2012 INTERAGENCY AUTISM COORDINATING COMMITTEE STRATEGIC PLAN UPDATE: QUESTION 3 WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

WHAT IS NEW IN THIS RESEARCH AREA, AND WHAT HAVE WE LEARNED IN THE PAST 18 MONTHS?

The past year has seen an explosion of research on genomic factors associated with autism. Sequencing of the entire coding portion of the genome (exome) *(1-3)* and copy number variation (CNV) analyses *(4)* indicate that as many as one thousand genes may contribute to autism risk. Many of these are submicroscopic changes in chromosomal structure (CNVs) or changes in the DNA sequence (single nucleotide variants, SNVs), that arise (*de novo*) in parental sex cells *(5)*. Results from multiple studies have revealed neurodevelopmental loci that confer risk across diagnostic boundaries *(6)*. Exome sequencing has identified ASD risk genes that encode proteins involved in chromatin modification (*CHD8*), neurotransmission (*GRIN2B*), neuronal excitation (*SCN2A*), microtubule binding (e.g., *KATNAL2)* and cell signaling and neurogenesis *(DYRK1A) (7-10)*. A convergence point linking these risk genes may be the altered expression and interaction of proteins important for signaling pathways that stabilize excitation-inhibition at synapses within neural networks *(11-14)*. Other risk genes related to metabolic disorders (eg, carnitine metabolism and branched chain amino acid synthesis *(15,16)* have also been identified. Collectively, genomic and exomic variants and mutations are estimated to account for about 10-25% of autism cases *(15)*. A substantial portion of ASD risk may be conferred by common variation acting in an additive fashion (32).

These complex results present major challenges, not only in understanding causes of autism, but also in identifying treatments effective for a large fraction of cases. "Autism" is likely several etiologically distinct disorders that converge on a common set of behavioral deficits. Moreover, there is already considerable evidence that the multiple autism genetic risk genes converge on a smaller number of biological mechanisms, suggesting targets for developing treatments aimed at the underlying biology, as opposed to requiring a specific treatment for each different mutation.

The complex genetics of autism necessitate investigations at the interface of genomics and environmental exposures that account for biotic (e.g., dietary factors) and xenobiotic (e.g., exposures to drugs and environmental toxicants) factors. New research has emphasized the substantive role for environmental causes (potentially as large as or larger than genetic heritability) in the etiology of autism *(17-19)*. A recent large US twin study *(17)* found that the comparison of concordance rates (the percent of times that both twin pairs have ASD where at least one twin has ASD) between dizygotic (DZ) and monozygotic (MZ) twins (i.e., fraternal vs. identical) supports a large etiologic role for non-heritable environmental, as well as heritable genetic, causes. This DZ twin concordance rate estimate was double a recent estimate of non-twin sibling recurrence risk published by the Baby Siblings Research Consortium (20). This supports the idea that the prenatal period, when DZ twins differentially share 'environment' to a greater extent than non-twin siblings, is of special interest with respect to environmental influences. The importance of the prenatal window in autism etiology is further supported by a new molecular study of autism brain tissue samples that noted an absence of an expected cortical gene expression pattern (21) that is known to emerge during fetal development (22).

Comment [A1]: Discussion Point: Should the new paper by O'Roak et al. be included (Science, Nov. 15, 2012)? It shows that rare mutations are recurrent.

Comment [A2]: Discussion Point: Is there a way to make this more consistent with the statement about synapses in Question 2?

Comment [A3]: Discussion Point: This paragraph covers a lot of ground (16 references – many in Nature and Cell). Is it clear for a broad audience? Would it be clearer as a few bullets of "what we know now"?

Comment [A4]: Discussion Point: Perhaps add to or revise this sentence to make it more understandable.

Comment [A5]: Discussion Point: Does the subcommittee agree with this conclusion?

Comment [A6]: Discussion Point: Perhaps begin the paragraph with this sentence.

Comment [A7]: Discussion Point: The DZ rate from Hallmayer was .21 for male twins; the recurrence rate in the Baby Sibs was 18.7% overall and 26.2% for males (Ref 20). Doesn't this suggest the opposite conclusion?

Comment [A8]: Discussion Point: Cortical gene expression is heavily influenced by postnatal development. Perhaps delete this sentence.

A list of candidate environmental exposures was identified for future study developed in a workshop of experts supported by NIEHS and Autism Speaks. The list included: lead, methylmercury, polychlorinated biphenyls, organophosphate, pryerthroid, and organochlorine insecticides, endocrine disruptors, automotive exhaust, polycyclic aromatic hydrocarbons, brominated flame retardants, and perfluorinated compounds *(23)*. Recent evidence has emerged that certain of these environmental chemicals (specific congeners) are particularly relevant to autism because they alter gene expression and signaling pathways regulated by the proteins they encode, that contribute to autism. In particular, developmental exposure of rodents to certain polychlorinated biphenyls (PCBs) has been shown to alter activity-dependent dendritic growth by mechanisms implicated in autism *(24-26)*, and have been detected in higher levels in a syndromic form of autism *(27)*. Insecticides are known to target neurotransmitter systems known to be impaired in autistic children (*28-29*). One strategy for identifying environmental risk factors for ASD may be to focus on factors that converge on the same signaling pathways as known ASD susceptibility genes *(30- 31)*.

Comment [A9]: Discussion Point: This sentence is unclear. With over 1000 genes involved, can this be specific? Delete?

Genetic factors can amplify adverse effects triggered by environmental exposures by converging to dysregulate the same signaling systems at critical times of development. Larger potentially more easily detectable effects can be found by conditioning on genotypes related to the common signaling systems. This past year the first study reporting candidate genotype modification of an environmental exposure on autism risk was published - offering empirical evidence backing a broad causal paradigm (gene-environment interaction) in ASD etiology. A protective effect of periconception vitamin use on ASD risk was found to be dependent on both maternal and child genes coding for one-carbon metabolizing variants (13). These findings have to be viewed with caution, however, and must be replicated.

Comment [A10]: Discussion Point: Is there a reference that could be inserted for this statement?

Finally, a 2012 meta-analysis of existing epidemiologic studies found evidence supporting an independent effect of advancing maternal age on ASD risk (a similar 2010 analysis showed an association between paternal age and ASD risk (14). Also, a series of studies confirmed the correlation between paternal age and *de novo* mutation rate (1-4) and showed that the majority of *de novo* ASD mutations are from the father's genome *(2, 5)*. While a *de novo* mutation mechanism seems most important in driving associations between paternal age and autism risk, the mechanism behind the maternal age association remains unknown. Furthermore, the role environmental factors may play as antecedent causes or interacting factors in mechanisms mediated by de novo mutations, or in other causal mechanisms, is unknown.

Comment [A11]: Discussion Point: How strong is this? Has it been seen in other studies? Kong et al. 2012 and Richenberg et al. 2006 both negative when father's age is regressed out.

WHAT GAPS HAVE EMERGED IN THE PAST 18 MONTHS?

Since our last update several new investigations have emphasized the substantive role for environmental factors in the etiology of autism (18 - 20). Environmental stressors, including chronic exposure to xenobiotic chemicals, can contribute to the positive associations among

Comment [A12]: Discussion Point: Only reference 19 provides new data and this reports mitochondrial function in 10 pts without evidence for environmental factors.

parental age, accumulations of mutations and errors in meiosis in parental gametes, and autism-promoting *de novo* CNVs in their children.

Given the universe of potential environmental factors, one of the challenges is prioritizing candidate exposures and lifestyle factors that can promote developmental neurotoxicity. Prioritization can be based on expert consensus (e.g. list of ten priority exposures developed in 2012), research findings pointing to windows of susceptibility, such as the prenatal and preconception period, screening of exposures that converge on the same signaling pathways as ASD susceptibility genes, and a focus on replicated findings, such as studies explicitly designed to reveal exposures mediating the proven association between parental age and autism risk. Elucidating exposures shown to influence de novo mutation during spermatogenesis is a priority. The exposures potentially mediating the maternal age autism risk association could involve a mechanisms associated with intrauterine environment. Challenges to accurately measure exposures in etiologic windows many years antecedent to the emergence of diagnosis are substantial. The 2012 NIEHS Strategic Plan includes exposure research as one of six major themes and there is little doubt that innovations in biomarker-based exposure assessment would be helpful in the autism research field.

Rapid throughput high-content screening is needed to be developed, validated and implemented in an effort to identify the most potent chemical and/or biochemical agents that alter neuronal connectivity, synaptic structure and plasticity, by interfering with signaling pathways implicated in autism and related disorders. Integration of physiological, biochemical, and morphological analysis of stem cell-derived neuronal and immunological models (based on iPSC or transdifferentiation technology) from patients that have been fully genotyped and deeply phenotyped are needed to understand gene x environment interactions and reveal exposure biomarkers.

Given the high degree of genetic heterogeneity in ASD, a high priority should be ascertaining family trios for comprehensive genomic analysis, including whole exome sequencing, CNV studies, and sequencing of mutations in non-coding regions. Understanding inherited variation in ASD has been hampered by lower effect sizes associated with transmitted variation (both rare and common) and the need for very large patient cohorts. Successful studies of common inherited variation in conditions like schizophrenia point to the need for larger patient cohorts and very large-scale collaborative mega-analyses.

Further, to understand the interplay of genetic susceptibility and environmental exposure, there is a need to combine genomics data with exposure measures, development and application of appropriate statistical methodologies, and even larger samples than required for studies focused on detecting either genetic or environmental main effects only. Otherwise, studies detecting effects run the risk of not being replicated. There is a need for novel analytic approaches that maximize power and minimize false discovery rate.

Studies continued to document metabolic (oxidative stress, low glutathione levels, redox imbalances, mitochondrial dysfunction) and immune system abnormalities (anti-brain antibodies and dysregulated cytokine production) in children with ASD and, in some cases, in their mothers

during gestation. It needs to be investigated when these abnormalities are present (e.g. at birth or acquired within the neonatal period) and whether they are etiologic.

Word count: 1467

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