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 2 YEARS?

The past two years have seen an explosion of research on genomic factors associated with autism, with more than 900 papers on "autism and genetics" listed in PubMed (an online database of biomedical research literature) in 2011 and 2012. Progress in genomics has been enabled by the advent of rapid, inexpensive, precise sequencing tools and the availability of large repositories of DNA samples. At the time of the initial *IACC Strategic Plan for ASD Research*,in 2009, most genomic research was focused on finding common variants in the genome, believed to act in an additive fashion. While these common variants are still of interest, recent research has mapped out four new areas for understanding the risk for ASD. First, there are as many as 1,000 rare changes in DNA structure or DNA sequence that contribute to ASD risk (Coe, Girirajan & Eichler, 2012; Neale et al., 2012; O'Roak et al., 2012b; Sanders et al., 2012). Sometimes these changes involve duplications or deletions of more than a million nucleotide bases (the building blocks of DNA) and sometimes only a few bases are altered, but the result in either case can be increased risk for ASD. Second, these changes are frequently spontaneous, or *de novo*, arising in sperm or eggs prior to conception (Iossifov et al., 2012). That is, if tested, neither parent would show these mutations in cells such as their blood cells, but the mutations could be found in the father's sperm cells, which divide throughout life. Third, most of the genetic findings implicated in ASD are not specific to ASD—they include neurodevelopmental loci, or regions in the DNA, that also confer risk for brain disorders such as schizophrenia, epilepsy, attention deficit hyperactivity disorder (ADHD), and intellectual deficit syndromes (Malhotra & Sebat, 2012). While rare and not specific to ASD, the same genomic changes are found repeatedly (O'Roak et al., 2012a). Finally, this complex picture of multiple, nonspecific, spontaneously-arising genetic factors is beginning to converge on a few biological pathways, particularly signaling pathways that stabilize activity at synapses, or junctions between neurons, in the brain (Devlin B, Scherer, 2012; Malhotra & Sebat, 2012; Veltman & Brunner, 2012; Zoghbi & Bear, 2012). However, synaptic genes are not the entire story; autism risk genes related to metabolic disorders (carnitine metabolism and branch chain amino acid synthesis) (Anney et al., 2012; Casey et al., 2012) have also been identified. Whereas genomic factors were estimated to account for up to 10% of autism cases in 2009, the most recent studies based on whole exome sequencing find currently identifiable genomic variants and mutations in 25% of cases (Devlin & Scherer 2012; Sanders et al., 2012).

These complex results present major challenges, not only in understanding causes of autism, but also in identifying treatments that will be effective for a large fraction of cases. "Autism" is likely several etiologically distinct disorders, or disorders with different sets of causal factors, 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 biological pathways, as opposed to requiring a specific treatment for each different mutation.

The complexity of autism risk necessitates research on the interface between genomics and environmental exposures, including research on how biotic (e.g., dietary factors) and xenobiotic (e.g., exposures to drugs and environmental toxicants) factors may interact with genetic susceptibility. New research has emphasized the role of non-genomic risk factors. The largest U.S. twin study compared the concordance rates (the likelihood that both twins share an ASD diagnosis) in identical (monozygotic) twins, who share 100% of their DNA, and fraternal (dizygotic) twins, who share 50% of their DNA. In contrast to earlier, higher estimates, the ASD concordance rate for male identical twins was 77% (58% for strict autism, a smaller subset of ASD) and for male fraternal twins was 31% (21% for strict autism) (Hallmayer et al., 2011). The lower concordance rate for identical twins in this study compared to the rates identified in previous studies suggested that genomic factors (including spontaneous mutations) might be less important than previously claimed from twin studies. In addition, since the concordance rate in fraternal twins was considerably higher than the traditional figure of 3 – 10% estimated for siblings, the study appeared to support the importance of the prenatal environment, which is shared by fraternal twins but not by non-twin siblings. A recent report from the Baby Siblings Research Consortium, however, challenged the previously mentioned traditional figure of a 3-10% recurrence rate in siblings; the study, using a larger sample size and updated methodology, suggests that the non-twin male sibling rate of developing ASD is 26.2%, in the range of concordance for male fraternal twins (Ozonoff et al., 2011). Thus, the rate of autism in fraternal twin siblings and in non-twin siblings may be more similar than previously thought.

A list of candidate environmental exposures identified for future study was developed in a 2010 workshop of experts supported by the National Institute of Environmental Health sciences (NIEHS) and Autism Speaks. The list, published in 2012, included: lead, methylmercury, polychlorinated biphenyls, organophosphate, pyrethroid, organochlorine insecticides, endocrine disruptors, automotive exhaust, polycyclic aromatic hydrocarbons, brominated flame retardants, and perfluorinated compounds (Landrigan, Lambertini & Birnbaum, 2012). These compounds are widely distributed within the environment and have known neurodevelopmental effects that may be relevant to autism. For example, insecticides are known to target neurotransmitter systems known to be impaired in autistic children (Roberts et al., 2007; Shelton, Hertz-Picciotto & Pessah, 2012). Within the past year, developmental exposure to specific types of PCBs (polychlorinated biphenyls, compounds used in many industrial applications as insulators, coolants and plasticizers) in rodents was reported to alter activity-dependent growth of neuron dendrites by mechanisms implicated in autism (Pessah, Cherednichenko & Lein, 2010; Wayman et al., 2012a; Wayman et al., 2012b), and these chemicals were detected in higher levels in brains of individuals with a syndromic form of autism (Mitchell et al., 2012). In addition, a study of exposure to traffic pollution which involved examination of residential history of individuals and regional measurement of nitrogen dioxide and particulate matter found an increased risk for autism among children exposed to the highest levels of pollution, even after controlling for ethnicity, parental education, smoking during pregnancy, or living in a densely populated region (Volk et al., 2012).

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 (Pessah & Lein,

2008; Stamou & Lein, *in press).* Genetic factors can amplify the effects of environmental exposures by disrupting the same signaling systems during critical periods of development. The task of detecting environmental risks can be facilitated by the use of analytic approaches that incorporate genetic information. This enables identification of those combinations of exposures and genes that confer the highest risk. The value of this approach in the field of autism was demonstrated this past year, when a protective effect of vitamin use during the months before and after conception on ASD risk was found to be dependent on both maternal and child genes coding for one-carbon metabolizing variants (Schmidt et al., 2011). These findings have to be viewed as preliminary, however, and must be replicated.

Finally, a 2012 meta-analysis of existing epidemiologic studies found evidence supporting an independent effect of advancing maternal age on ASD risk (Sandin et al., 2012)—a similar 2011 analysis showed an association between paternal age and ASD risk (Hultman et al., 2012). Also, a series of studies confirmed the correlation between paternal age and *de novo* mutation rate (Neale et al., 2012; O'Roak et al., 2012b; Sanders et al., 2012) and showed that the majority of *de novo* ASD mutations are from the father's genome (Iossifov et al., 2012; O' Roak, 2012b). 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 that environmental factors may play as preceding causes or interacting factors in mechanisms mediated by *de novo* mutations, or in other causal mechanisms, is unknown.

WHAT GAPS HAVE EMERGED IN THE PAST 2 YEARS?

Although the 2011 strategic plan update reported that environmental research is an understudied area that has been given insufficient attention and requires heightened priority, there continues to be a need for significant attention to this area of research, with new insights about *de novo* mutations suggesting a potential link between environmental and genomic factors. Given the universe of potential environmental factors, one of the challenges is prioritizing candidate exposures and lifestyle factors that could potentially increase risk for autism. Prioritization can be based on expert consensus (e.g., list of ten priority exposures developed in 2012) (Landrigan, Lambertini & Birnbaum, 2012), research findings pointing to windows of susceptibility, such as the preconception and prenatal periods, 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 association between parental age and autism risk. The challenges to accurately measuring exposures in critical developmental time windows many years prior 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 needs 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 neuronal and immunological cellular models is needed. These models should be

based on cells derived using new techniques such as induced pluripotent stem cell (iPSC) technology (in which one type of adult cell, such as skin, is first reprogrammed into a stem cell and then induced into a different type of cell, such as a neuron) or transdifferentiation technology (similar to iPSCs, except that adult cells are directly reprogrammed into a different type of mature cell without having to go through the intermediate pluripotent stem cell stage). Furthermore, this research must be conducted on samples collected from patients that have been fully genotyped and deeply phenotyped in order to understand gene-environment interactions and reveal exposure biomarkers.

Given the high degree of genetic heterogeneity in ASD, a high priority should be placed on ascertaining family trios (two parents and one affected child) for comprehensive genomic analysis, including whole exome sequencing (sequencing of only the coding regions of DNA), CNV studies, and sequencing of mutations in non-coding regions of DNA. Understanding inherited genetic variation in ASD has been hampered by the lower effect size (the strength of the relationship between the genetic variation and the ASD phenotype) that is characteristic of research into rare and common genetic variants associated with ASD as well as 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 analyses.

Further, to understand the interplay of genetic susceptibility and environmental exposure, genomics data must be combined with exposure measures, and appropriate statistical methodologies must be developed and applied. With this approach, larger samples are required than for studies focused on detecting either genetic or environmental main effects alone, in order to detect these small interactive effects. Novel analytic approaches must also be developed to maximize accuracy in detecting effects when they exist.

Finally, studies continued to document metabolic (e.g., oxidative stress, low glutathione levels, redox imbalances, mitochondrial dysfunction) and immune system abnormalities (e.g., anti-brain antibodies and dysregulated cytokine production) in individuals with ASD and, in some cases, in their mothers during gestation. Additional research should investigate when these abnormalities are present (e.g., at birth or acquired within the neonatal period) and whether they are related to risk for autism.

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