Molecular Basis of Autism Spectrum Disorders

Carla Vila de la Puente

Biomedical Science Degree, 2013

Universitat Autònoma de Barcelona

Introduction

- Leo Kanner in 1943 identifies four main characteristics of Autism:
  - Inability to relate well with people.
  - Serious difficulties in communication and language development.
  - Persistent insistence on sameness.
  - Early onset of the disorder, which is evident in the first three years of life.

- According to DMS-V, ASD is a group of 4 developmental disorders with symptoms that are seen on a continuum ranging from mild to severe expression.

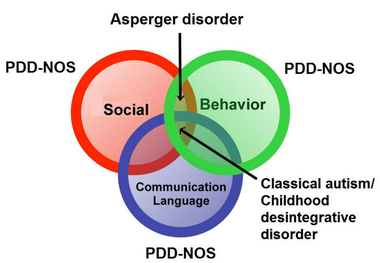

Figure 1. ASD main characteristics (Adapted from http://parentinghealthybabies.com/autism-spectrum-discorder-asd-in-children/).

- Heterogeneous as notable for its variability as for its features.
- Thirty years ago autism was very rare (4 of 10.000) but today ASD prevalence range is at about 0.6%-0.8% in preschool children and 1% in school children and adults.

Objectives

- Provide an overview of the main characteristics of ASD.
- Emphasize in the genetic alterations and their pathways related to ASD fisiopathology.

Methodology

First search of books, official websites, and Pubmed database reviews to get the basic principles. After that, Pubmed database original articles and important reviews were selected based on the journal impact and the date of publication.

ASD biomarkers

- Hyperserotonemia.
- Immune system dysfunction.
- Decreased GABA receptor → Increased ratio of excitation to inhibition.
- Abnormal rate of symmetric brain growth.
- Altered brain region size (amygdale, striatal nucleus).
- Mitochondrial dysfunction.
- Structural abnormalities in the “social brain”:

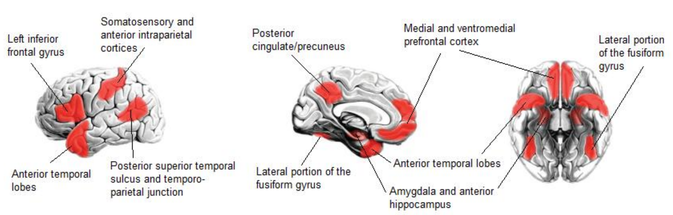

Figure 2. Areas of the “social brain” (Adapted from Gotts *et al*., 2012)

Etiology

- ASD is a complex human genetic disorder that involves interactions between genes and environment:

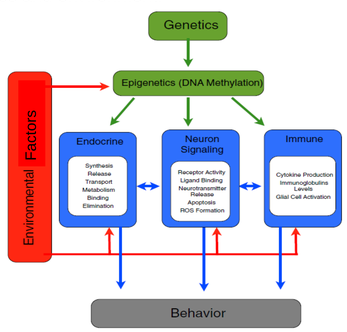

Figure 3. Complexity of gene and environment interactions in ASD (Adapted from Schwartzer *et al*., 2012)

- Principal genes associated with high for ASD (susceptibility genes):

Table 1. Genes associated with ASD (Adapted from Toro *et al*., 2010).

Genes	Chromosome	Function	Evidence
FMR1	Xq27	Synaptic translation	Mutations
MECP2	Xq26	Chromatin remodeling	CNV, mutations
TSC1	9q24.13	mTOR/PI3K pathway	CNV, mutations
TSC2	16p13.3	mTOR/PI3K pathway	CNV, mutations
NF1	17q11.2	mTOR/PI3K pathway	CNV, mutations
PTEN	10q23.31	mTOR/PI3K pathway	CNV, mutations
RFWD2	1q25.2-q25.2	Ubiquitination	CNV
NRXN1	2p16.3	Synaptic CAM	CNV, mutations, SNP
CNTN4	3p26.3	Synaptic CAM	CNV
MEF2C	5q14.3	Transcription factor	CNV, mutations
SYNGAP1	6p21.3	Synaptic Ras GAP	CNV
CNTNAP2	7q35-7q36.1	Synaptic CAM	CNV, rare variants[a]
UBE3A	15q11-q13	Ubiquitination	CNV
SHANK3	22q13	Synaptic scaffold	CNV, mutations
NLGN3	Xq13.1	Synaptic CAM	Mutation
NLGN4	Xp22	Synaptic CAM	CNV, mutations
GRIA3	Xp25	Synaptic receptor	CNV
SEMA5A	5p15.2	Axonal guidance	SNP
MET	7q31.2	Tyrosin kinase	SNP
PARK2	6q26	Ubiquitination	CNV
FBXO40	3q13.3	Unknown function	CNV

- Environmental factors examples: pesticides, air pollution, drugs, paternal age, maternal nutritional status, etc.

Conclusions

- Impaired neuronal network connectivity strongly indicates the basis of behavioral and cognitive abnormalities in ASD.
- It is clear that ASD has a strong genetic component.
- None of the current treatments are based upon a specific understanding of the causes of ASD.

- **FUTURE CHALLENGE**: determine the signaling pathways in which disease risk genes function, in order to translate this knowledge into mechanism-based therapeutics.

Physiopathology

- Neurobiological basis of ASD: altered patterns of neural connectivity → reduced long-range functional connectivity in the cortex and enhanced local connectivity in multiple brain regions.

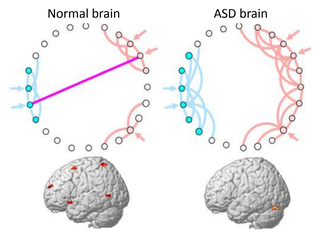

Figure 4. Potential effects of network connectivity patterns on brain activation (Adapted from Belmonte *et al*., 2004).

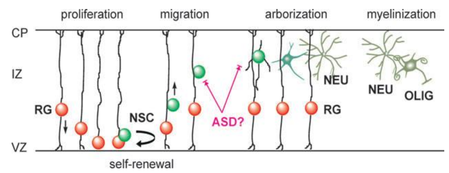

Figure 5. Steps for the generation of new (cortical) neurons (Adapted from Maurer *et al*., 2012).

- Changes in ASD connectivity could be due to:

1. Dendrite spine growth

2. Synapse formation and stabilization

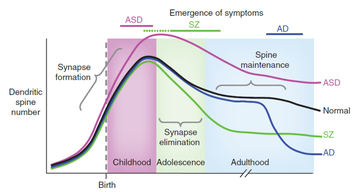

Figure 6. Lifetime trajectory of dendritic spine number in ASD (pink) (Adapted from Penzes *et al*., 2011).

2.1. Synaptic adhesion proteins

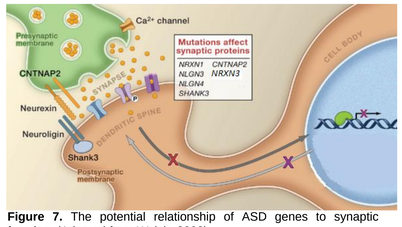

Figure 7. The potential relationship of ASD genes to synaptic function. (Adapted from Walsh, 2008).

2.2. mTOR/PI3K pathway → *TSC1/TSC2, NF1 and PTEN*

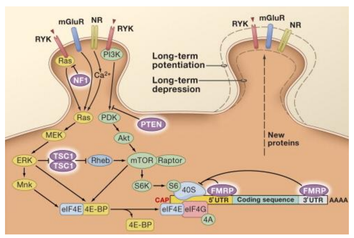

Figure 8. The MET and mTOR/PI3K pathway, and genes implicated in ASD risk (Adapted from Kelleher and Bear, 2008).

2.3. Ubiquitination → UBE3A

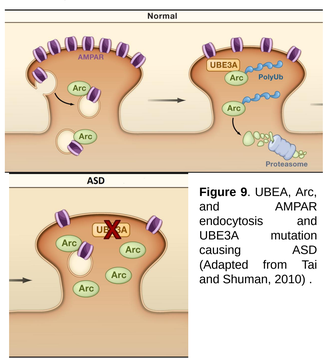

Figure 9. UBEA, Arc, and AMPAR endocytosis and UBE3A mutation causing ASD (Adapted from Tai and Shuman, 2010) .

2.4. Abnormal level of transcription regulatory proteins → *MECP2* and *FMR1*

Current treatment

- The principal treatments for ASD now a days, are based on behavioral interventions → ABA.
- A wide variety of potential interventions for ASD have been championed, but few have been subjected to the rigors of controlled clinical trials.
- Data shows all this available treatments for ASDs have an inconsistent efficacy.