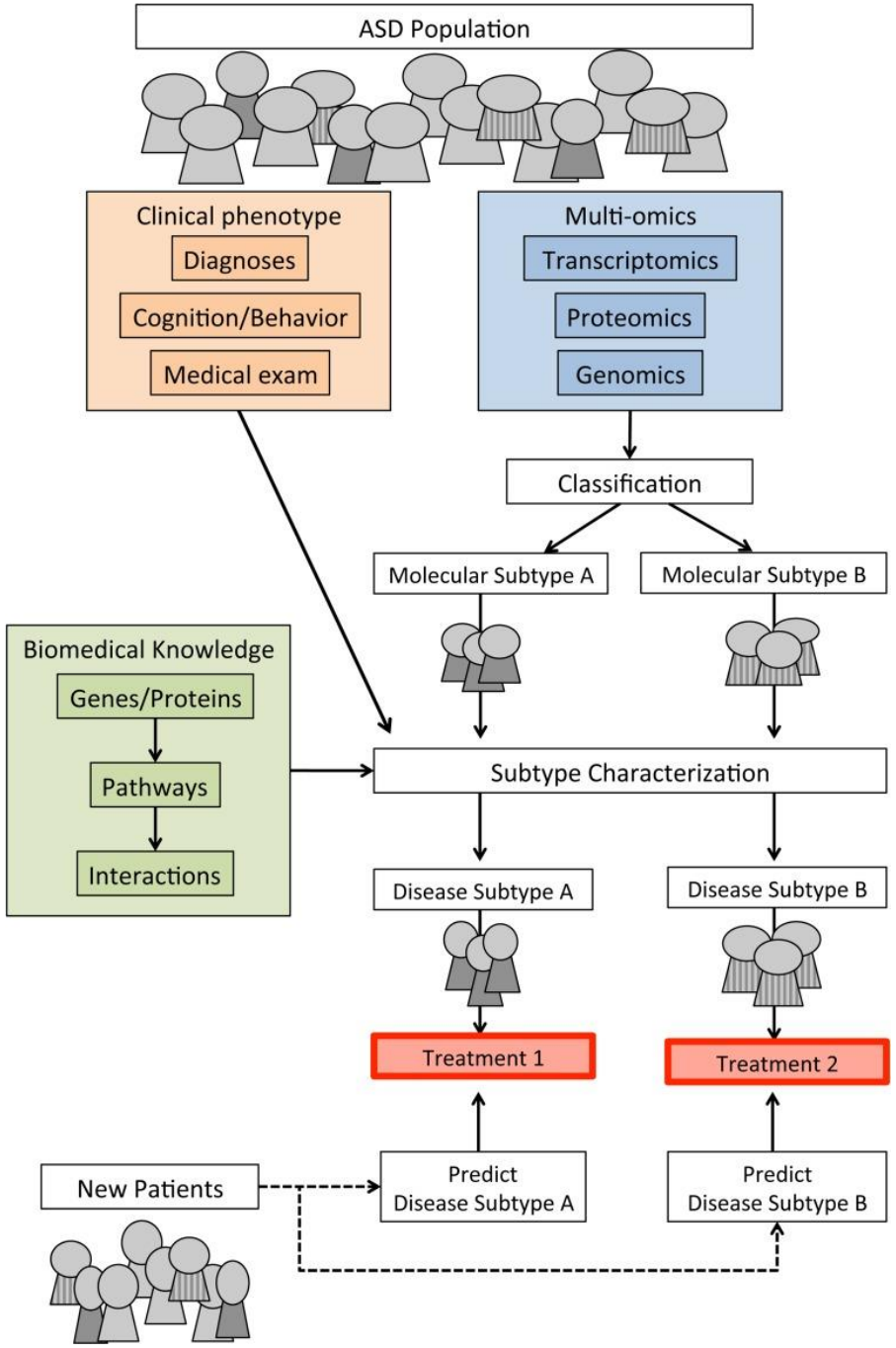
nature neuroscience

Whole genome sequencing resource identifies 18 new candidate genes for autism spectrum disorder

Ryan K C Yuen[1], Daniele Merico[1,2], Matt Bookman[3,4], Jennifer L Howe[1], Bhooma Thiruvahindrapuram[1], Rohan V Patel[1], Joe Whitney[1], Nicole Deflaux[3,4], Jonathan Bingham[3,4], Zhuozhi Wang[1], Giovanna Pellecchia[1], Janet A Buchanan[1], Susan Walker[1], Christian R Marshall[1,5], Mohammed Uddin[1], Mehdi Zarrei[1], Eric Deneault[1], Lia D'Abate[1,6], Ada J S Chan[1,6], Stephanie Ko
Worrawat Engchuan[1], Edward J Higginbotha
Thomas Nalpathamkalam[1], Wilson W L Sun
Emily Kirby[8], William Van Etten[9], Simon Tw
Bonnie MacKinnon Modi[1,7], Barbara Kellam[1],
Lonnie Zwaigenbaum[13], Marc Woodbury-Sr
Krissy Doyle-Thomas[15], Ann Thompson[14],
Isabel M Smith[17], Xudong Liu[18], Rob Nicolson
Annette Estes[24], Louise Gallagher[25], Beth A
Brendan J Frey[2,30], James T Robinson[31], Lisa
Melissa T Carter[12,34], Joachim Hallmayer[35],
Robert H Ring[40], David Glazer[3,4], Mathew T



The future…


ASD Population
Clinical phenotype
Diagnoses
Cognition/Behavior
Medical exam
Multi-omics
Transcriptomics
Proteomics
Genomics
Classification
Molecular Subtype A
Molecular Subtype B
Biomedical Knowledge
Genes/Proteins
Pathways
Interactions
Subtype Characterization
Disease Subtype A
Disease Subtype B
Treatment 1
Treatment 2
New Patients
Predict Disease Subtype A
Predict Disease Subtype B

Thank you for your attention

ISTITVTO SVPERIORE DI SANITA

CASA Centro Autismo e Sindrome di Asperger

UNIVERSITAS ATHESINA STUDIORUM

CIMeC

UNIVERSITÀ "CAMPUS BIO-MEDICO" DI ROMA

UMBERTO I POLICLINICO DI ROMA

A.O.U. AZIENDA OSPEDALIERA UNIVERSITARIA POLICLINICO "G.MARTINO"

EUGENIO MEDEA

Bambino Gesù OSPEDALE PEDIATRICO

Institute of Applied Sciences and Intelligent Systems

Science App