Autism: Genes and Neurobiology, OH MY!!

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Review of 2015

- Autism: Facts, Myths, What to do After Diagnosis
  - History of autism
  - DSM-V changes from DSM-IV
  - Known risk factors
  - Parts of the brain affected by autism
  - Facts
  - Myths
  - Local resources
Today’s Presentation

- What is autism?
  - DSM-V
- Genetics
- Associated disorders
- Neurotoxins
- Brain anatomy and autism
- Neurochemical differences
- Neurologic differences
What is Autism?

DSM-V
Autism Linkages and Associations

- Perhaps the most “genetic” of behavioral disorders
- 1,000 risk genes associated with autism
  - Not causal
- 10 – 25% associated with a medical condition
- 20 syndromes can present as autism
  - Phenotype overlap can cause over-diagnosis of autism
- Chromosomal event 15%
  - 20 of 23 chromosomes have regions that may be important for autism
  - Chromosomes 2, 7, 15, 22
  - Sex chromosomes
Associated Disorders and Dendritic Spines

- Fragile X
- Tuberous sclerosis
- Angelman syndrome
- Landau Kleffner
- Prader-Willi syndrome
- Tardive dyskinesia
- Rett syndrome
- Williams syndrome (7q)
- Untreated PKU
Parts of the Brain Affected by Autism

Cerebral Cortex:
A thin layer of gray matter on the surface of the cerebral hemispheres. Two thirds of this area is deep in the tissues and folds. This area of the brain is responsible for higher mental functions, general movement, perception and behavior reactions.

Basal Ganglia:
This is gray masses deep within the cerebral hemisphere that connects the cerebrum and the cerebellum. It helps regulate automatic movement.

Corpus Callosum:
This consists of closely packed bundles of fibers that connect the right and left hemispheres of the brain and allows them to communicate with one another.

Amygdala:
This is responsible for all emotional responses including aggressive behavior.

Hippocampus:
This makes it possible to remember new information and recent events.

Brain Stem:
The Brain Stem is located in front of the cerebellum and serves as a relay station, passing messages between various parts of the body and the cerebral cortex. It controls the primitive functions of the body essential to survival including breathing and heart rate.

Cerebellum:
This is located at the back of the brain. It fine tunes motor activity, regulates balance, body movements, coordination and the muscles used for speaking.
Brain Anatomy and Autism

- Three central findings
  - Increase in brain weight
  - Truncation in the dendritic tree development of neuron in limbic structures
  - Decrease in the number of Purkinje cells in the cerebellum

- Autism is “Connectivity Disorder”
  - Within a regions
  - Between regions
  - Over connectivity
  - Under connectivity
Dr. Eric Courchesne, Neuroscientist  
UC San Diego Autism Center of Excellence

- Frontal lobe, temporal lobe
  - Social and language communication functions
    - Very complex situations, wires slowly, frontal lobe wires last
  - Too many brain cells that produce too many connections were produced during second trimester of gestation
    - Over-connected (freeway in Los Angeles at 5:00 pm)
    - Typical “pruning” does not occur at the same time but decades later
  - Many individuals with autism “get better” later in life
  - Early intervention can alter the outcome positively, rewiring the brain
    - “Genetics of recovery”

- [https://www.youtube.com/watch?v=YYY2XGEmc1s](https://www.youtube.com/watch?v=YYY2XGEmc1s)
Neurotransmitter (Neurochemical) Differences

- **Serotonin**
  - >25% children with autism are hyperserotonemic
- **Opiate activity**
  - Elevated endorphins
- **Cortisol**
  - High rate of nonsuppression after dexamethasone
- **Growth hormone**
  - Delayed response to L-dopa
Chromosome 2

243 million base pairs

- Autism susceptibility gene on 2q24-q33
- Deletion in 2q32 associated with autism
- SLC25A12/AGC1, candidate genes for autism in 2q24-q33
- Numerous candidate genes in 2q24-q33
- 3 regions examined in 2q24-q33
- Evidence for association between autism and genes AGC1, ITGA4, and STK39
Chromosome 7

- Reelin gene involved in neuronal migration
- FOXP2 gene involved with inherited language deficit not related to autism
- Gene for neurotransmitter known to be abnormal in autistic brains
- Gene related to the gene involved in Angelman syndrome
- Engrailed 2 – gene related to cerebellar production

VERY IMPORTANT
Chromosome 15

- UBE3A gene involved in Angelman syndrome shows association
- Inconsistent results for genes responsible for parts of GABA receptor

X Chromosome
Risk Genes for Autism

- Risk genes share pathways
- Some risk genes involve cell adhesion
  - Signaling
  - Synapsis formation
  - Neural migration
  - Dendritic growth
- Deletions
- Duplications
- Translocations
Reward processing is how individual perceives rewards. Reward processing is a prerequisite to motor movement. Implicit learning involves abstract processing. Motor skills affect repetitious motor behaviors and difficulty with motor planning.
Another function of CNTNAP2 involve connectivity

Significantly stronger local connectivity in the frontal cortices of the brain
- Particularly right hemisphere
  - Responsible for memory, learning, reasoning, problem solving
  - All contribute to effective communication

When connectivity is too compressed, acts like freeway traffic in Los Angeles at rush hour
- Messages get jammed

Significantly sparse connections to the long-range areas of the brain
- Striatum (part of the basal ganglia) very sparse
- Striatum facilitates voluntary movement (core deficit in autism)
- Roadway analogy: like driving on a very bumpy dirt road with huge potholes, making passage very slow and difficult because there isn’t a roadway to a particular area
Oxytocin Receptor Gene: OXTR

- Oxytocin key regulator of social and affiliative behavior
  - When administered nasally in humans increases:
    - Memory for faces
    - Ability to infer the mental state of others
    - Generosity
    - Trust
  - After administration of OXTR to individuals with ASD, display more appropriate social behavior
MET Gene

- Social orientation and face processing
- Understanding and internalizing the emotional states in others
- Marks eye gaze
- Ability to imitate
- Visual association regions
  - Fusiform gyrus
  - Temporal cortex
  - Medial parietal region
  - Inferior frontal region
- Don’t get information from looking at faces
- Regulates when to pay attention and when to close off
SHANK3 Gene

Dr. Joseph Buxbaum
Director of the Seaver Autism Center

https://www.youtube.com/watch?v=G5GTVg7-GiI

• Most common single-gene cause of autism
• 1%
• Missing SHANK3 gene causes changes in social and motive behavior
Genes are not causal

Multiple genes, gene-gene interactions, causal in autism

Genes have region-specific effects
  - Decreased longer range connectivity
  - Increased local connectivity in risk carriers

Task positive: individual is paying attention to the task

Task negative: individual no longer paying attention
Neural Signatures of Atypical Brain Development

- Kevin A. Pelphrey, Ph.D. Yale University, Distinguished Lecturer Series
- Cognitive neuroscience
  - Neuroimaging
  - Imaging genomics
  - Eye tracking
  - Virtual reality
  - Looking at brain basis of ASD
- Social Perception
Social Brain

- Tasks of social brain
  - Tell people apart
  - Perceive intent of others and intent of their actions
  - Analyzing intention
  - Sharing attention and intentions
  - Representing another person’s perceptions and beliefs
Social Brain (cont)

- Three brain regions
  - Superior temporal solcus (STS) region
  - Amygdala region
  - Orbital frontal cortex (OFC)
References

- Lorna Wing, OBE, FRCPsych, English psychiatrist, author
- Dr. Eric Courchesne, Neuroscientist
  UC San Diego Autism Center of Excellence
- Ricki Robinson, MD, MPH, is co-director of Descanso Medical Center for Development and Learning in La Canada, California and a Clinical Professor of Pediatrics at the Keck School Medicine of USC, author
- Joseph Buxbaum, Ph.D.
- MIND Institute Lecture Series on Neurodevelopmental Disorders 2014
- Susan Bookheimer, Ph.D., UCLA Brain Research Institute
  - Clinical Neuropsychologist, Resnick Neuropsychiatric Hospital
  - Joaquin Fuster Professor of Cognitive Neuroscience, Psychiatry and Biobehavioral Sciences
  - Professor, Center for Autism Research and Treatment (CART)
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  - Tennenbaum Center for the Biology of Creativity
- Kevin Pelphrey, PhD
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