Peeling the Onion
Understanding the Neurobiology of Autism
Spectrum Disorders
Thursday May 8, 2014

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Medical Director
Seattle Children’s Autism Center

Layers of the ASD Onion
- Layer of DNA
- Layer of the Brain
- Layer of the Mind
- Layer of the Community

A History of Autism

1. Reports of autistic-like disorders can be traced far back in history
2. Brother Juniper a follower of St. Francis of Assisi was described as “naively innocent and lacking of social intuition”. This was described as due to his “saintliness”.
3. Kanner describes a report by Martin Luther of a child that sounded like he was severely autistic. Luther recommended that the child be taken to a river and drowned because he “had no soul”.
4. “Victor” the boy found living in the wild of Aveyron, southern France, at the end of the 18th century. J.M.G Itard was the first to describe a child treated for what sound like severe autism.

Kanner, L (1964) A History of the Care and Study of the Mentally Retarded p 7
Lane, H (1977) The Wild Boy of Aveyron
Brother Juniper, Martin Luther and Victor, “the wild boy of Aveyron”

More modern ideas begin to appear

• Starting in the late 1800s, the idea that autism might be a “brain disorder” began to appear with Maudsley (1867) suggesting these children had “childhood psychosis”.

• De Sanctis (1906) and Heller (1909) described children who developed normally and then lost skills.

• Potter (1933) described “childhood schizophrenia”.

• Margaret Mahler (1952) described children who would cling to their parents but showed no feeling towards them.

• 1967 Bruno Bettelheim published *The Empty Fortress: Infantile Autism and the Birth of the Self* which notoriously accused mothers as the cause of Autism - the “refrigerator mom” theory. This has been thoroughly refuted but held sway into the late 1970s and still is believed in some quarters.

Leo Kanner
1896-1981

• Kanner after emigrating to the USA from eastern Europe became the first US Child Psychiatrist at Johns Hopkins.

• Founded the Department of Child Psychiatry and was its chair from 1930-59

• 1943 wrote “Autistic Disturbances of Affective Contact”

• Kanner was the first to suggest that genetic factors may be part of the cause of autism, but rejected the idea that there was a problem in the brain.

• Under the influence of the Freudians he advocated that “cold, detached, rigid, humorless parents” were part of the cause of autism.
### Kanner’s Cases - 11 children, 8 boys, 3 girls

- *Inability to relate themselves in the ordinary way to people and situations from the beginning of life*
- *Personal pronouns repeated as heard*
- *Extreme autistic aloneness*
- *Excellent rote memory*
- *Delayed echolalia*
- *Literalness*
- *Loud noises and moving objects are reacted to with horror*
- *Limitation in the variety of spontaneous activity*
- *Anxiously obsessive desire for the preservation of sameness*

### Hans Asperger

1906-1980

- Educated as a pediatrician in Vienna the same place that Kanner trained.
- Early childhood very similar to those children he subsequently described.
- His landmark paper “Autistic Psychopaths in Childhood” 1944 was virtually unknown in the west until after his death.
- Original paper was translated for Uta Frith, a British developmental psychologist, who along with Lorna Wing, showed the similarities between Asperger and Kanner’s work in the early 80’s.

### Asperger’s Cases

- His paper described 4 boys who had similar characteristics:
  - Behavioral features that persist over time
  - Odd language that may be delayed initially but is well developed except for unusual adult language and odd prosody and original odd phrasing
  - Counter to popular belief he described some children as severely cognitively impaired, not the “high functioning” often associated with his syndrome.
  - Significant behavior problems in all the cases, with very poor social and play skills

- Noted similar features in the parents of his cases though generally of less severe degree
- Noted also poor clumsy physical skills
- He did not find a single girl who exhibited similar features
- Many of his cases showed “splinter skills”, especially math skills
- Did not emphasize perseverative narrow interests that we usually associate with his “syndrome”.
Lorna Wing 1928 - Present

- Mother of an autistic daughter and Psychiatrist, she founded the National Autistic Society in 1962
- 1982 wrote "Asperger's Syndrome, a clinical account" after discovering the work of Hans Asperger
- She is given credit along with a number of other British scholars including Michael Rutter and Simon Baron-Cohen with helping to define what we now call the "Autistic Spectrum"

Published articles about Autism

<table>
<thead>
<tr>
<th>Year</th>
<th>Articles</th>
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<tbody>
<tr>
<td>2007</td>
<td>1000</td>
</tr>
<tr>
<td>2008</td>
<td>1500</td>
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<td>2009</td>
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Serious Science
Layers of the ASD Onion

- Layer of DNA
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Autism is familial

- In the early 80s the first scientific reports appeared that questioned the notion that ASD was a behaviorally mediated disorder and rather that it was a biologically mediated disorder of brain function.

- Rutter in 1977 observed that monozygotic twins had a very high rate of concordance for autism (72%) vs. dizygotic twins (0%), strongly suggestive that autism has a genetic component.

- Future twin studies have continued to show substantial concordance in identical twins though the percentages have shifted suggesting bigger role of environmental factors.

DNA Primer
Genetics Models

- **Common allele model**
  - Genes may relate to traits that vary in the general population (e.g., sociability, anxiety, language)
  - Relatively common alleles, each with small effect act together to increase risk

- **Familial / Broader Phenotype**
  - Likelihood of several genes (>15)
  - GABRB3, UBE3a (15q)
  - FoxP2 (7q)

- **Rare allele model**
  - De novo duplications/deletions "hot spots" involved in synaptic processes
  - Individually rare, highly penetrant
    - Currently accounts for ~11% of cases
    - 15q11
      - region implicated in Angelman & Prader Will Syndrome, Lymphoma, Celiac disease
    - UBE3a
    - 16p11
      - duplications implicated in Schizophrenia/Tuberous Sclerosis / TSC2
      - 22q13 – SHANK3
        - Incr Intellectual Disability

- **Double Hit Hypothesis**
  - {De novo + inherited}
    - Foxp2 (7q) + CNTNAP2 (7q)
    - SONTA 2q+ 15q11.2

- **SFARI:** [https://sfari.org](https://sfari.org) [SFARI gene search tool]

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**Table 1 | ASD-related syndromes**

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Copy Number Variation (CNV)

**Normal**

A B C D E F G H I J

**Inversion**

A B C G F E D H I J

**Deletion**

A B C G H I J

**Duplication**

A B C D E F D E F G H I J

Large *de novo* CNVs occur in ASD about 6%

**The Simons Simplex Collection**

*innovation, courage, connections*

2000 families, one mission

*The Simons Simplex Collection* is a bold new initiative to search for the cause of autism. Researchers at seven sites in North America will collect DNA samples from families with just one child affected by an autism spectrum disorder. The results will be available to the best scientific minds in the world for search for clues that will lead to important breakthroughs. The Simons Foundation, a New York-based philanthropic organization, has committed millions of dollars to the Simons Simplex Collection, and will continue edge autism research.
CNV analysis in SSC

From Regions to Genes

Exome Sequencing in Autism

- Selected 20 individuals
  - No family history of mental illness
  - No BAP in family members
  - Significantly impacted by ASD symptoms
- Identified neurologically expressed gene-disrupting mutations in 4 individuals (25% of sample)
- These 4 individuals were more impaired
Exome Sequencing in Autism

- Replicated exome study in 209 individuals with ASD
- Identified 248 neurologically expressed gene-disrupting mutations in 25% of the sample
- Based on this number of mutations, we can estimate there are 384-821 autism risk loci

Oroak et al, 2012

Autism Genes Exist on Every Chromosome


Global Contribution of Types of Genetic Variation to ASD

Figure 2. The Percentage of Variance Explained by Various Forms of Genetic Risk Factors for ASD

Stein et al Neuron 77: Jan. 2013

Networks

- The genetic networks that have a lot of autism risk genes are related to a variety of important neurologic cellular function.
- These networks are shown to be enriched in areas of animal and human brain tissue associated with functions affected in ASDs.
- Different networks may distinguish autism from intellectual disability.
- Understanding dysfunctional genetic networks could serve as targets for specific biologic intervention.
- Gene expression profiles might serve as a biologic marker for ASDs or other neurodevelopmental disorders.