Exploring the Etiology of Autism:
*Polygenic risk and the social environment*

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Phenotype of Autism

1. **Difficulties in Social Communication/Social Interaction**
   - Difficulty engaging in back-and-forth conversation
   - Difficulties with nonverbal communication
   - Difficulty understanding social relationships

2. **Restricted/Repetitive Behaviors**
   - Repetitive body movements, use of objects, or speech
   - Insistence on sameness
   - Unusually strong interests
   - Unusual interest in sensory aspects of the environment

Diagnostic Tools

- Symptom/behavior checklists, such as DSM-V
- Screening Instruments, e.g.
  - M-CHAT
- Behavior based assessments, e.g.
  - CARS
  - GARS
- Autism Diagnostic Observation Schedule (ADOS)/Autism Diagnostic Interview (ADI)
- Limitations
The Problem

- Impact of diagnosis on individual families
- Estimates have increased from:
  - 2-5 in 10,000 (in 1977) to 1 in 68 today in US
- Possible reasons:
  - Broadened diagnostic criteria
  - Inclusion of cases with known genetic causes or severe mental retardation
  - True increase in prevalence?
- Implications for public health:
  - Escalating demand for education and therapeutic resources, with intensive therapy currently the only recognized intervention

Proposed Etiologies

1940s • “Infantile autism” first described by Kanner (1943) and later, by Hans Asperger
  - Initially thought to be of neuropathological origin
1950s • Described as “Refrigerator Mother” Syndrome, implicating parenting deficiencies
1970s • Twin studies suggest genetic etiology
1990s • Widespread public concern about “environmental etiology” e.g. MMR vaccination
2000s • Proposed genetic predisposition with “second hit” from environmental factors
Associated Family Characteristics
Parent of autistic children more likely to display:
- Social reticence
- Communication difficulties
- Preference for routines and difficulty with change
- Recurrent depression and anxiety disorders
- Increased head circumference

Etiology of Autism
- Genetic Etiology
- Environmental Etiology
- Genetic Predisposition + Environmental “2nd Hit”

Evidence for Genetic Etiology
- Increased incidence in siblings
  - Almost 100-fold increase in relative risk compared with general population
- Higher concordance rate in monozygotic twins
  - 36-91% compared with <1% in dizygotic twins
- Association with several specific genetic disorders, e.g.
  - Fragile X disorder, Angelman Syndrome
  - Rett Syndrome
Evidence for Genetic Etiology (cont.)

- Genetic susceptibility markers identified on genome-wide array analyses
  - Genes encoding for neuronal cell adhesion molecules (Wang, 2009)
  - Copy number variations (Glessner, 2009)
  - Genes regulated by neuronal activity (Morrow, 2008)

- However, individual markers explain only small amount of variance
- Epigenetic factors

Epigenetic Mechanisms

- Developmental factors
- Environmental factors
- Single Nucleotide Polymorphisms (SNPs)

Health Endpoints

- Autism
- Schizophrenia
- Mental retardation
- Diabetes

DNA Methylation and Epigenetics

- Early life somatosensory stimulation results in hypomethylation of GR promoter, resulting in enhanced hippocampal GR expression and a reduced HPA stress response (SFN Abstracts, 2002)

- Could early life experience play an epigenetic role in the development of neurodevelopmental disorders, such as autism?
Evidence for Social/Environmental Factors in Autism

- A high proportion of Romanian adoptees with severe early privation found to display autistic features (6% + 6% with milder autistic features)
  - Symptoms related to severity of deprivation
  - Indistinguishable from other autistic patients on ADI/ADOS
  - Differences include equal sex ratio, normal head circumference, and some improvement by age 6
- Higher rates of autism also seen in congenitally blind children

Evidence for Social/Environmental Factors in Autism

- Abundance of literature supporting the role of maternal behavior in programming infant neural development
  1. **Cognitive development** (hippocampal L-LTP, synaptogenesis, spatial learning and memory)
  2. **Stress reactivity** (CRF production, GR and Carbamazepine A receptor expression, behavioral manifestations of anxiety)
  3. **Maternal behavior** in female offspring (Oxytocin and estrogen receptor expression, licking/grooming/nursing behaviors)

Oxytocin

- 9 amino acid peptide synthesized in the hypothalamus and released into the bloodstream via the post pituitary
  - Uterine contraction in childbirth
  - Milk let down during suckling
- Central neuromodulatory effects also present
  - Maternal care
  - Female pair bonding (voles)
  - Decreases infant isolation distress call
  - Improved social memory and spatial learning/memory (e.g. mouse knockout models) (Ferguson et al, 2000)
  - Pup grooming/stereotypies (Pederson, 2002)
- Released in CNS in response to non-noxious sensory stimulation (light touch, warmth, etc)
Oxytocin and Autism
- Autistic subjects have lower plasma OT concentrations than controls (Modahl, 1998; Green, 2001)
- Intravenous OT infusion reduces stereotypic behaviors in autistic/Asperger group (Hollander, 2003)
- Intranasal OT results in enhanced emotion recognition (Guastella, 2010) and social behavior (Andari, 2010).

Face Processing and Autism
- Key role of social perception in the development of autism
- Face processing impaired in children with autism (ERP and fMRI studies)
- Development of face perception occurs during infancy and early childhood
- Eye gaze aversion, a core characteristic of autism, is not present from birth, but develops over the first 6 postnatal months (Jones and Klin 2013).

Case Study
- 3 year old African American boy
- Parents have borderline intellectual functioning aged in their 40s; concerned aunt and grandmother arranged appointment
- Born Small for Gestational Age (SGA) at 37 weeks
- No other medical concerns
- History of prolonged television exposure from infancy
Case Study (Cont.)

- Behavioral observations:
  - minimal use of language, apart from phrase repetition/echolalia
  - Frequent head banging
  - Tends to play alone
  - Rigidly lines up toy cars
  - Upset with any change in routine
  - Sensitivity to loud noises; pain insensitivity

Intervention Options

- Applied Behavioral Analysis (ABA)
- Parent focused intervention e.g. Denver Developmental Model, ImPACT
- Communication Focused Interventions
- Sensory Motor Interventions e.g. sensory integration
- Integrative Programs e.g. social skills training

Intervention Options (cont.)

- Atypical antipsychotics, such as risperidone, for severe tantrums, hyperactivity and lability
  - Side effects include dyskinesias, weight gain and associated metabolic problems (glucose and lipids)
- Evidence for effectiveness of behavioral treatment is limited, based on randomized controlled trials (Ospina, 2008)
Non-ASD

ASD

EXTRINSIC RISK

Social / Environmental

INTRINSIC RISK

Neurobiological / Genetic

Genetic syndromes & variants e.g. Fragile X, CNVs

Social or sensory deprivation e.g. institutional care, blindness

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Study Design

- Enroll pregnant women and download smart phone app
- Collect data during pregnancy
  - Experience of stress, depression, social support, pregnancy complications
- Video record infant/child social development using smart phone over first 2 postnatal years
- Test for polygenic risk for autism from newborn blood samples
- Screen for autism or other developmental delays at 2 years
Summary

**Core phenotypic features of autism**
- Impairment in social communication
- Restricted repetitive and stereotyped behaviors

**Etiological factors**
- Genetic predisposition
- Social / environmental / epigenetic factors

**Interventions**
- Behavioral therapies, especially parent focused
- Speech and occupational therapy
- Medication