National Institute of Environmental Health Sciences
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Concept Clearance

Environmental Contributors to Autism Spectrum Disorders (ASD)

Introduction

Autistic disorder and related conditions, known collectively as autism spectrum disorders (ASD), are characterized by significant impairments in reciprocal social communication and the presence of repetitive and/or restricted behaviors and interests. The symptoms of ASD emerge in the first three years of life. Some individuals are mildly impaired by their symptoms, while others are severely disabled. As a lifelong condition, the collective burden of ASD on affected individuals and families is enormous. Once thought to be rare, recent studies report that ASD affects as many as 1 in 88 children within the United States. The prevalence of ASD has risen dramatically over the past twenty years, and recent data indicate that the upward trend continues. Part of this increase reflects changes in diagnostic criteria, increased awareness by families, educators and clinicians and the availability of services for affected individuals. These factors alone are unlikely to fully explain the dramatic increase, however, and a portion may reflect changes in the patterns and/or intensity of environmental exposures.

Coordination of federal research efforts in autism

The rising prevalence of ASD has had impact in several areas, raising awareness and stimulating interest of the general public, strengthening advocacy efforts on behalf of affected families, attracting new researchers to the field and spurring an acceleration and intensification of federal ASD activities. The Interagency Autism Coordinating Committee (IACC) brings together five NIH Institutes that support autism research, other relevant Department of Human Health and Services (DHHS) agencies, autism advocacy organizations and public members. This committee is charged with developing and annually updating a Strategic Plan for Autism Research. NIEHS is a member of the IACC and has participated in the major NIH autism research initiatives, including the Autism Centers of Excellence (ACE) program and several linked program announcements (PAs) that have solicited and funded research to addresses objectives within the Strategic Plan. Overall, NIH funding of ASD research has seen significant growth, rising from $56 million dollars in 2001 to an estimated $169 million dollars in 2012. Over that same period of time, NIEHS investment in ASD research has grown from zero dollars in 2001 to an estimated eight million dollars in 2012.

Recent progress in understanding autism etiology

The increased attention and funding for ASD research in the past decade have spurred considerable progress in identifying etiologic risk factors and the underlying pathobiology. The pattern of brain abnormalities observed in individuals with ASD point to a process that begins in early prenatal life. Multiple lines of evidence support a strong genomic basis for ASD, including results from twin and family studies and the known association with single gene disorders and chromosomal abnormalities. Recent findings point to an unexpected role for rare structural genomic variations, ranging from de novo insertions and deletions to single nucleotide variation. To date, a very large number of rare structural variants have been linked to ASD, with different genes, or sets of genes affected in different individuals with ASD.   Many ASD genes appear to converge on a few common biologic pathways, including those focused on synaptic maturation and maintenance. A role for epigenomics is suggested by the presence of ASD in individuals with disorders associated with epigenetic mutations (Fragile X syndrome) or that involve key epigenetic regulatory factors (Rett syndrome), parent of origin effects and/or linkage with imprinted chromosomal regions..

Some progress has been made in identifying environmental contributors to ASD and their interaction with genomic susceptibility. For example, results of several studies report an increased risk of ASD associated with exposure to traffic-related air pollution during gestation. Other environmental factors with suggestive evidence for an association with ASD include maternal exposure to pesticides, infections, dietary folate and specific pharmaceuticals. An enhanced susceptibility to environmental exposures is suggested by the presence of abnormal immune responses, metabolic and mitochondrial abnormalities observed in some individuals with ASD. A few studies are beginning to lend support to the idea of gene-environment interaction in autism. For example, the protective effect of prenatal vitamin use depends upon genetic variation in folate metabolism genes. A recent study using genetically engineered mice reported that PBDE exposure enhanced the effects of an ASD-related genetic defect. Both maternal and paternal age at conception increase risk for ASD in the offspring, and this may reflect, in part, the accumulation of exposure-related genetic abnormalities in germ cells. Finally, there has been speculation that exposures affecting ASD risk act through epigenomic mechanisms. This is a plausible hypothesis given the demonstrated role of epigenomics in ASD and the increasing data available to support the impact of environmental chemicals on epigenomic regulation.

Research Goals and Scope of planned NIEHS initiative

Despite the progress cited above, additional attention is needed to accelerate the pace of research aimed at identifying environmental contributors to ASD. Research challenges and opportunities in this area have been identified from a number of sources, including NIEHS-sponsored autism workshops in 2010 and 2011 and the most recent yearly updates to the IACC Strategic Plan. Experts convened for these meetings agreed that the evidence for the role of the environment is growing, but too slowly. There are too few studies focused on the role of the environment in ASD. The published epidemiologic findings are intriguing, but most need independent replication

and the pathobiology underlying reported associations is unclear. Very few mechanistic studies using in vitro approaches or model systems have been initiated. While many environmental exposures have known neurodevelopmental effects, and merit investigation as ASD risk factors, few have been studied in sufficient detail. Investigators have not exploited fully existing epidemiologic and clinical data and samples that could be used for the study of environmental contributors to ASD. For the most part, genetic and genomic studies are occurring in parallel with those on the environment, with little attention to a consideration of joint genetic and environmental contributors.

Research questions and approaches meriting additional attention

Human studies in clinical and population samples are needed to:

- overlay environmental exposure data on existing GWAS data to assess the interplay of common genetic variation and environmental exposure in ASD.
- explore the relationship between environmental exposures, inherited and de novo rare structural variation (e.g., copy number variation, single nucleotide variation) and ASD risk
- investigate how environmental exposures may mediate the reported association of parental characteristics (e.g., maternal and paternal age, maternal metabolic and immune-related conditions) with ASD risk
- identify and validate biomarkers of susceptibility to exposures (e.g., changes in gene expression, metabolic profiles, mitochondrial response), explore their interrelationships and their relevance to ASD risk and related phenotypes
- determine time periods during peri-conceptional, gestational, perinatal, and early childhood associated with greatest autism risk from environmental exposures
- use postmortem materials or other extant biospecimens to determine levels of specific environmental chemicals and their relation to ASD risk and/or expression
- identify specific patterns of epigenetic and epigenomic alterations (e.g., DNA methylation and hydroxymethylation, histone modifications, higher order chromatin remodelling and non coding RNA regulation), in ASD and explore their potential association with and/or regulation by environmental exposures.

Studies using in vitro, cellular and whole organism models are needed to:

- develop and apply screening approaches to identify candidate exposures that interact with biologic pathways/genes implicated in ASD
- capitalize on genetically engineered models that recapitulate features of ASD or ASD-related endophenotypes to determine how exposures alter expression of those phenotypes
- elucidate the mechanism/underlying biology related to exposures that have been reported as ASD risk factors in human studies (e.g., role of inflammation and oxidative stress response in traffic-related air pollution)

- explore use of induced pluripotent stem cells (iPSc) from genetically and clinically characterized individuals with ASD to explore patterns of sensitivity/resistance to candidate environmental exposures

Mechanism and justification

The growth of autism funding targeted at identifying environmental contributors is insufficient for the urgency of the problem to be addressed. Additional effort is needed to increase the number of applications and their success rate. It is notable that the majority of the autism grants funded by NIEHS in the past five years occurred in response to targeted Request for Applications (RFAs), including the American Recovery and Reinvestment Act (ARRA) autism initiatives, NIEHS/EPA Children's' Centers RFAs, and the Autism Centers of Excellence (ACE) RFAs. Other applications proposing studies on autism and the environment often cite the existing NIH omnibus program announcements (PAs) for autism research but there is no set aside or special review, resulting in a very low success rate.

To remedy these shortcomings, a three year Program Announcement with a special review (PAR) is proposed. This approach has been used successfully by NIEHS to build research programs in other understudied and high priority areas, including obesity, developmental origins of health and disease and climate change. The proposed autism and environment PAR is intended to:

- stimulate the interest of investigators in developing proposals that address environmental contributors to autism;

- provide a consistent review climate for those applications, one with a critical mass of expertise in autism as well as environmental health science/toxicology;

- provide a better basis for funding decisions by enabling direct comparisons among a group of applications that have been reviewed side by side, rather than spread over different submission cycles and study sections; and

- ultimately, increase the number of studies, investigators and approaches being applied to address the role of the environment in the etiology of ASD.

A diversity of approaches and exposures of interest are needed to advance this field of research and will be solicited by the PAR, with the intent to have the broadest possible impact. Investigators with sufficient preliminary data and well developed proposals for human studies and/or interdisciplinary studies that combine human and non-human mechanistic studies will be eligible to submit R01 proposals. Investigators with less developed ideas and/or who are pursuing exploratory, high risk/high payoff studies and have little or no preliminary data will be encouraged to submit R21 proposals.

The PAR will be released in January 2014 and will be active for three years, with a single receipt date each year (see Table 1). The Center for Scientific Review (CSR) will convene a special emphasis panel (SEP) to review applications submitted. NIEHS plans to set aside two-three million dollars to fund applications submitted for the first year of the PAR. Applicants for the next two years of the PAR will benefit from the focused review and will receive programmatic priority in funding discussions but there

will be no separate pool of funds set aside. We will consider making changes to the PAR (e.g., restricting focus to mechanistic non-human studies) depending upon the results obtained the first year.

Table 1. Tentative timeline for PAR Environmental Contributors to Autism Spectrum Disorders

Release PAR in NIH Guide	Receipt Date	Review Date	Council	Earliest funding
January 2014	April 2014	July 2014	September 2014	December 2014
	April 2015	July 2015	September 2015	December 2015
	April 2016	July 2016	September 2016	December 2016

Exposures of interest to NIEHS include industrial chemicals or manufacturing byproducts, endocrine disrupting chemicals, metals, pesticides, herbicides, air pollutants and other inhaled toxicants, particulates or fibers, secondary tobacco smoke exposure and fungal/bacterial or biologically derived toxins. Other NIH institutes with a potential interest in participating in the PAR include NINDS, NICHD and NIMH. Depending upon their participation, the PAR may be broadened further to include lifestyle and nutrition factors infectious agents, pharmaceutical and other medical exposures.