UNCOVERING THE ETIOLOGY OF AUTISM SPECTRUM DISORDERS: GENOMICS, BIOINFORMATICS, ENVIRONMENT, DATA COLLECTION AND EXPLORATION, AND FUTURE POSSIBILITIES

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A clear and predictive understanding of the etiology of autism spectrum disorders (ASD), a group of neurodevelopmental disorders characterized by varying deficits in social interaction and communication as well as repetitive behaviors, has not yet been achieved. There remains active debate about the origins of autism, and the degree to which genetic and environmental factors, and their interplay, produce the range and heterogeneity of cognitive, developmental, and behavioral features seen in children carrying a diagnosis of ASD. Unlocking the causes of these complex developmental disorders will require a collaboration of experts in many disciplines, including clinicians, environmental exposure experts, bioinformaticists, geneticists, and computer scientists. For this workshop we invited prominent researchers in the field of autism, covering a range of topics from genetic and environmental research to ethical considerations. The goal of this workshop: provide an introduction to the current state of autism research, highlighting the potential for multi-disciplinary collaborations that rigorously evaluate the many potential contributors to ASD. It is further anticipated that approaches that successfully advance the understanding of ASD can be applied to the study of other common, complex disorders. Herein we provide a short review of ASD and the work of the invited speakers.

1. Autism Spectrum Disorders a Brief Introduction

Autism spectrum disorders (ASD) are characterized by a range of clinical features that can vary from individual to individual in both the degree of severity and variability of the clinical presentation. This can include abnormalities in language, reciprocal social interactions, and/or other communication skills as well as repetitive behaviors[1]. Autism spectrum disorders are divided into three basic categories: autistic disorder (frequently referred to as autism), Asperger syndrome, and pervasive developmental disorder (PDD-NOS)[1]. These disorders, as of 2008, affect 1 in 88 children, and are more prevalent in males than females[2]. The prevalence estimates of ASD have increased, above increases due to changes in diagnostic criteria[1,3]. In addition, children with ASD often have intellectual disability, estimated as high as 68% of ASD cases[4], and approximately 75% have lifelong disability requiring social/educational support[5]. The presence of ASD can have a significant impact on the quality of life of affected persons, but also for their family and/or other caregivers.

2. The Pacific Symposium on Biocomputing (PSB) ASD Workshop

Many studies have been investigating the connection between genetic variation and ASD. Twin studies have indicated that ASD are highly heritable[6,7]. Linkage studies have implicated a polygenic basis for autistic disorder[8]. However, genome-wide association studies (GWAS) for ASD have identified few potential loci associated with ASD[9–11]. Copy-number variation (CNV) studies, in contrast, have been more successful in identifying genomic regions associated with an increased risk for autism, and also other neurodevelopmental disabilities such as schizophrenia and epilepsy, with overlap of several genomic regions[5,12,13]. Copy number variations can be deletions, duplications, inversions, or translocations. While the location of CNVs may differ from individual to individual with ASD, these CNVs can still result in similar clinical features and outcomes[12].

During the workshop, Dr. Santhosh Girirajan and Dr. Evan Eichler will describe work investigating the genetic and phenotypic heterogeneity of neurodevelopmental disorders in the context of CNVs, particularly for ASD[12,14–16]. Dr. Girirajan's research has been focused on the discovery of genetic variants associated with the causation, diagnosis, and biological interpretation of ASD. A recent manuscript by Girirajan et al. showed evidence that individuals with autism have higher numbers of larger copy-number variants, and that these are more duplication based instead of deletion events[17].

Dr. Eichler will be speaking about the successful application of exome sequencing for children with ASD and their parents, as well as work determining copy-number variant (CNV) burden differences across neurodevelopmental phenotypes. Dr. Eichler is a leader in study of the relationship between CNVs and human disease and has focused his research on building an understanding of the evolution, pathology and mechanism(s) of recent gene duplication and DNA transposition within the human genome[18]. This research has included discovery of these important genomic regions, development of methods to assess their variation, detection of rapid gene evolution, and identifying the correlation between discovered genetic variation and phenotypic differences, including autism spectrum disorders.

Dr. Neale will describe the impact of high-throughput sequencing on ASD gene discovery, highlighting the contribution of rare variation to ASD as well as the pleiotropic effects of ASD associated mutations. His talk will also review challenges that remain in this field for detection and interpretation of inherited and de-novo rare-variants in ASD. Dr. Neale has conducted analyses for genetic data focused on psychiatric illness, particularly ADHD and autism, but also Tourette's obsessive compulsive disorder, schizophrenia[19] and eating disorders.

Investigation of environmental risk factors for ASDs is a growing research field[19,20]. The wide heterogeneity of ASD symptoms, and how to best ascertain individuals for study, are challenging. Different clinical features and the range of severity across individuals may stem from varying genetic contributors, but could also be due, in part, to variations in environmental exposures. Further, increasing rates of ASD indicate the potential for environmental exposure playing an important role in the etiology and/or heterogeneity of ASD. There is also a need for the exploration of gene-environment interactions[20]. Identifying both genetic variants concomitant with environmental exposure may provide important insights into the etiology of ASD.

Dr. Heather Volk will be speaking at the workshop, describing her work exploring the relationship between environmental exposure and the etiology of autism. Her research focuses on the environmental and genetic epidemiology of autism and other neurodevelopmental disorders and on gene-environment interactions in complex disease. Oxidative stress and inflammation may play a key role in ASD, with adverse prenatal effects. Dr. Volk will describe the impact of exposure to traffic-related air pollution on prenatal development and risk of ASD. In two recent reports by Volk et al., children with autism were more likely be have the highest exposure to traffic-related air pollution during gestation and the first year of life, compared to non-autistic controls[21] and maternal residence at time of delivery was more likely to be close to a freeway for autism cases vs. controls[22].

Dr. Pessah will be describing work from the UC Davis Medical Investigation of Neurodevelopmental Disorders (MIND) Institute. Researchers at the MIND Institute are among the world's experts on molecular and environmental contributors to ASD as well as the use of epidemiological data for testing the cellular and molecular mechanisms of ASD. These researchers have established the most comprehensive database in the world of the environmental exposures of children with confirmed ASD or atypical development, linked to an extensive archive of clinical samples, and Dr. Pessah will describe interdisciplinary approaches that leverage this unique set of resources.

Epigenetic changes are another potential contributor to the etiology of ASD. Epigenetics is the study of heritable changes in chromosomes, not encoded in the DNA sequence, including DNA methylation and chromatin organization. DNA methylation is an important link between genetic and environmental interaction, as DNA hypomethylation is known to lead to genome instability. "Environmental epigenetics" explore this connection, identifying important environmental influences on epigenetic change[23]. For example, arsenic, cadmimum, benzene and other exposures have been associated with DNA methylation in genes, as well as dietary factors[23]. The invited speaker, Dr. LaSalle of the MIND Institute, has performed pioneering studies on the epigenetic etiologies of ASD. The clinical applications of her research include understanding the pathogenesis of the neurodevelopmental disorders autism, Rett syndrome, Prader-Willi syndrome,

Dup15q syndrome, and Angelman syndrome, through identifying epigenetic pathways disrupted in rare genetic disorders on the autism spectrum. Dr. LaSalle's recent research is on environmental exposures affecting the DNA methylome and employing novel bioinformatics methods for analysis and visualization of epigenomic data relevant to autism.

An important part of any research is any potential ethical implications of those discoveries, this is true for ASD research as well. Because of the large numbers of individuals affected with autism, and the impact on children and families, as well as the potential for environmental exposure during pregnancy/youth to play a role, publications and press outside of the research-manuscript realm are more likely to report research results from studies of environmental exposures and ASD. A well known example is a paper published in 1998 in The Lancet[24], later retracted, linking measles, mumps, and rubella (MMR) vaccine and autism. A review by the Institute of Medicine clearly showed no link between the thimerosal-containing vaccines after review of over 200 studies[25]. However the controversy that emerged over vaccines due to the initial publication has had a lasting impact on parents choosing to vaccinate children, and public health, even while autism is no more common among vaccinated than unvaccinated children[26].

With the increasing amount of ASD research and the recent extension of research in different complex directions, there are a range of important ethical considerations when reporting the results of ASD studies to families, clinicians and the research community. Dr. Newshaffer is an epidemiologist and his currently involved in large risk factor epidemiology studies, autism phenotyping studies, genomic and epigenomic research, and studies focused on the utilization and evaluation of health care and behavioral intervention services[1,27–29]. He will discuss a number of issues including the uncertainty, comprehension, inadvertent harm, as well as appropriate roles of clinicians, scientists, and the media, in ASD communication.

3. Conclusions

While a complete understanding of ASD is still growing, through comprehensive and collaborative efforts we may begin to identify additional pieces of the ASD puzzle that can be linked with our existing current knowledge to grow a clearer picture of these disorders. The collaboration of multiple domain-experts will be required to effectively analyze the growing genetic and epidemiological data being collected. To foster these cross-disciplinary interactions and research projects, we have developed this workshop for PSB, to share the current knowledge of the genetic and environmental contributions to ASD and to highlight methods for future research in this field, including important ethical considerations. The intention is to grow new ideas, collaborations, and possibilities for future research in this field, between current autism spectrum researchers and other scientists in attendance at PSB. In addition to improving the understanding of the etiology of ASD, methodologies developed for the ASD field have the potential for expanding and improving the study of other common, complex disorders.

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