

Report 2: Identification of pre-, peri-, and post-natal environmental factors that contribute to variation in neurodevelopmental outcomes

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Brief History: Our understanding of the role of early developmental exposures on the developing nervous system is still extremely limited. Studies of the etiology of conditions such as autism spectrum disorder (ASD), schizophrenia, and depression, suggest that both genetic susceptibility and environmental factors contribute to risk. For example, in the case of ASD, the prevalence of this condition has increased by over 600% over the past few decades. Three sources of evidence indicate that environmental risk factors are contributing to the increased prevalence of autism: First, epidemiological studies indicate that factors such as broadening of the ASD diagnosis, diagnostic substitution, increased awareness and access to services, only account for approximately 50% of the increase in ASD prevalence. Second, numerous studies have identified several environmental risk factors, such as reproductive assistive technology, infection during pregnancy, suboptimal birth conditions and prematurity, advanced parental age, and exposure to pesticides and air pollutants, can contribute to increased risk for ASD. Third, a recent study involving a relatively large sample of identical and fraternal twins showed that the concordance rate for ASD in fraternal twins was much larger than previously reported and much larger than that in non-twin sib pairs, implicated the role of a shared prenatal environment. By identifying the specific environmental risk factors, along with the mechanism of risk, prevention of neurodevelopmental disorders and promotion of optimal outcomes is possible.

Discussion Highlights: The following challenges and scientific areas of investigation were highlighted:

1. Phenotyping: Better characterization of sub-phenotypes and more rapid and quantitative phenotyping methods that can be used in large epidemiological studies targeted to neurodevelopmental disorders; development of etiologically relevant endophenotypes that can be incorporated into broader, general population-based studies
2. Role of de novo CNVs to increased risk of neurodevelopmental disorders
3. The need for animal models for neurodevelopmental disorders
4. Effects of reproductive assistive technologies on risk for neurodevelopmental disorders
5. Influence of air pollution and other environmental contaminants on risk for neurodevelopmental disorders.
6. Family studies as a method for better understanding of environmental risk factors for neurodevelopmental disorders.
7. Epigenetic influences
8. Cross-collaborative (cross-breeding) project as a way of screening for environmental contributors to environmental risk

9. Usefulness of induced pluripotent stem cells for screening potential toxicants that may have etiological significance.
10. Need for better exposure assessment methods.

Recommendations:

1. There is a need for better characterization of sub-phenotypes among neurodevelopmental conditions, such as ASD, that can inform etiologic heterogeneity. For example, are there specific phenotypes that can be linked to specific exposures?
2. There is a need to develop etiologically relevant endophenotypes for neurodevelopmental disorders
3. Recent studies show that there is an increased rate of de novo CNVs in regions of the genome where ASD risk genes are located. There is a need to identify environmental risk factors that are contributing to the increased rates of de novo CNVs, and the biological mechanisms involved. Among the candidate environmental factors that need to be explored are reproductive assistive technologies, such as ICSI and IVF, advanced parental age, hormones, and nutrition.
4. Studies that compare the phenotypes, exposures, and rates and types of de novo CNVs in fraternal twins, identical twins, and siblings, and their parents are recommended. Such studies would provide insight into the mechanisms by which de novo CNVs may be contributing to the etiology of neurodevelopmental disorders.
5. There is a critical need to better understand the biological mechanisms/pathways that underlying neurodevelopmental disorders, such as ASD. Approaches to increasing our understanding include gene knock-out and knock-in mice, mice bred for neurodevelopmental phenotypes (e.g. social withdrawal, repetitive behaviors), systems biology approaches and pathway analysis of genetic findings, induced pluripotent stem cells, among others. Once biological mechanisms are better understood, it will be possible to study candidate environmental influences on these pathways.
6. As genomics research identifies potential biologic pathways underlying neurodevelopmental disorders, studies examining the influence of environmental influences on these pathways (eg., capitalizing on work done in the toxicogenomics, and other such initiatives) should be conducted.
7. Studies on the contribution of environmental contaminants, such as air pollution, pesticides, and others, to the etiology of neurodevelopmental disorders are needed.
8. There is a continuing need for large cohort (case-control, prospective, high risk siblings, and others) epidemiological studies that can identify the unique and combined effects of environmental risk factors and their interaction with underlying genetic susceptibility. The National Children's Study offers a unique and important opportunity to study gene-

environmental interactions and their contribution to the etiology of neurodevelopmental disorders, such as ASD, ADHD, depression, schizophrenia, intellectual disability, and so on.

9. Studies that explore the role of nutrition during the pre-conception, prenatal, and postnatal period as a contributor to variations in intellectual abilities and neurodevelopmental outcome are needed.
10. Studies are recommended that explore the role of epigenetic mechanisms in the etiological of neurodevelopmental disorders.

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