

Etiology of Autism



**Institute of Medicine
Immunization Safety Review
Committee**

**National Academy of
Sciences**

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The National Institutes of Health (NIH)

No Single Cause; No Single Cure

- Genetic
- Infectious
- Neurologic
- Metabolic
- Immunologic
- Environmental

Etiological Hypotheses

- No single cause; no single cure
- Early onset autism vs regressive autism
- Regression in other disorders
 - Rett's syndrome
 - Glutaric Aciduria

Some Possible Mechanisms for Immune Developmental Disorders

- Inadequate protection against viral or other pathogens results in fetal/child infection
- Maternal immune defect results in inadequate protection or autoimmune attack of developing fetal brain
- Pre or postnatal genetic immune defect in child plus antigenic trigger result in autoimmune attack of brain

Immune findings in autism

Warren et al.

■ C4B "null allele"

- 25/50 subjects vs. 17/85 controls

■ Extended HLA haplotype B44-S30-DR4

- 14/50 subjects vs. 2/85 controls

■ HVR-3 sequence 1

- 17/50 subjects vs. 2/85 controls

Limitations in Immune Hypotheses of Autism

- **No autopsy studies of brains from individuals with autism have demonstrated immune pathology**
- **Comparison across studies difficult: autism assessment, control groups, and immune measures vary across studies**

Limitations in Immune Hypotheses of Autism

- **No immune mechanism has been elaborated to explain how immune defects alter brain anatomy or physiology in a specific pathway that results in autism**
- **There is no immune animal model for autism**
- **Treatment studies do not support clinical use of IVIG**

NICHD/NIDCD



**Network on the
Neurobiology and Genetics
of Autism:**

**Collaborative Programs of
Excellence in Autism
(CPEAs)**

CPEA Network



- 10 multidisciplinary programs
- Each a unique research program
- All study etiology, brain structure &/or function, & developmental course of autism
- Collaborate on studies that no single project can carry out alone
- Common diagnostic & core measures

Some CPEA Research Findings

- Genetic hotspots in autism (with international consortium), esp. Ch.7
- Hox A1 gene
- Chromosome 15

Some CPEA findings

- Evid. of autism behaviors by 8 - 12 mos
- Also evidence of subgroup with later regression after normal development
- Functional brain differences in processing social and auditory info
- Immune indicators, possible immune assay found in autism
- Differences in head circumference, children and adults

CPEAAutism Regression/ Vaccination Study


- Co-funded by Centers for Disease Control in Atlanta, National Immunization Program
- Assess temporal association between MMR vaccination and onset of autism (early onset vs regressive)
- Replicate studies of persistent measles infection in autism cases vs healthy controls

CPEA Autism Regression/ Vaccination Study - Stage 1

- 1600 well-diagnosed cases of autism
- 1250 healthy controls
 - individual vaccination records
 - records of onset of autism - ADI-R
 - age of onset
 - age of recognition
 - age of diagnosis

CPEA Autism Regression/ Vaccination Study - Stage2

- Replicate findings re abnormal measles antibody titers and persistent measles infection

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- 250 early onset autism cases
 - 250 regressive autism cases


 - 250 healthy controls matched to early onset
 - 250 healthy controls matched to regressive cases

CPEA Autism Regression/ Vaccination Study

**[http://www.nichd.nih.gov/
about/crmc/mrdd/autism/
autism.cfm](http://www.nichd.nih.gov/about/crmc/mrdd/autism/autism.cfm)**

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The Longitudinal Cohort Study of Environmental Effects on Child Health and Development



NICHD/NIH

CDC

EPA

Other agencies

Children -- Increased Vulnerability to Environmental Exposures

- Critical windows of vulnerability during development
- Children have immature mechanisms for detoxification
- Differences in metabolism and behavior may yield higher exposure in the same environment

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Why a longitudinal study?

- Links between many exposures and children's health not adequately investigated (*esp. mixtures*)
- Infers causality
- Life-stage effort
 - Timing of exposures
 - Timing of outcome
- Typical studies limited in size & scope
- National resource for other studies

Aims

- Do environmental agents affect the health and development of children?
- How do environmental agents (timing, mixtures, interactions) affect children's health and development?
- Are certain conditions exacerbated by environmental exposures?

Longitudinal Cohort Study



**[http://www.nichd.nih.gov/
despr/cohort/](http://www.nichd.nih.gov/despr/cohort/)**