NIEHS Investments in Autism Research

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Principles Guiding Investments

Autism has both an environmental and genetic component—understanding gene environment interplay is a priority

- Autism research is an integral part of a larger program that supports children’s environmental health research
- A mix of research approaches are needed—from population-based studies to laboratory investigations of relevant cellular and molecular mechanisms
- Strong partnerships, with other federal entities and public stakeholders are essential to speed discovery and ensure rapid translation to public health
- Fundamental investments in exposure science and toxicology will benefit autism research
Children’s Environmental Health and Disease Prevention Centers (NIEHS/EPA Partnership)

Program Description:

- Created to enhance communication, innovation and research excellence in Children’s Environmental Health, using integrated multidisciplinary approaches

- UC Davis Children’s Center is focused on autism etiology and supports research projects and service and facility Cores
  - Epidemiology of autism risk (Project 1)
  - Clinical and cellular immunology (Project 2)
  - Mouse Models (Project 3)
  - Analytical Chemistry, Molecular Genomics, Statistics Cores (Service Cores)
  - Community Outreach and Translation
**CHARGE Epidemiology Study Design**

- **CHILDhood Autism Risks from Genetics and the Environment**
- Case control study with 3 groups: ASD; Developmental Delay (DD); children with Typical Development (TD), ages 24-60 months
- Goal: To identify causes and contributing risk & protective factors for childhood autism, understand etiologic heterogeneity
- Population based recruitment: 1300 families
- Clinical confirmation of diagnosis
- Extensive collection of environmental, medical, lifestyle, sociodemographic, & phenotypic information
- Linkage to state-of the art laboratories through Center Core resources
Recent study results from CHARGE

- Blood mercury (Hg) concentrations are similar for children with ASD vs. Typical Development (TD) (Hertz-Picciotto et al. Env Health Persp 2009)

- Gene expression differs in ASD vs. TD children, particularly in NK cells (Gregg et al. Genomics 2008)


- Numerous immune markers distinguish children with ASD vs. TD
  - Maternal auto-antibodies to fetal brain (Braunschweig et al. Neurotox 2008)
  - Child’s total IgG levels are reduced (Heuer et al. Autism Res 2008)
  - Child’s IgG4 levels are increased (Enstrom et al. Brain Behav Immun 2009)
  - Child’s TGF-beta levels are reduced (Ashwood et al. J Neuroimmunol 2008)

- Regression found to be as high as 44% when both language and social skills are taken into account (Hansen et al. Ambul Ped 2008)

- Sleep patterns differ for ASD vs. TD controls (Krakowiak et al. J Sleep Res 2008)

- Docosahexaenoic acid (DHA) is significantly lower in certain lipid subclasses among children with ASD as compared with TD controls (Wiest et al. Prostaglandins, Leukot, Essent Fatty Acids 2009)
EARLI: Early Autism Risk Longitudinal Investigation

- NIH Autism Centers of Excellence (ACE) Network R01
- Lead institute: NIEHS, cofunding by NIMH, NICHD, NINDS
- Four site study enrolling mothers with at least one child with autism who are planning to become pregnant or in the early stages of a subsequent pregnancy
- Enriched risk cohort design offers advantages for detecting autism risk and g x e interplay
- Prospective, real time data collection during critical periods of early development avoids disadvantages of retrospective methods of exposure assessment
- Enrollment began Spring 2009; enrollment target is 1200 mothers
Data collection for an EARLI Study participant

- A wide array of data and biologic specimens are being collected throughout pregnancy and during the first three years of the new baby’s life.
  - Mother—blood, hair, urine, saliva, placenta, cord blood, breast milk
  - Father—blood, semen
  - Baby—blood, hair, meconium, urine
  - Older sibling—blood

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Mom

- Biological samples

Home

- Environmental samples
- Maternal report
Hypotheses being pursued in EARLI Study

- The EARLI study is based on a ten year timetable
- A small number of ‘exemplary aims’ were chosen for the first five years of the project. These aims:
  - can be accomplished with small sample size and limited follow-up
  - are designed to demonstrate analytic feasibility
  - are focused on association between autism risk and maternal autoimmune biomarkers, prenatal environmental exposures, epigenetic vulnerability, and gene-environment interaction

- EARLI infrastructure and data collected under the auspices of Autism Center of Excellence (ACE) funding will provide ample opportunities for ancillary studies and pursuit of additional etiologic hypotheses
  - EARLI collaboration with Infant Brain Imaging Study (funded by Autism Speaks)
  - Environment, the Perinatal Epigenome and Risk for Autism and Related Disorders (Funded by NIEHS and NIH Epigenetics Roadmap)
American Recovery and Reinvestment Act (ARRA)

- Provided funding for four new NIEHS projects solicited through Heterogeneity of ASD initiatives

- These projects expand the range of exposures being investigated for association with autism risk and leverage existing resources being supported through other agencies
  - Genome-wide Environment Interaction Study for Autism: The Study to Explore Early Development (SEED) study
    Danielle Fallin, Johns Hopkins University
  - Prenatal Exposure to Polyfluoroalkyl Compounds in the Early Markers of Autism (EMA) Study
    Lisa Croen, Kasier Permanente Northern California
  - Investigating Gene-Environment Interaction in Autism: Air Pollution
    Rob McConnell, University of Southern California
  - Prenatal factors and risk of autism in a Finnish national birth cohort
    Alan Brown, Columbia University
American Recovery and Reinvestment Act (ARRA)

• NIEHS ARRA funding provided supplements to existing grants to:
  – Hire additional outreach coordinators for EARLI study to speed pace of enrollment
  – Support hiring of new personnel to speed analysis and dissemination of findings from CHARGE study
  – Support home visits for dust collection to measure additional environmental exposures in CHARGE study
Partnerships in Environmental Public Health

- Supplemental funding provided to UC-Davis Children’s Center to facilitate interaction with diverse communities and support dissemination of findings in English and Spanish.

- Support for Autism Risk Communication conference to bring together stakeholders (including parents, educators, community clinicians, scientists, media, policy-makers) all concerned with ethical issues surrounding how information on autism risk factors is communicated.
Epigenetics/Epigenomics Programs

**Environmental Epigenetics Program:** To examine the impact of gene-environment interactions on diseases by studying alterations in gene expression as influenced by environmental exposures

- Epigenetic Interaction of MECP2 and Organic Pollutants in Neurodevelopment
  *Janine LaSalle, UC-Davis*

**Epigenetics Roadmap Program:** NIEHS co-leads trans-NIH Roadmap efforts in epigenomics to understand the importance of epigenetic marks and how environmental exposures may alter them

- Environment, the Perinatal Epigenome and Risk for Autism and Related Disorders
  *Danielle Fallin/Andy Feinberg, Johns Hopkins University*
Genes Environment and Health Initiative

- Will provide new tools for autism researchers to measure exposures and identify interactions of exposures with genetic variation

EXPOSURE BIOLOGY PROGRAM
- Develop technology and biomarkers

GENETICS PROGRAM
- Identify genetic variants
  - GWA Studies
  - Data Analysis
  - Replication
  - Sequencing
  - Database
  - Function
  - Translation

GXE
The Laboratory of Neurobiology (LN) investigates the cellular and molecular processes in the developing and aging nervous system that increase its vulnerability to environmental toxicants.

The Synaptic and Developmental Plasticity Group, led by intramural investigator Serena Dudek, studies the regulation of synaptic effectiveness and how synaptic changes early in development are consolidated to last a lifetime.

These studies can help inform ideas about the role of brain connectivity and synaptic development and plasticity in autism.

Major areas of research in Synaptic and Developmental Plasticity Group:

- Transcriptional regulation by neuronal activity to consolidate synaptic plasticity
- Synapse elimination during brain development
- Critical periods of synaptic plasticity during development
The Epidemiology Branch investigators study a wide range of health effects linked to environmental exposures.

The Pediatric Epidemiology Group, led by Walter Rogan, studies the effects of environmental chemicals on childhood growth/development.

The Biomarker-based Epidemiology Group, led by Matt Longnecker, is focused on health effects of early exposure to background levels of environmental contaminants:

- NIEHS is supporting the collection of additional biologic specimens from pregnant women in the Norwegian Mother & Child study (MoBa), an ongoing long-term prospective cohort study of 100,000 pregnant women and their babies.

  These samples can be used for investigation of autism gene environment interplay in the Autism Birth Cohort (ABC) study nested within MoBa (funded by NINDS).
Toxicity testing has relied traditionally on cancer endpoints.

Increased interest in neurodevelopmental outcomes.

NTP is currently exploring an Integrated Testing Protocol for Examining the Effects of Developmental Exposure on the Nervous, Reproductive, and Immune Systems which includes:

NIEHS funding for autism research has grown considerably over the past 10 years.

NIEHS investment in autism research in fiscal year 2009 was approximately 9.3 million dollars (including 4.9 million dollars in ARRA funding).

NIEHS supported studies span from human epidemiology to mechanistic laboratory investigations.

Infrastructure for large scale human studies (CHARGE, EARLI) is in place to enable identification of environmental risk factors and gene environment interplay.

Biologic markers for subtypes of autism with possible etiologic relevance (e.g., immune alterations) have been identified.

NIEHS support for basic research in neurotoxicology and exposure science will be essential for understanding and informing human studies in autism.

Future NIEHS autism activities will emphasize:
- opportunities identified in IACC Strategic Plan
- coordination with other federal agencies
- meaningful involvement of affected communities
- translation of findings to public health & prevention
### Thanks

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