# Management of ASD



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# Sharing

- Lets hear your stories…….



- Learning

  spectrum

  varying familiarity

# ADI  Autism Dynamic Intervention

- Established in 2008
- Integrated intervention approach

**Photos displayed after taking informed consent from the students' parents and the therapists**

1. What are Autism Spectrum Disorders ?
2. What causes it?
3. What medications can we use ?
4. Other modalities – Which, When & How?
5. What about the many other ones ?



1. What are Autism Spectrum Disorders ?

neurobehavioural disorder

social communication disorder

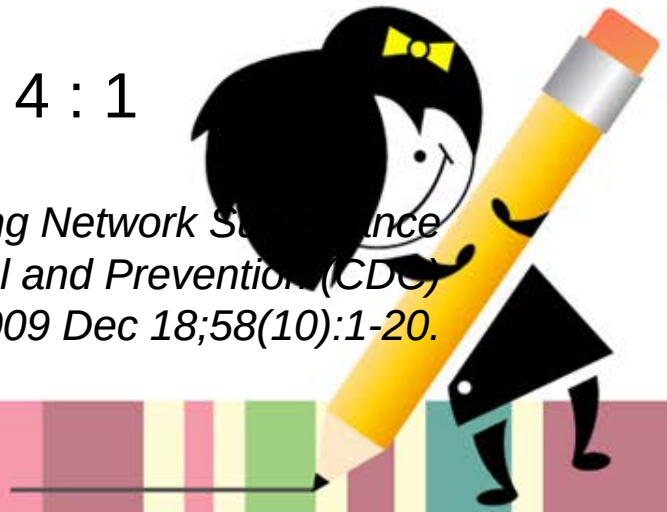


# What are the NEW numbers?

- Prevalence rates vary with the criteria of diagnosis
- 1% or one child in every 110
- Males 1:70; Females 1:315
- Male – Female ratio is about 3 - 4 : 1



*Autism and Developmental Disabilities Monitoring Network Surveillance*
*Centers for Disease Control and Prevention (CDC)*
*MMWR Surveill Summ. 2009 Dec 18;58(10):1-20.*



About

# 1 in 88

children has been identified with an autism spectrum disorder.

According to the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network.

# The magnitude

- ASDs are one of the most prevalent neurodevelopmental disorders

- More children are diagnosed with ASDs each year in the United States than AIDS, cancer, and diabetes combined.



- SES
- Geographical location (developed, Korea/Japan-3%)
- Migration
- Gender
- Cultural factors (Whites I1/2 year>African American>Latino)
- Diagnostic substitution (ID)



# What are the clinical features?

***"Within Oneself"***

A spectrum of neuropsychiatric disorders characterized by deficits in

- social interaction
- communication
- unusual and repetitive behavior



Social emotional reciprocity

Developing maintaining relationships

Non verbal communication

**Impaired social communication**

Stereotyped repetitive speech/motor /use of object

Excessive adherence to routines

Restricted fixated interests

Sensory input hypo/hyper

**Repetetive/restricted patterns of behaviour**

# Clinical Features

- Usually before 3 years of age, depending on demand
- Neuroregression

## 1. Impairment in Social Interaction

- Socialization & Reciprocity
- Eye – Eye Contact
- Joint Attention Impairment



## 2. **Impairment in Communication**

### Verbal

- 30 – 40 % never use language
- Delay in acquisition
- Echolalia, Pronoun Reversal
- Lack of abstract



### Nonverbal

- Lack of Protodeclarative pointing

### Play

- Lack of Imaginative Play
- Lack of Functional Play

### Imitation

## 3. Restricted Activities, Patterns of Behavior

- Stereotypical Movements
- Rigid Routines
- Fixated interests
- Difficulty with change




Difficulty using non-speech behaviors for social interaction

# Myths about Autism Spectrum Disorders

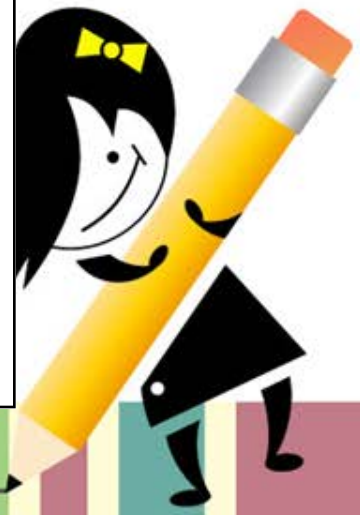
## MYTH #1

## "All individuals with ASD avoid eye contact and social contact".



- ✓ People with ASD are diverse & unique so we should avoid using **all** or **every** when describing those with this disorder.

- ✓ Although social difficulties are a hallmark of ASD, many people with ASD display affection, initiate social interaction and enjoy social activities



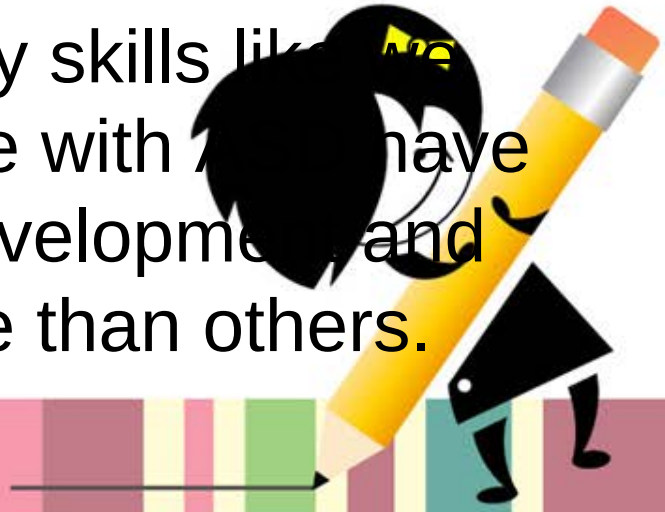
# Myths about Autism Spectrum Disorders

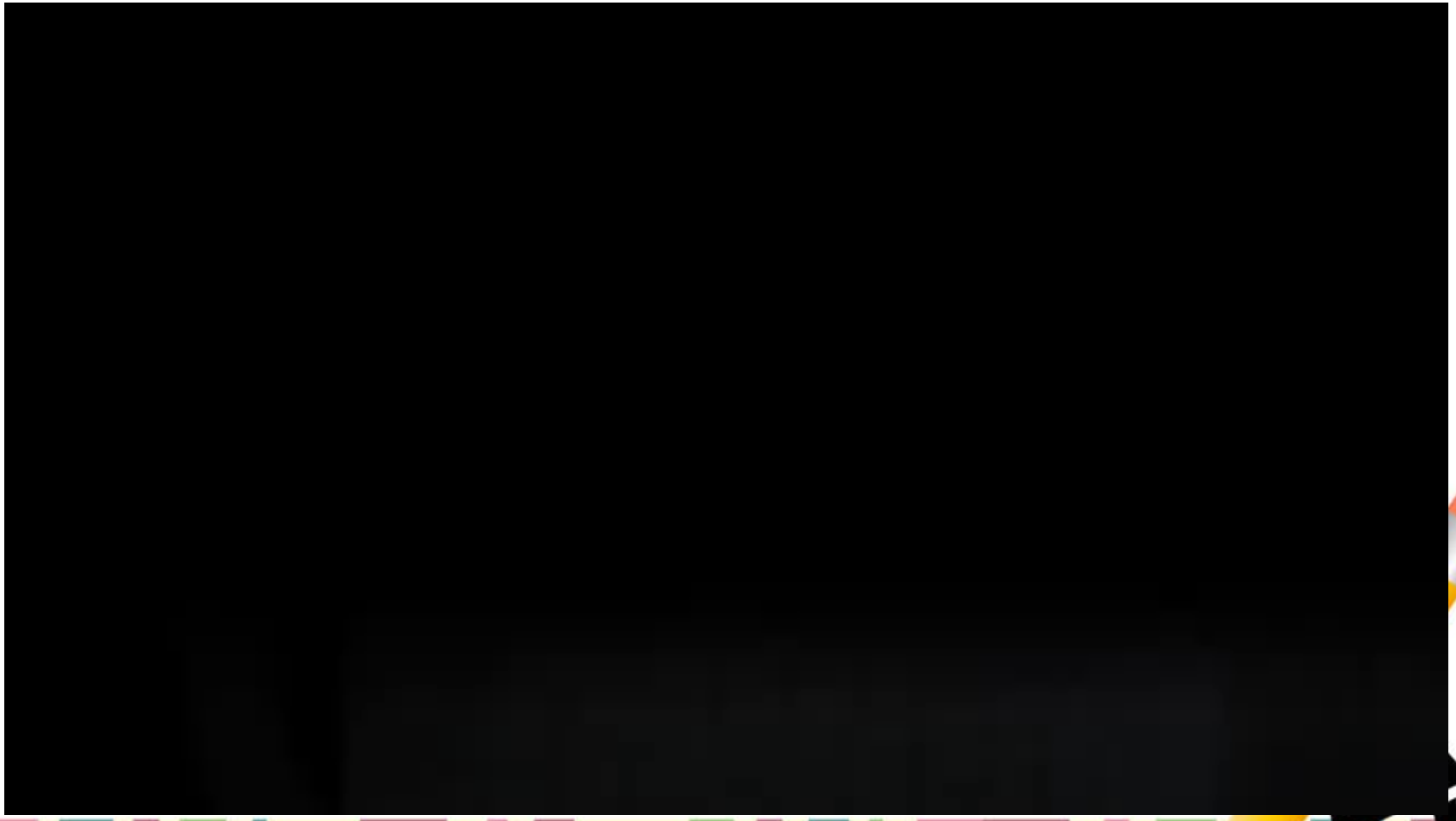
## MYTH #2

"People with ASD possess extraordinary skills or talents"



The vast majority of people with ASD do not possess the same extraordinary skills like [illegible] saw in "Rainman". Most people with [illegible] have an uneven scattering of skill development and some skills may stand out more than others.





# Literature speaks….

Co morbidity ranges from 9-89%

- Depression 26%
- Anxiety 25%
- ADHD 25%
- Conduct disorder 16%
- ODD 15%

(Kanne, Abbacchi, & Constantino, 2009)

- SAD - 29%
- ADHD - 28%
- ODD - 28%
- GAD 13%
- Panic disorder 10%
- Enuresis 11%.

(Simonoff et al, 2008)



- 24%- had three or more disorders.
- 57% - one or two psychiatric disorders

# 4. Comorbidity [1]

About 70% of individuals with autism spectrum disorder may have one comorbid mental disorder, and 40% may have two or more comorbid mental disorders (Siminoff, 2008)

- Intellectual disability **~ 45%**
- Language disorders **Variable**
- ADHD **28 – 44%**
- Tic disorders **14 – 38%**
- Motor abnormality **≤ 79%**
- Epilepsy **8 – 30%**
- Gastrointestinal problems **9 – 70%**
- Immune dysregulation **≤ 38%**
- Genetic syndromes **~ 5%**





1. Lai M et al. Lancet 2014; 383: 896 – 910

# 4. Comorbidity (contd) [1]

| | |
|---|---|
| • Sleep disorders | **50 – 80%** |
| • Anxiety | **42 – 56%** |
| • Social anxiety disorder | **13 – 29%** |
| • Generalised anxiety disorder | **13 – 22%** |
| • Avoidant personality disorder | **13 – 25%** |
| • Depression | **12 – 70%** |
| • Obsessive-compulsive disorder | **7 – 24%** |
| • Psychotic disorders | **12 – 17%** |



1. *Lai M et al. Lancet 2014; 383: [illegible] 910*

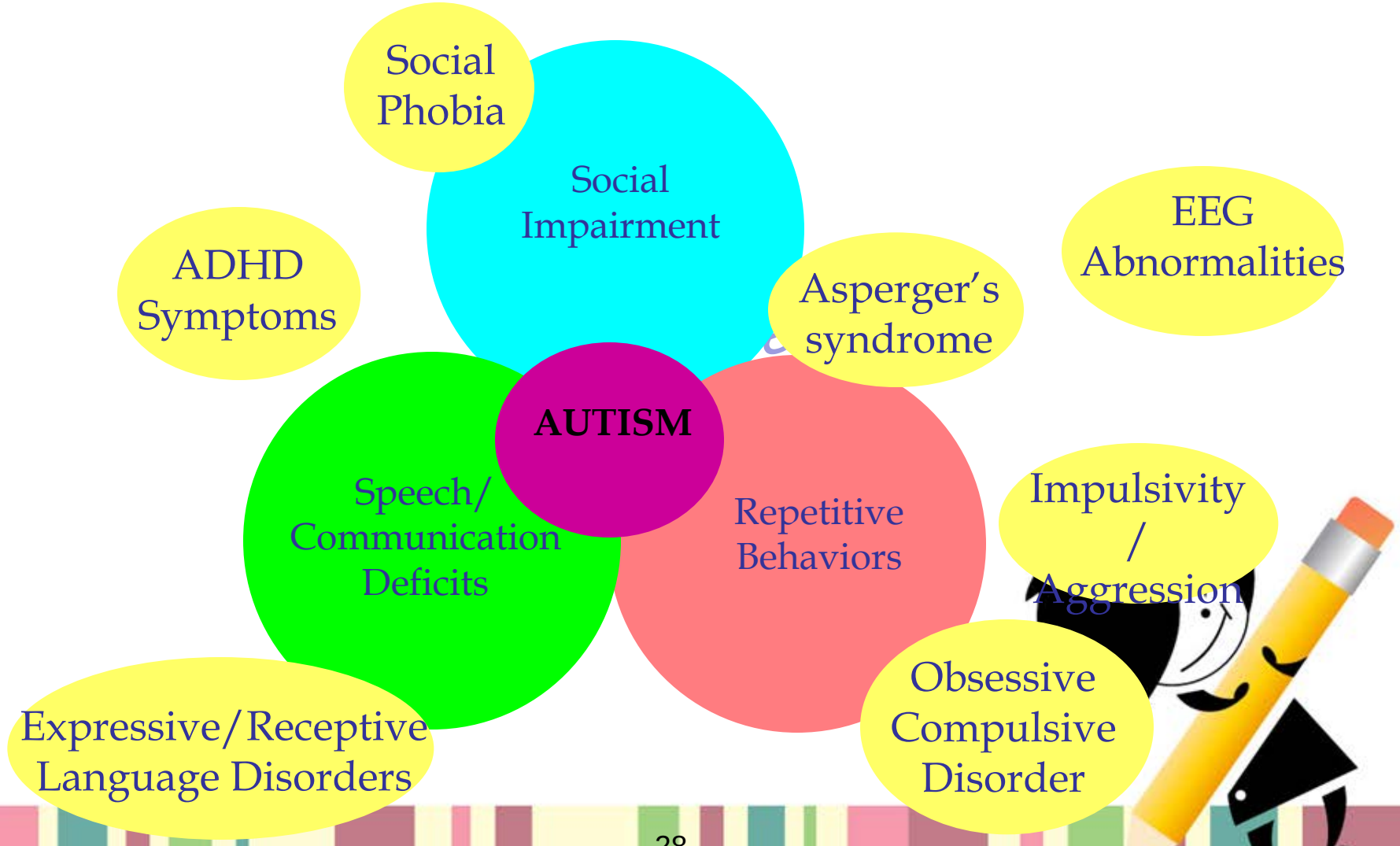
# 4. Comorbidity (contd) [1]

| | |
|---|---|
| • Substance use disorders | **≤ 16%** |
| • Oppositional defiant disorder | **16 – 28%** |
| • Eating disorders | **4 – 5%** |
| • Paranoid personality disorder | **0 – 19%** |
| • Schizoid personality disorder | **21 – 26%** |
| • Schizotypal personality disorder | **2 – 13%** |
| • Borderline personality disorder | **0 – 9%** |
| • OCPD | **19 – 32%** |
| • Aggressive behaviours | **≤ 68%** |
| • Self-injurious behaviours | **≤ 50%** |
| • Pica | **~ 36%** |
| • Suicidal ideation or attempt | **11 – 14%** |



*1. Lai M et al. Lancet 2014; 383: 896 – 910*

# Symptom Domains and Associated Features of ASD



# DIAGNOSING ASD

## DSM 5

Only **2 domains** need to be addressed:



1) Social / Communication deficits

2) Fixated interests / Repetitive behaviors

# Changes in DSM

- ASD instead of PDD & subtypes
- Age
- Three features to two broad features (social interaction, communication and repetitive behaviour)
- Specifiers for different aspects (intellectual impairment, language impairment, medical or genetic condition or environmental factor, neurodevelopmental, mental or behavioral disorder, catatonia)
- Severity specifiers (support, substantial support, very substantial support)




**A. Persistent deficits in social communication and social interaction across multiple contexts as manifested by the following**

1. Deficits in social emotion reprocity, ranging from social approach

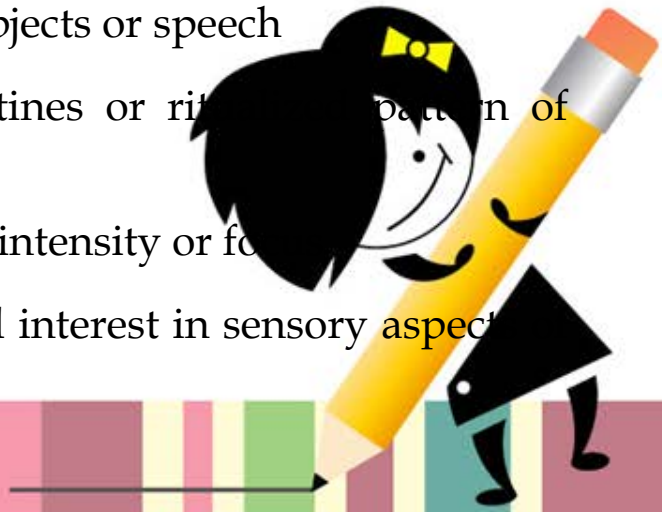
   and failure of normal back and forth conversion to reduced sharing of interest, emotions and affect

1. Deficit in non-verbal communications
2. Deficit in developing, maintaining and understanding relationship



**B. Restricted, repetitive pattern of behavior, interest or activities as manifested by at least two of the following**

1. Stereotyped or repetitive motor movements, used of objects or speech
2. Insistence on sameness, inflexible adherence to routines or rit pa n of verbal or non-verbal behavior
3. Highly restricted, fixated interest that are abnormal in intensity or fo
4. Hyper- or-hypo reactivity to sensory input or unusual interest in sensory aspect the environment



# Diagnostic Criteria – DSM 5

**C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)**

**D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning**

**E. These disturbances are not better explained by intellectual disability or global developmental delay.**



# 299.00
# Autistic Disorder



*Revised January 26, 2011*

| Severity Level for ASD | Social Communication | Restricted interests & repetitive behaviors |
|---|---|---|
| Level 3<br><br>'Requiring very substantial support' | Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning; very limited initiation of social interactions and minimal response to social overtures from others. | Preoccupations, fixated rituals and/or repetitive behaviors markedly interfere with functioning in all spheres. Marked distress when rituals or routines are interrupted; very difficult to redirect from fixated interest or returns to it quickly. |
| Level 2<br><br>'Requiring substantial support' | Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions and reduced or abnormal response to social overtures from others. | RRBs and/or preoccupations or fixated interests appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress or frustration is apparent when RRB's are interrupted; difficult to redirect from fixated interest. |
| Level 1<br><br>'Requiring support' | Without supports in place, deficits in social communication cause noticeable impairments. Has difficulty initiating social interactions and demonstrates clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. | Rituals and repetitive behaviors (RRB's) cause significant interference with functioning in one or more contexts. Resists attempts by others to interrupt RRB's or to be redirected from fixated interest. |

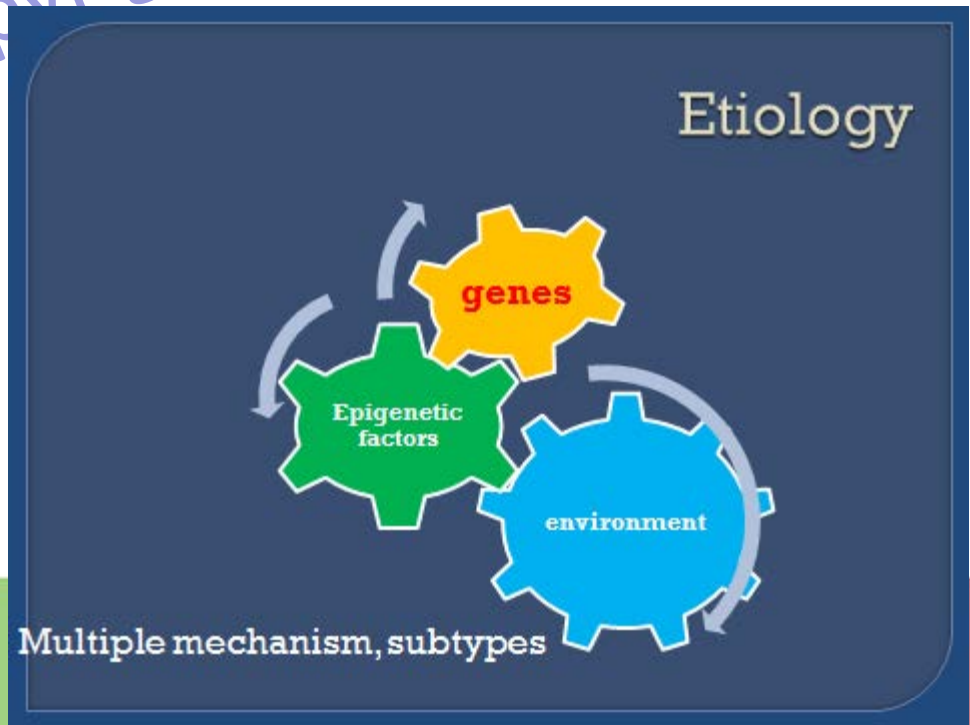
# CAUSES of ASD

- Environmental
- Genetic
- Gene-Environment interplay

  interaction

  correlation

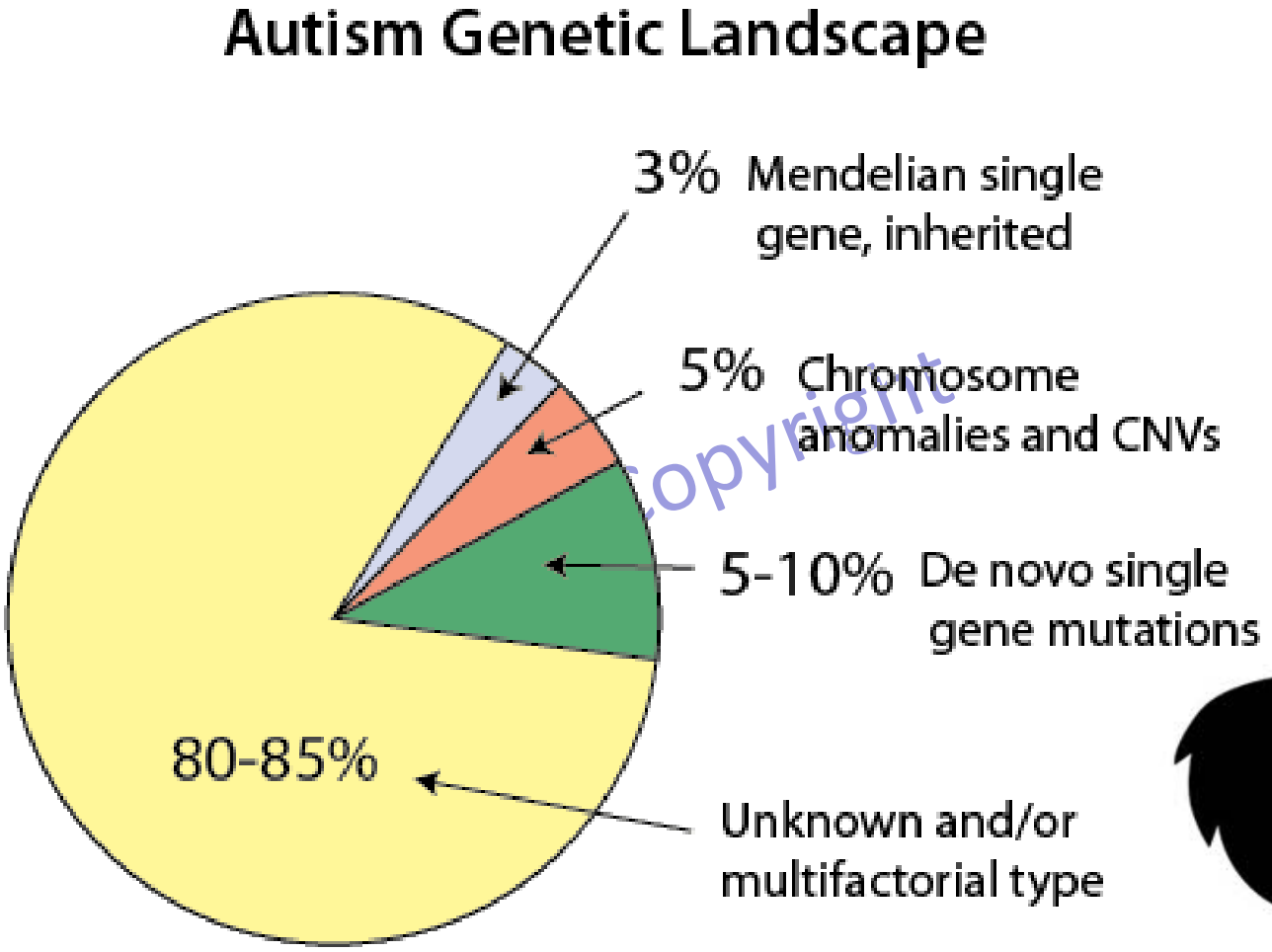




- Twins Identical: 36-95% chance of other child being autistic
- Twins nonidentical:0-30% chance of other child being autistic
- Siblings of an affected individual have 2–18% (20%) chances of being autistic
- Siblings and parents of an affected show subtle cognitive or behavioural features



# Genetics in ASD






https://www.peds.ufl.edu/divisions/genetics/programs/autism_card/genetics.htm

# Methods of genetic studies in ASD

- Cytogenetic study; from light microscopy to molecular cytogenetic (CNV) to DNA based microarray detections of structural variation



- Linkage studies

- Genetic association studies

- Genes representing diverse biological pathways

  ( synaptic function, regulation of transcript expression and epigenetic modification)
- Genes confer shared risk to a wide range of neurodevelopmental abnormalities and psychopathology



Talkowski, M. E., Minikel, E. V., & Gusella, J. F. (2014). Autism spectrum disorder genetics: diverse genes with diverse clinical outcomes. *Harvard review of psychiatry*, *22*(2), 65-75.

# Syndromic ASD

Some of the monogenic (syndromic) conditions associated with the ASD phenotype are

- Rett (RTT) syndrome (MECP2 gene; Amir et al.,1999),
- Fragile X syndrome (FXS, FMR1),
- Tuberous sclerosis (TSC1 and TSC2; Wiznitzer, 2004),
- Neurofibromatosis (NF1),
- Timothy syndrome (CACNA1; Splawski et al., ),
- Cortical dysplasia–focal epilepsy syndrom (CNTNAP2; Strauss et al., 2006).



# Copy Number Variation (CNV)

- De novo : 7-10% of simplex families
  2-3% of multiples families
  ~ 1%in non ASD controls



- Inherited  upto 50% of ASD subjects

# Loci identified with genome wide linkage analysis

Brain Research Bulletin 88 (2012) 543–552 http://dx.doi.org/10.1016/j.brainresbull.2012.05.017

| Chromosome | Loci | Candidate genes | Ref. |
|---|---|---|---|
| 1 | 1p34.2 | Regulating synaptic membrane exocytosis 3 (*RIMS3*) | Kumar et al. (2010) |
| 2 | 2q | | Buxbaum et al. (2001); Shao et al. (2002) |
| | 2q31–2q33 | *GAD1*, *STK17B*, *ABI2*, *CTLA4*, *CD28*, *NEUROD1*, *PDE1A*, *HOXD1*, *DLX2* | Rabionet et al. (2004) |
| | 2q31 | *SLC25A12* | Segurado et al. (2005) |
| | 2q24–2q33 | *SLC25A12*, *CMYA3* | Blasi et al. (2006a) |
| | 2q24–2q33 | *SLC25A12*, *STK39*, *ITGA4* | Ramoz et al. (2008) |
| | 2q34 | Neuropilin-2 (*NRP2*) | Wu et al. (2007) |
| 3 | 3q25–3q27 | HTR3C | Noor et al. (2010) |
| 5 | 5q31 | Paired-like homeodomain transcription factor 1 (*PITX1*) | Philippi et al. (2007) |
| | 5p14.1 | | Ma et al. (2009) |
| | 5p15 | *SEMA5A* | Weiss et al. (2009) |
| 6 | 6q | Abelson's helper integration 1 (*AHI1*) | Alvarez et al. (2008) |
| | 6q27 | | Weiss et al. (2009) |
| 7 | 7q22.1–7q31 | | Cukier et al. (2009) |
| | 7q31 | Laminin beta-1 (*LAMB1*), Neuronal cell adhesion molecule (*NRCAM*) | Sakurai et al. (2006); Hutcheson et al. (2004); Marui et al. (2009) |
| | 7q32 | NADH-ubiquinone oxidoreductase 1 alpha subcomplex 5 (*NDUFA5*) | Noor et al. (2010) |
| | 7q31–7q33 | Wingless-type MMTV integration site family member 2 (*WNT2*) | Marui et al. (2010) |
| 11 | 11p12–p13 | | Szatmari et al. (2007) |
| 12 | 12q14 | | Ma et al. (2007) |
| 15 | 15q11–q13 | Angelman syndrome gene (UBE3A) | Nurmi et al. (2001) |
| | 15q11–q13 | | Kim et al. (2008) |
| | 15q13 | Amyloid precursor protein-binding protein A2 (*APBA2*) | Sutcliffe et al. (2003) |
| 16 | 16p11–13 | 4-Aminobutyrate aminotransferase (*ABAT*), CREB-binding protein (*CREBBP*), glutamate receptor, ionotropic, NMDA 2A (*GRIN2A*) | Barnby et al. (2005) |
| | 16p11.2 | | Shinawi et al. (2010); Kumar et al. (2008, 2010) |
| 17 | 17q11.2 | | McCauley et al. (2005) |
| 19 | 19p13 | | McCauley et al. (2005) |
| 20 | 20q13 | | Weiss et al. (2009) |
| 22 | 22q13 | *SHANK3* | Qin et al. (2009) |
| X | Xp22.11 | *PTCHD1* | Noor et al. (2010) |

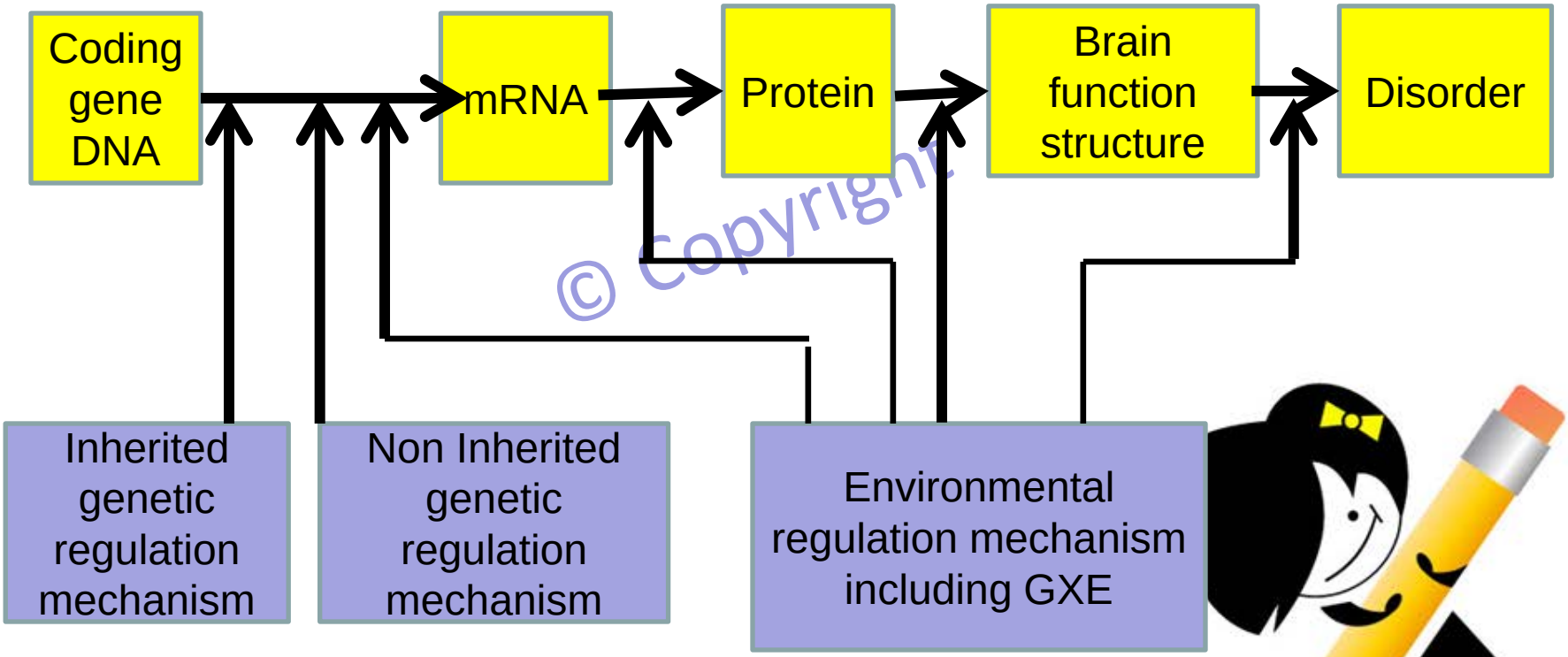
# Selected candidate genes

| Genes | Loci | Positive results | Negative/unconfirmed results |
|---|---|---|---|
| *REIN* | 7q22 | Li et al. (2008); Ashley-Koch et al. (2007); Dutta et al. | |
| *SLC6A4* | 17q | | 9); Ma et al. co et al. 6a); 2001); Betancur et al. |
| *GABR* | 15q | | estrini et al. |
| *NLGN* | 3q2 (*NL* | | lisaukko-oja et al. (2004); |
| | Xp22.3 (*NLGN4*), Yq11.2 (*NLGN4Y*) | et al. (2003) | Talebizadeh et al. (2004) |
| *OXTR* | 3p24–3p25 | Liu et al. (2010b); Gregory et al. (2009); Lerer et al. (2008); Jacob et al. (2007); Wu et al. (2005b) | |
| *MET* | 7q31.2 | Campbell et al. (2006, 2008, 2010); Jackson et al. (2009); Sousa et al. (2009) | |
| *SLC25A12* | 2q31 | Turunen et al. (2008); Silverman et al. (2008); Segurado et al. (2005); Ramoz et al. (2004) | Chien et al. (2010); Rabionet et al. (2006); Blasi et al. (2006a) |
| *GluR6* | 6q21 | Kim et al. (2007); Shuang et al. (2004); Jamain et al. (2002) | Dutta et al. (2007b) |
| *CNTNAP2* | 7q35 | Poot et al. (2010); Arking et al. (2008); Alarcon et al. (2008); Bakkaloglu et al. (2008); Rossi et al. (2008); Strauss et al. (2006) | |
| *GLO1* | 6p21.3–6p21.2 | Sacco et al. (2007); Junaid et al. (2004) | Wu et al. (2008); Rehnstrom et al. (2008) |
| *TPH2* | 12q21.1 | Coon et al. (2005) | Sacco et al. (2007); Ramoz et al. (2006b) |

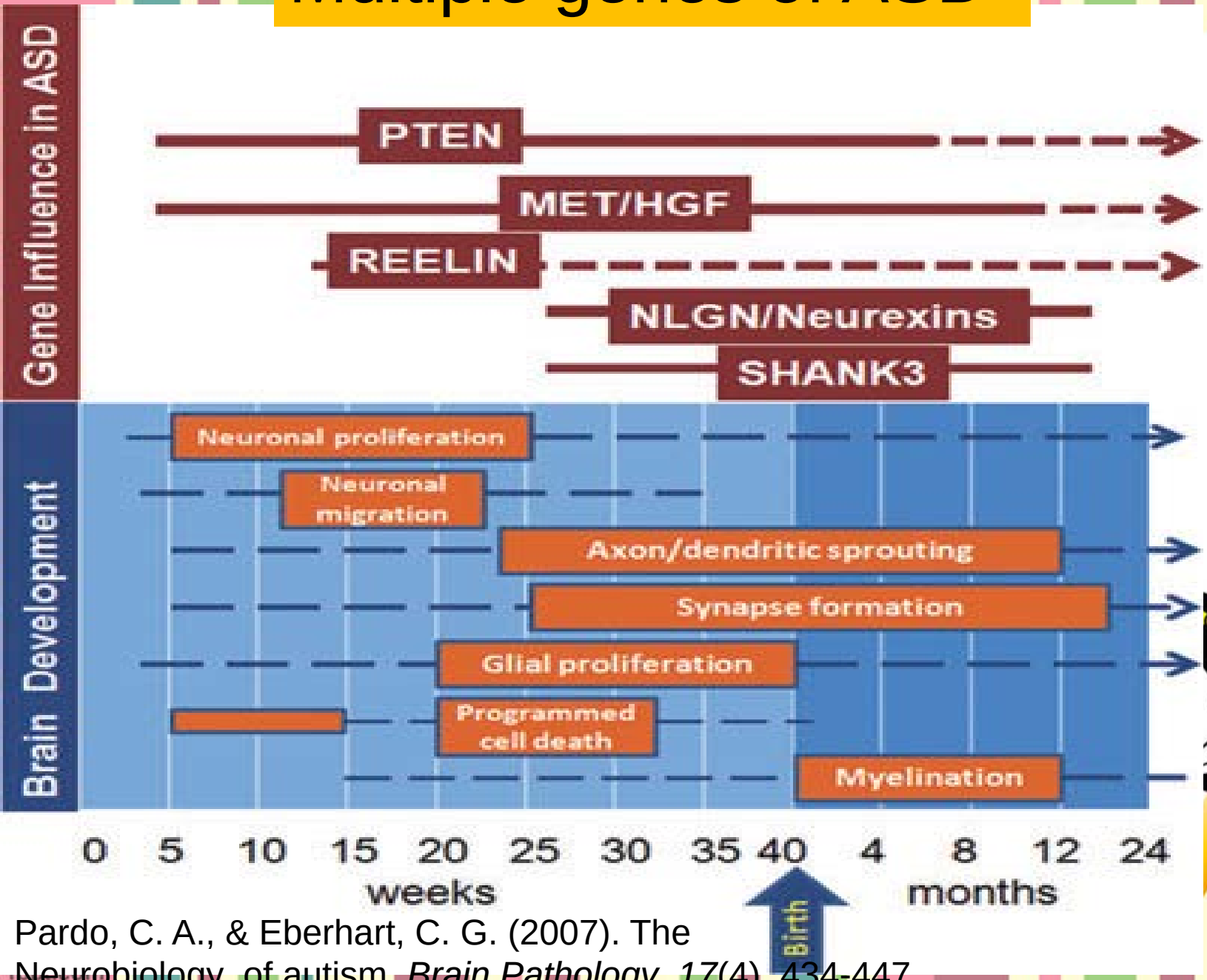
Neurogenesis
Neuronal migration
Synaptogenesis
axon pathfinding
Neuronal/glial structure regionalization


Brain Research Bulletin 88 (2012) 543–552 http://dx.doi.org/10.1016/j.brainresbull.2012.05.017

# How genes and environment work together



# Multiple genes of ASD




Pardo, C. A., & Eberhart, C. G. (2007). The Neurobiology of autism. *Brain Pathology*, *17*(4), 434-447.

# Proteins in The Brain

- Neuroligin-1: Protein “bridges” that allow excitatory connections between neurons.
- Neuroligin-2: Protein “bridges” that allow inhibitory connections between neurons.
- An abnormality in either produces symptoms specific to autism.
- Large study showed mutations in
- SCN2A gene among those with autism
- SCN2A controls production of neuroligins!



# More Evidence

- High rates of mutations/SNPs* or triplet* repeats in RELN gene (chromosome 7q22).
- RELN gene controls production of Reelin protein.
- Reelin protein abnormalities cause structural and cognitive deficits.
- **Genes control the production of Proteins!



*SNP – single nucleotide polymorphism (a type of mutation in a DNA sequence)

- *A triplet refers to three nucleotides in a row – a code for a specific amino acid. Proteins are built with amino acids.

# Proteomics

- The large-scale study of proteins, particularly their structures and functions.
- Proteomics facilitates potentially being ‘‘closer’’ to the underlying pathophysiological processes.
- By using proteomic tools, it is possible to identify quantitative and qualitative

  protein patterns in order to establish

  specific diagnostic and prognostic biomarkers.



# Environmental

- California twin study
- Results indicated that ASD was 55% attributable to the environmental factors shared by twins, a much greater percentage than predicted by earlier twin studies




- Tchaconas, A., & Adesman, A. (2013). Autism spectrum diso[illegible]pediatric overview and update. *Current opinion in pediatrics*, *25*(1), 130-[illegible]


# Prenatal

- advanced paternal and maternal age at birth
- gestational diabetes, gestational bleeding
- multiple birth, being first born compared to being third or after
- parental immigration, especially maternal immigration but also paternal immigration, is a risk factor for ASD
- *in utero* exposure to two known teratogenic medications thalidomide and valproate, abortifactant misoprostol
- ? In vitro fertilisation



# Perinatal

- prematurity
- abnormal presentation in general and breech presentation in particular
- planned cesarean section



# Postnatal

- Conditions potentially related to hypoxia,

umbilical-cord complications,

low 5-min Apgar score, being SGA, low birth weight,

fetal distress, meconium aspiration,

birth injury or trauma,

summer birth,

feeding difficulties,

neonatal anemia, ABO /Rh incompatibility,

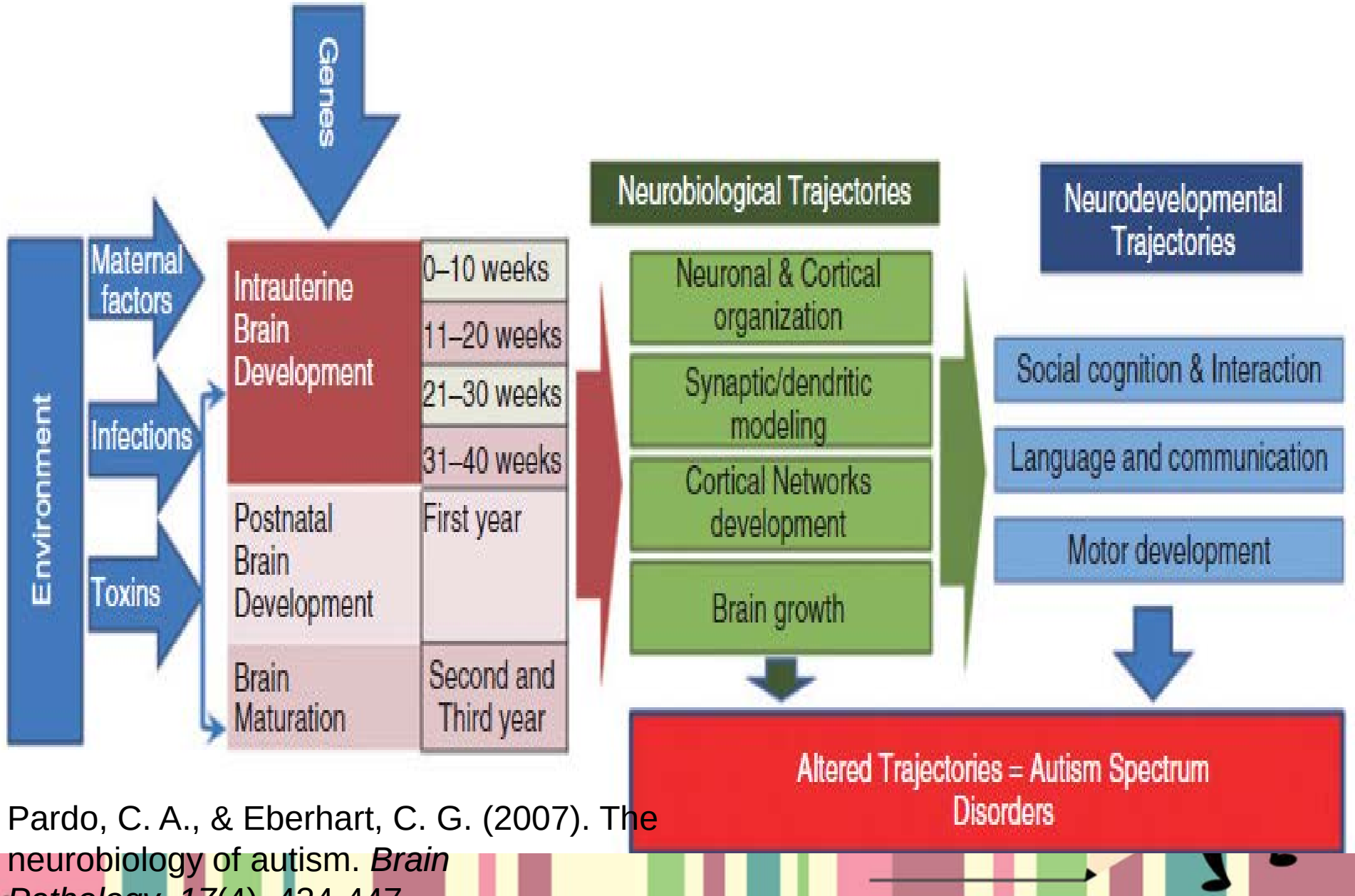
hyperbilirubinemia

were significantly($P$ <0.05) associated with autis



- Air pollution
- Maternal depression (pre and postnatal)
- Use of SSRI






Pardo, C. A., & Eberhart, C. G. (2007). The neurobiology of autism. *Brain Pathology*, *17*(4), 434-447.

# Epigenetics

- The term refers to heritable changes in gene expression that does not involve changes to the underlying DNA sequence
- a change in phenotype without a change in genotype.
- Epigenetic change is a regular and natural occurrence but can also be influenced by several factors including age, the environment/lifestyle, and disease state.



# Life span=long movie

cells= actors and actresses (essential units of movie)


DNA= script (instructions for all the participants of the movie to perform their roles)



DNA sequence = words on the script

Genes = certain blocks of these words that instruct key actions or events to take place

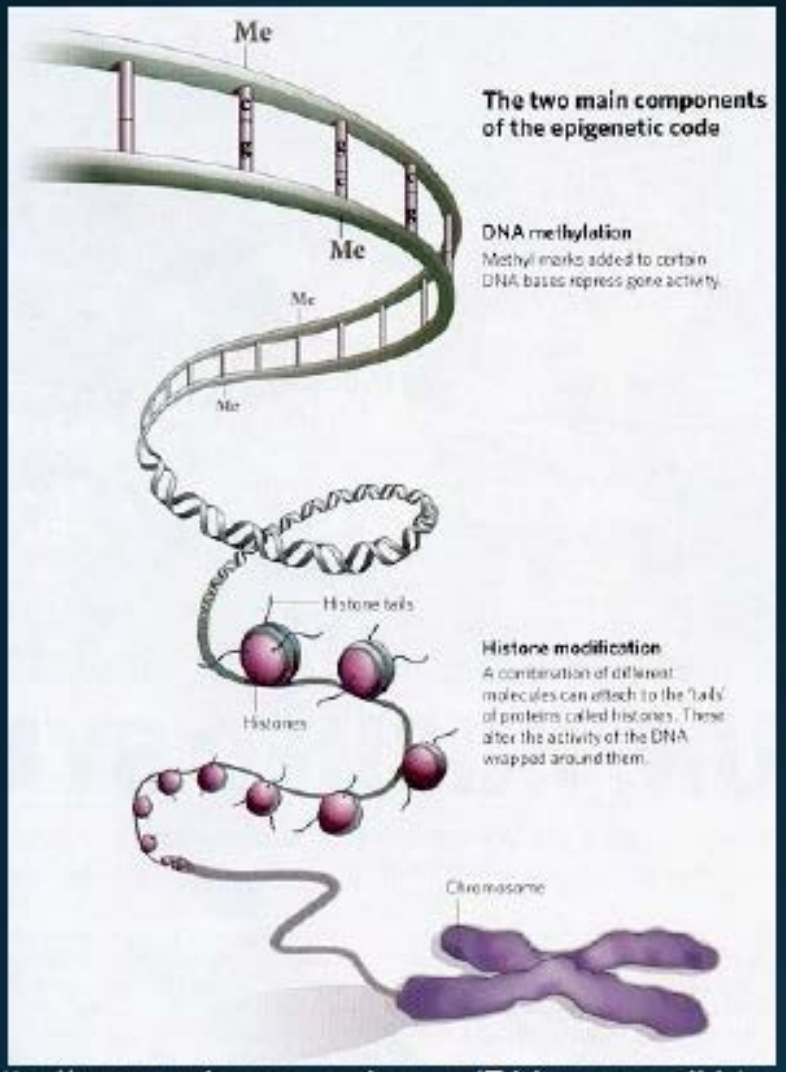
Genetics = Screenwriting

Epigenetics = Directing

# Mechanisms

- DNA Methylation
  - addition of methyl groups to DNA at CpG sites
- Chromatin/Histone modifications
  - Addition and removal of acetyl groups from DNA

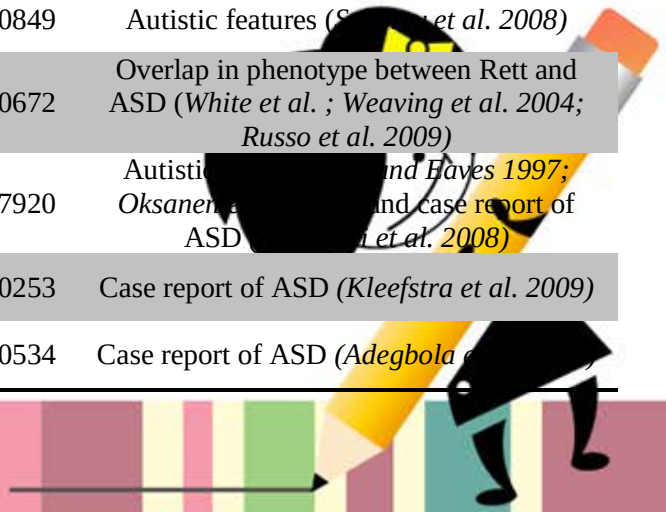
Epigenetic Mechanisms




http://www.universe-review.ca/F11-monocell.htm

# Genetic syndromes co-morbid with ASD and idiopathic ASD are caused by mutations in genes involved in epigenetic regulation

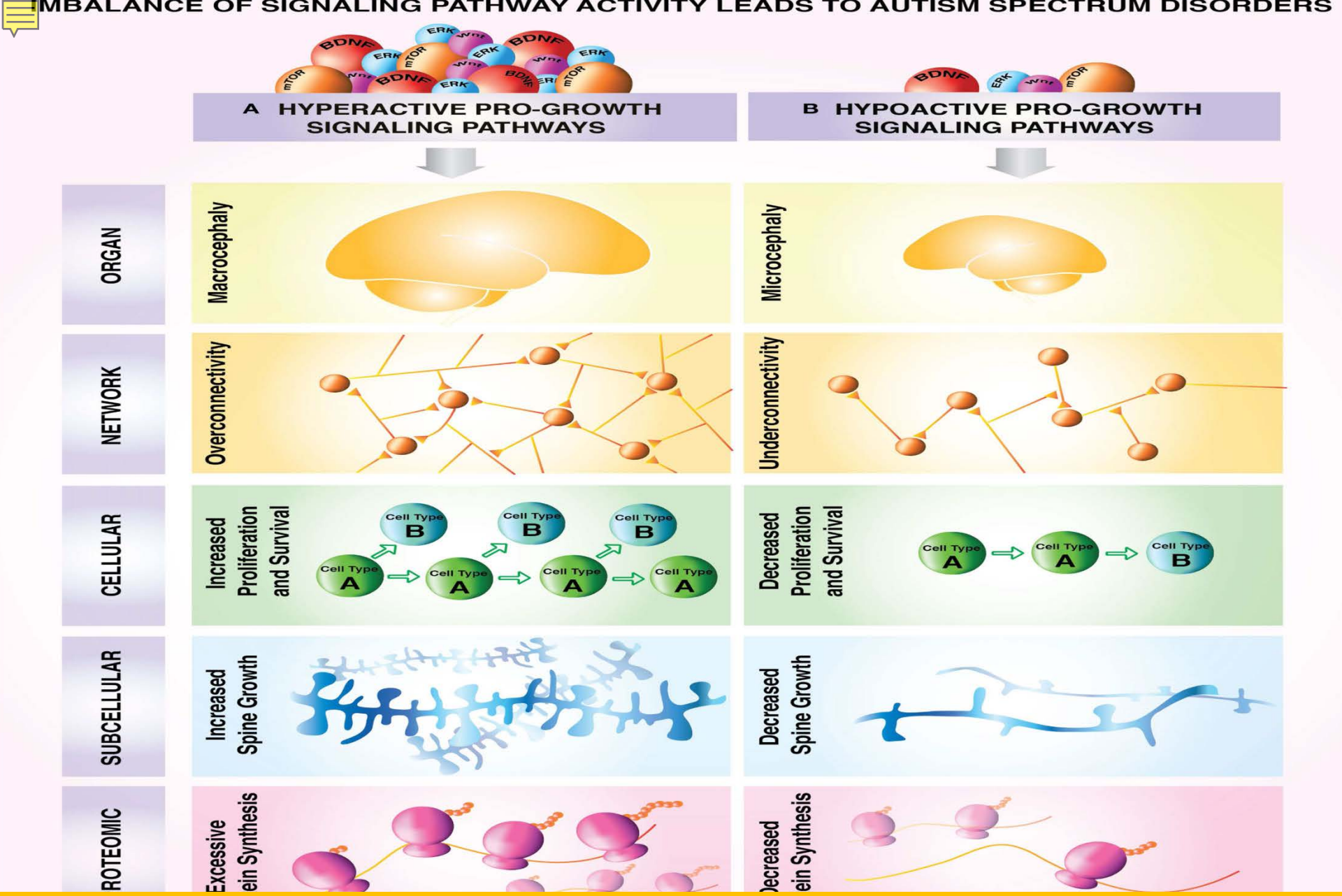
| Gene | Function | Locus | Disorder | OMIM | Autism/autistic features |
|---|---|---|---|---|---|
| ***CHD7*** | ATPase/Helicase-Chromatin remodeler | 8q12 | CHARGE syndrome | 214800 | 15-50% risk of ASD *(Hartshorne et al. 2005; Smith et al. 2005; Johansson et al. 2006)* |
| ***CHD8*** | ATPase/Helicase-Chromatin remodeler | 14q11.2 | ASD | 610528 | One of the most frequent recurrent *de novo* mutations found in idiopathic ASD by exome sequencing: 5 mutations/1144 cases *(Neale et al. 2012; O'Roak et al. 2012)* |
| ***NSD1*** | H3K36 methyltransferase | 5q35 | Sotos syndrome | 117550 | Autistic features *(Rutter and Cole 1991; Mouridsen and Hansen 2002; Sarimski 2003; Ball et al. 2005)* +Case reports of ASD *(Morrow et al. 1990; Zapella 1990; Trad et al. 1991; Mouridsen and Hansen 2002)* |
| ***CREBBP, EP300*** | Histone acetyltransferase | 16p13 | Rubinstein-Taybi syndrome | 180849 | Autistic features (S et al. 2008) |
| ***MECP2*** | Methyl binding protein | Xq28 | Rett syndrome | 300672 | Overlap in phenotype between Rett and ASD (*White et al. ; Weaving et al. 2004; Russo et al. 2009)* |
| ***MLL2*** | H3K4 methyltransferase | 12q13.12 | Kabuki syndrome | 147920 | Autisti nd Eaves 1997; Oksanen nd case report of ASD et al. 2008) |
| ***EHMT1*** | H3K9 methyltransferase | 9q34 | 9q subtelomeric deletion syndrome | 610253 | Case report of ASD *(Kleefstra et al. 2009)* |
| ***KDM5C*** | H4K4 demethylase | Xp11 | Intellectual disability | 300534 | Case report of ASD *(Adegbola* |



# Neurotransmitters and neuromodulators

- 25-50% elevated serotonin
- Dopamine, norepinephrine, acetylcholine, oxytocin, opiods, cortisol, glutamate, GABA
- OT and AVP






Subramanian, M., Timmerman, C. K., Schwartz, J. L., Pham, D. L., & Meffert, M. K. (2015). Characterizing autism spectrum disorders by key biochemical pathways. *Frontiers in neuroscience*, *9*.

# Autism and The Brain

| Areas of Possible Difficulty | Functions |
| --- | --- |
| Prefrontal Cerebral Cortex | Social thinking |
| Hypothalamus | Attachment behaviors<br>emotional learning |
| Fusiform Gyrus | Face recognition |
| Middle Temporal Gyrus | Recognition facial<br>Expression |
| Pulvinar | Emotional re[illegible]ce |



# Cognitive and emotional processes

- Theory of Mind
- Weak central coherence
- Executive dysfunction
- Enhanced perceptual functioning



Refrigerator mother to proteomics

Parenting matters
As do genes!!

# Clinical guidelines

**All children with ASD**

1. Three generation family history

2. Detailed physical examination to identify known syndromes

3. Chromosomal Microarray Oligonucleotide Array-Comparative Hybridization
OR
Single-Nucleotide Polymorphism Microarray

**Specific testing**

**MALES:** DNA testing for Fragile X

**FEMALES:** MECP2 sequencing

**MACROCEPHALY** (>2.5 SD's above the mean): PTEN gene sequence analysis

**Genetic counseling for all families**

**Negative Test (no etiology identified):**
Counseling about recurrence risk (up to 20% based on infant sib studies)

**Positive Test (etiology identified):**
Counseling about specific mutations and associated clinical features, including comorbidities, treatment, prognosis

Baker, E., & Jeste, S. S. (2015). Diagnosis and Management of Autism Spectrum Disorder in the Era of Genomics: Rare Disorders Can Pave the Way for Targeted Treatments. *Pediatric Clinics of North America*.

# Medical work up for ASD

- Genetic testing: indicated for all individuals with ASD
- Metabolic testing: not indicated routinely, consider if multisystem involvement (cardiac,hepatic, renal), lactic acidosis, severe anemia
- MRI: perform if focal neurologic examination, macrocephaly, genetic syndromes associated with structural brain abnormalities
- EEG: perform for episodes concerning for seizure, language regression, specific genetic syndromes associated with epilepsy
- Polysomnograph: May be useful for diagnosing treatable sleep disorders (insomnia) and for diagnosing nocturnal seizures.

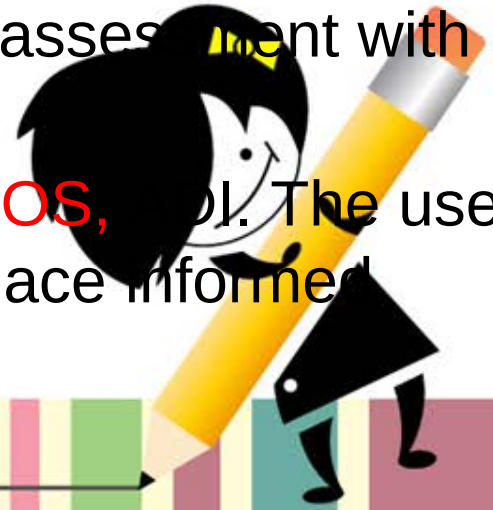


Baker, E., & Jeste, S. S. (2015). Diagnosis and Management of Autism Spectrum Disorder
Era of Genomics: Rare Disorders Can Pave the Way for Targeted Treatments. *Pediatric C*
*North America*.

# Screening and Diagnosis

- Current AACAP recommendations
  - ASD surveillance at all developmental & psychiatric assessments of children
  - ASD specific screening (e.g., M-CHAT) at 18 and 24 month visits or when surveillance raises concern
- If the screening indicates significant ASD symptomatology a thorough diagnostic evaluation is essential
- Evaluation should include multi-disciplinary assessment with the clinician coordinating it
- Diagnostic instruments commonly used: ADOS, DISCO. The use of such instruments supplement but not replace informed clinical judgement





# Next steps

- **Psychiatric Assessment**
  1. Clinical – Diagnosis / Comorbidity
  2. Scales

     - Modified Checklist for Autism in Toddlers (M-CHAT)
     - Childhood Autism Rating Scale (CARS)
     - Indian Scale for Assessment of Autism (ISAA)



- **Pediatric Assessment**

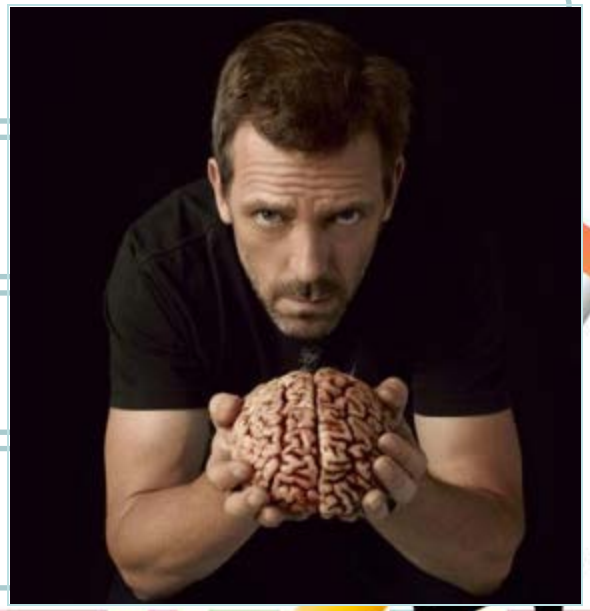
- **Assessment of Abilities**
  - ABLLS - R

- **Assessment of Speech & Language**

- **Assessment of Sensory Issues**

# Differential Diagnosis


- Significant cognitive impairment 25-50
- Developmental language disorder
- Childhood schizophrenia
- Anxiety disorders
- ADHD with social immaturity
- Affective disorders



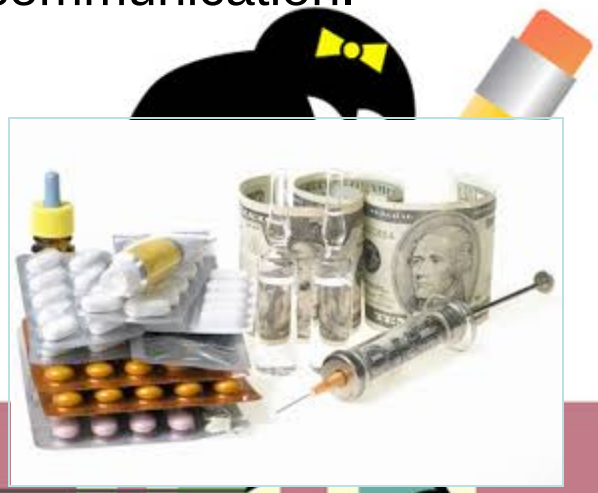
# Differential Diagnosis


- Child neglect/abuse
- Sensory impairment
- Epileptic encephalopathy
- Motor mannerisms
- Schizoid personality disorder
- Dementia/degenerative disorder

# Treatment

- Treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches.
- Treatment options vary by age and developmental status.
- Chronic management is often required to maximize functional independence and quality of life by:
  - Minimizing core deficits in social skills and communication.
  - Facilitating development and learning.
  - Promoting socialization.
  - Reducing maladaptive behaviors.
  - Educating and supporting families.





# Medication Indications

- Unresponsive to nonpharmacological intervention
- Behavior has a negative impact on function
- Medication-responsive problem
- Benefits outweigh potential side effects
- Understanding it is symptomatic treatment, not a cure
- Not a substitute for appropriate educational and behavioral programming

# Pharmacotherapy Statistic

- 56% of children with ASD are prescribed at least one psychoactive medication per year, and 20% of those children use three or more concurrent psychoactive medications (national Medicaid data in 2001)



- Approximately 70% of children diagnosed with ASD between the ages of 8-21 years receive at least one psychoactive medication annually (national insurance company data in 2002)

# Types of Medication

- Antipsychotics (Typical and Atypical)
- Stimulants
- Antidepressants & Selective Serotonin Reuptake Inhibitors (SSRIs)
- Mood Stabilizers & Anticonvulsants
- Anti-anxiety and Benzodiazepines
- Sleep Medications

# Research

- Published reports & Open label clinical trials >> RCTs
- Treatment to target problem behaviors & level of impairment
- No single medication alleviates symptoms in all domains



*Maudsley Prescribing Gui Ed. 11*

# Focus

1. Social & Communication Impairment

2. Restricted Repetitive Behaviors & Interests

3. Comorbidity

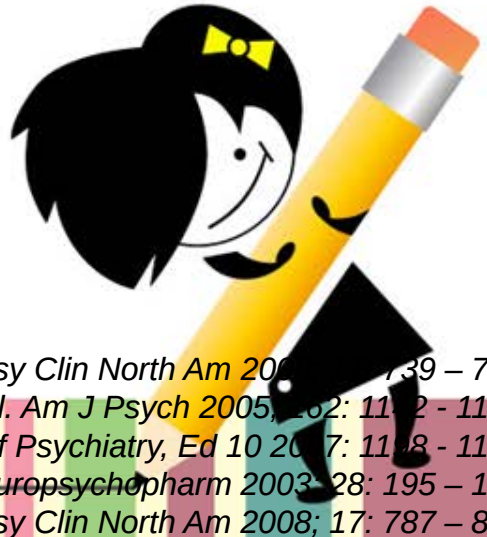
   - Hyperactivity
   - Irritability
   - Sleep



# Social & Communication Impairment

- No treatment consistently proven
- Risperidone has secondary effect through improvement in irritability [1,2]
- Aripiprazole
- Other SDAs [5,]
- Glutamatergic drugs – Amantadine, Lamotrigine [3]
- Tetrahydrobiopterin [3]
- Oxytocin [4]






1. Stigler K A, McDougle C J. Child & Adolesc Psy Clin North Am 200[illegible] 739 – 752
2. McDougle C J et al. Am J Psych 2005; 162: 11[illegible]2 - 1148
3. Synopsis of Psychiatry, Ed 10 20[illegible]7: 11[illegible]8 - 1199
4. Hollander E et al. Neuropsychopharm 2003; 28: 195 – 198
5. Posey D J et al. Child & Adolesc Psy Clin North Am 2008; 17: 787 – 801

# Restricted Repetitive Behaviors & Interests

- SSRIs [1, 2, 3]
  - Very few RCTs
  - All molecules have been tried
  - Increase activation – agitation
  - Increase in Suicidal behavior & Hostility
  - Hyponatremia
  - Benefits inconsistent
  - Optimal dose uncertain



- SDAs [4] / Anticonvulsants [1] / Oxytocin [1]

- Risperidone – associated irritability / aggression may reduce core repetitive behaviours [5, 6, 7]


1. Soorya L et al. Child Adolesc Psy Clin North Am 2008; 17 [illegible]53 – 771.
2. Buschbaum M S et al. Int J Neuropsychopharm 2001 [illegible] – 125.
3. McDougle C J et al. Arch Gen Psych 1996; 5[illegible] – 1008.
4. Hollander E et al. J Child Adol Psychopharm 2006; 16: 541 – 548.
5. McDougle C J et al. A J P2005; 162:1142-48
6. McCracken T J et al. N E J M 2002; 347:314-21
7. Arnold L E et al. J A A C A P 2003; 42:1443-50

# Comorbidity

- Frequent
- Troublesome
- Interferes with other therapies
- Needs to be addressed [1]



*1. Simionoff E et al. J Am Acad Child Adolesc Psychiatry 2008; 47: 921 - 929.*

# 1. Hyperactivity / ADHD

- Methylphenidate [1, 2]
  - highly variable responses
  - low initial doses : 0.125 mg / kg tid, small increments
  - side effects may be problematic
  - positive benefits [6]

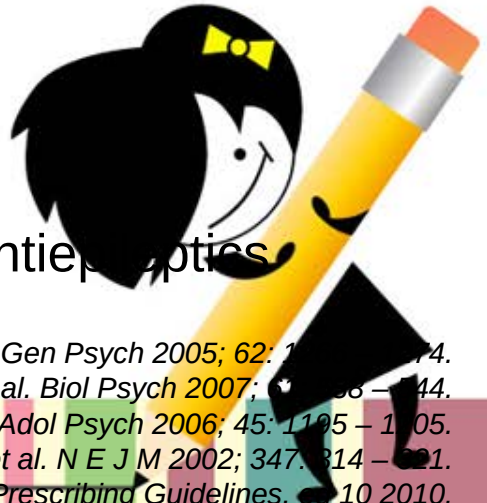
- Atomoxetine [3] only preliminary evidence

- Risperidone [4], aripiprazole

- Alpha 2 agonists (Clonidine / Guanfacine) [5]

- Little or no evidence [5] - SSRIs, Venlafaxine, BDZs, Antiepileptics






1. RUPP Autism Network. Arch Gen Psych 2005; 62: 1[illegible]74.
2. Posey D J et al. Biol Psych 2007; [illegible]44.
3. Arnold L E et al. J Am Acad Child Adol Psych 2006; 45: 1196 – 1205.
4. McCracken J T et al. N E J M 2002; 347: 314 – [illegible]21.
5. Maudsley Prescribing Guidelines, 10 2010.
6. Santosh P J et al. Child Care Health Dev 2006; 32:575-83

# 2. Irritability – Aggression

Includes **Self Injurious Behaviors & Tantrums**

- SDAs [1]: First line

  a. **Risperidone** FDA approved [2]

  b. **Aripiprazole** [4] FDA approved

  **c. Olanzepine**

**Mood Stabilizers / Anticonvulsants not as effective as SDAs 3**

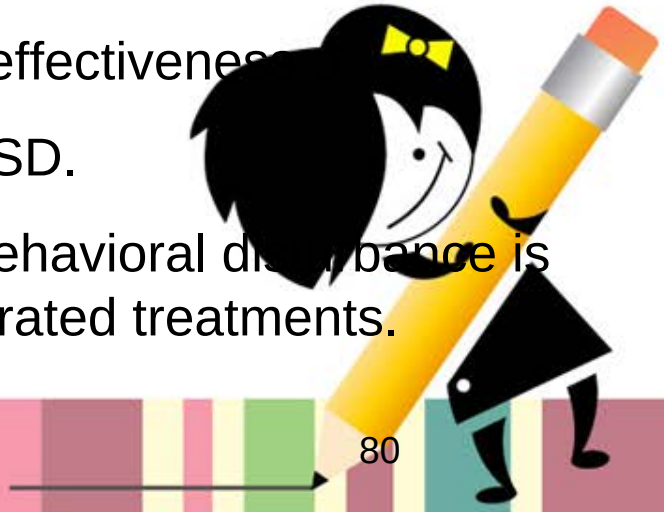



1. McDougle C J et al. J Clin Psych 2008; 69 Suppl 4: 15 – 20.
2. Stigler K A, McDougle C J. Child Adolesc Psych Clin North Am 2008; 17: 739 – 752.
3. Maudsley Prescribing Guidelines, ed 11 2012
4. 4. Douglas – Hall P et al. J CNS Dis 2011; 3:1-11
5. .

# Behaviour Disturbance Management

- Serious behavioral disturbance (irritability) involving severe tantrums, aggression, and self-injury frequent in ASD.
- A multimodal approach
- Individuals with mild irritability may benefit from treatment with an $\alpha_2$ adrenergic agonist.
- Risperidone and aripiprazole are the only two FDA–approved atypical antipsychotics medications for irritability in children and adolescents with autism.
- Evidence to date has been mixed regarding the effectiveness of other pharmacologic agents for irritability in ASD.
- Research into the pharmacotherapy of serious behavioral disturbance is needed to develop more effective and better tolerated treatments.







Child Adolesc Psychiatr Clin N Am. 2014 Jan;23(1):73-82

# 3. Sleep Issues

Onset / Maintenance / Terminal Insomnia /
Irregular Sleep – Wake Cycles

- Melatonin [1]



No seizure precipitation

- Risperidone

- Benzodiazepines [2] - Anxious child


1. *Andersen I M et al. J Child Neurol 2008; 23: 482 – 485.*
2. *Maudsley Prescribing Guidelines, ed 11 2012.*

# Table 2. Summary of Pharmacologic Treatment Options

| Generic (Brand) | FDA-Approved Indication | Dosing | Adverse Effects |
|---|---|---|---|
| Aripiprazole (Abilify) | Treatment of irritability associated with autistic disorder in patients 6-17 y | *Initial dose*: 2 mg/day<br>*Titration*: Increase to 5 mg after first 7 days of therapy. May further increase by 5-mg increments every 7 days to a max dose of 15 mg/day | Sedation, fatigue, increased appetite, headache, extrapyramidal symptoms, weight gain |
| Risperidone (Risperdal) | Treatment of irritability associated with autistic disorder in children and adolescents 5-16 y | **<20 kg**<br>*Initial dose*: 0.25 mg/day<br>*Titration*: May increase dose to 0.5 mg/day after first 4 days of therapy. After 14 days at 0.5 mg/day, may further increase by 0.25 mg/day at 2-wk intervals<br>**≥20 kg**<br>*Initial dose*: 0.5 mg/day<br>*Titration*: May increase dose to 1 mg/day after first 4 days of therapy. After 14 days at 1 mg/day, may further increase by 0.5 mg/day at 2-wk intervals | Increased appetite, nasal congestion, fatigue, vomiting, weight gain, QT prolongation, drooling, constipation, xerostomia |

*max: maximum. Source: References 37, 38.*

# Fluoxetine Dosing

- 2.5 mg / day for week 1
- 0.3 mg / kg / day for week 2
- 0.5 mg / kg / day for week 3
- 0.8 mg / kg / day  subsequently

**Max: 0.8 mg / kg / day**



# What does Cochrane Library have to say ?

1. No evidence of effect of **SSRIs** in children and emerging evidence of harm.

*Williams K et al. Cochrane Developmental, Psychosocial and Learning Problems Group. Published Online: 20 AUG 2013*

2. Benefits of **Risperidone** in irritability, repetition and social withdrawal.



*Jesner O S et al. Cochrane Developmental, Psychosocial and Learning Problems Group. Published Online: 24 JAN 2007*

3. With **Aripiprazole**, children showed less irritabil… hyperactivity, and stereotypies. Notable side effec…e weight gain, sedation, drooling, and tremor.

*Ching H. Cochrane Developmental, Psychosocial and Learning Problems Group. Published Online: 16 MAY…*

4. Clinicians considering the use of **TCAs** need to be aware of the limited and conflicting evidence of effect and the side effect profile.

*Hurwitz R et al. Cochrane Developmental, Psychosocial and Learning Problems Group. Published Online: 14 MAR 2012*



5. There is no evidence that single or multiple dose intravenous **Secretin** is effective. Not recommended as a treatment for ASD.

*Williams K et al. Cochrane Developmental, Psychosocial and Learning Problems Group. Pu[illegible]: 18 MAR 2012*

- Applied Behavior Analysis
- Special Education
- Occupational Therapy
- Speech & Communication Therapy



# Principles

- Early Intervention
- Intense intervention
- Low Child – Therapist Ratio
- Parental Involvement
- Peer Interaction
- Structure
- Reappraisal



# Screening

- No big smiles or other warm, joyful expressions by six months or thereafter
- No back-and-forth sharing of sounds, smiles, or other facial expressions by nine months or thereafter
- By 13 months no back-and-forth gestures, such as pointing, showing, reaching, or waving bye
- Not answering to one's name when called
- No babbling – mama, dada, baba
- No single words, no simple pretend play by 18 months



- No two-word meaningful phrases (without imitating or repeating) or lack of interest in other children by 24 months
- **Any loss of speech or babbling or social skills**
- **Regression at any age is cause for immediate referral**



# Longitudinal outcome

- 15% of DSM IV did not meet criteria on follow up
- <5%-25% have a very good outcome
- Usually improvement with age
- Having higher IQ and speech by 5years is a predictor for improvement
- Transition troubles



1. Mass collection of DNA
2. Compare cases and controls to identify ASD associated variants
3. Identify relevant detective proteins
4. Perform large scale screening in ASD patients
5. Create models of defective variant proteins
6. Develop clinical trials based on target interventions
7. Generate new target treatments



Connolly, J. J., & Hakonarson, H. (2014). Etiology of autism spectrum disorders: A genomics perspective. *Current psychiatry reports*, *16*(11), 1-9.

**ASD treatment**

# Thank You