

## 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

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## 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

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## 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

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## The Problem

**Prevalence Rates of Autism in the United States (1997 to 2012)**

Parent Report of Children Aged 3-17 years<sup>1</sup>      Community Services Survey of Children Aged 0-8 years<sup>2</sup>

Year	Autism	Intellectual Disability
1997-99	~2.0	~6.8
2000-02	~3.8	~7.2
2003-05	~5.8	~7.5
2006-08	~7.2	~6.8

Year	Autism or PDD
2000	~6.5
2002	~6.5
2004	~8.5
2006	~10.5
2008	~13.5
2010	~15.5
2012	~15.5

<sup>1</sup>Walden et al. 2011, 127(6):1034-42. <sup>2</sup>MMWR Surveillance Summary, 2016;65(3):1-23. PDD, Pervasive developmental disorder.

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## 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

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### 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



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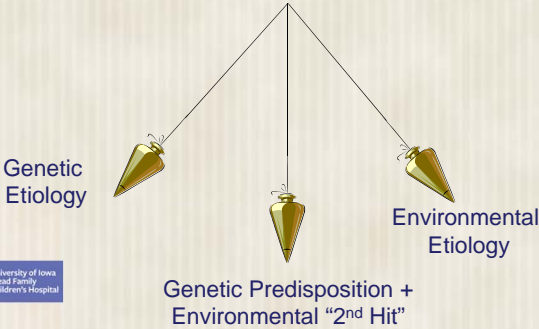
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### Etiology of Autism



Genetic Etiology

Environmental Etiology

Genetic Predisposition + Environmental "2nd Hit"



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### 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



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## 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




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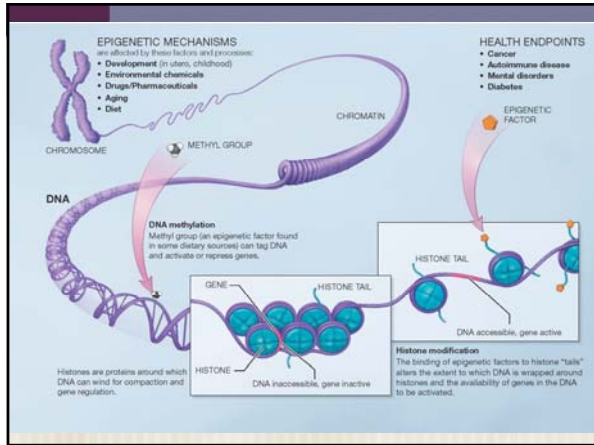
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## DNA Methylation and Epigenetics

- 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?




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### 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 includes equal sex ratio, normal head circumference, and some improvement by age 6
- Higher rates of autism also seen in congenitally blind children




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### 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 Carbamazapine A receptor expression, behavioral manifestations of anxiety)
  3. **Maternal behavior** in female offspring (Oxytocin and estrogen receptor expression, licking/grooming/ nursing behaviors)




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### 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)




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### 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).



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### 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).



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### 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



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### 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



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### 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



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### 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)



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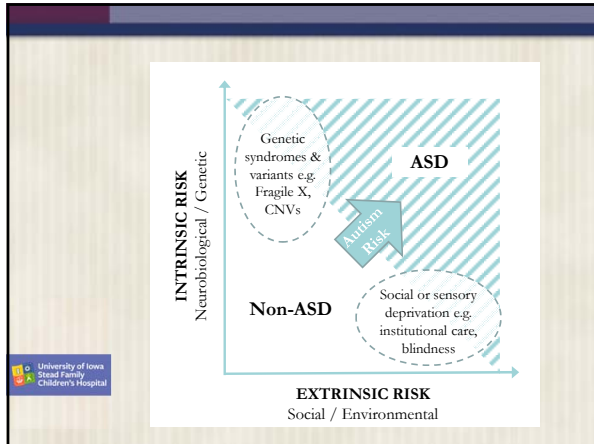
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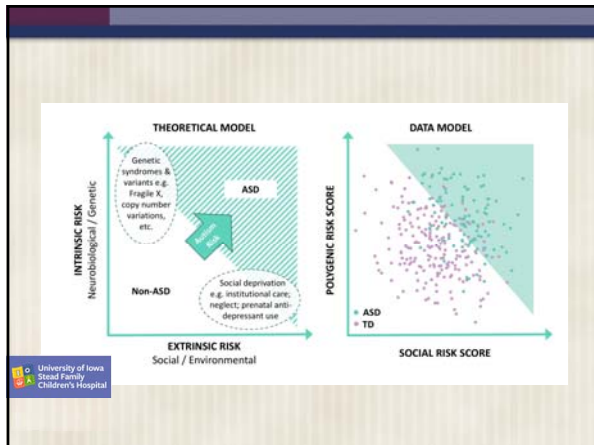
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### Study Design

- 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

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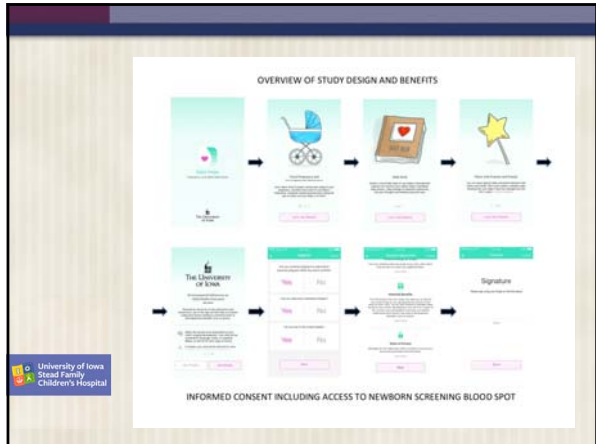
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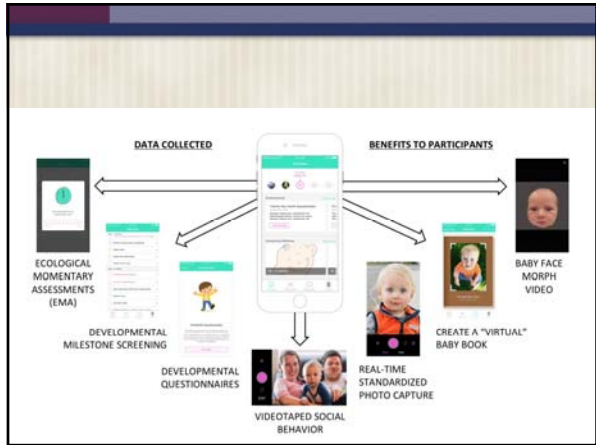
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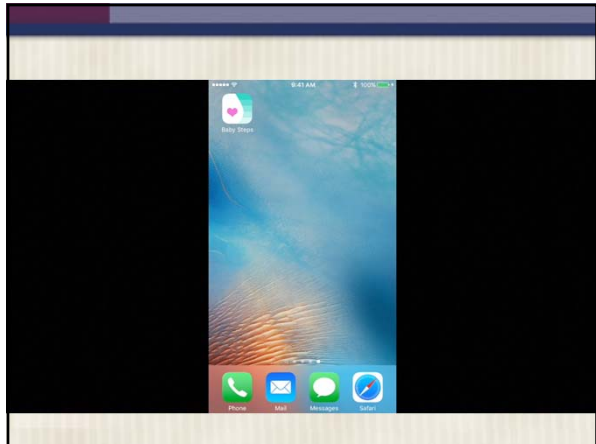
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## Summary

- 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



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