Untangling the genetic architecture of complex disorders

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Bio: Dr. Girirajan is an Associate Professor in the Biochemistry and Molecular Biology and the Department of Anthropology at Pennsylvania State University. Dr. Girirajan is a Medical Doctor by training, with an MBBS degree from Bangalore University, India. He then completed his PhD in Human Genetics from the Medical College of Virginia, VCU, under the supervision of Dr. Sarah Elsea (now at Baylor College of Medicine), and performed his postdoctoral training from the University of Washington in Dr. Evan Eichler's lab. In the Eichler lab, he was mainly interested in understanding the mechanisms and phenotypic implications of large-scale genomic rearrangements in complex diseases.

The primary focus of his lab at Penn State is to discover and characterize genetic changes including genomic deletions and duplications and single nucleotide mutations contributing to neurodevelopmental disorders such as autism, intellectual disability, schizophrenia, epilepsy, and congenital malformation. The research incorporates high-throughput genomic techniques including array comparative genomic hybridization, genome, and transcriptome sequencing, computational approaches, and model organisms to understand the genetic basis of human complex diseases.

Abstract: Recent advances in genomic technologies have identified effects of different classes of genetic variants that vary in effect size and population frequency towards complex disorders such as autism, intellectual disability, and schizophrenia. Several themes have emerged from these studies that present challenges in our understanding of the functional basis of these disorders. First, most gene discoveries for these neurodevelopmental disorders rely on identifying de novo mutations. In fact, only less than 25% of cases of complex disorders could be attributed to de novo mutations in single genes. Second, the same variant or gene has been associated with different clinical outcomes, such as the 15q13.3 deletion associated with both autism and epilepsy. Third, incomplete penetrance and variable expressivity have a complicated clinical diagnosis and genetic counseling. These challenges render our understanding of genetic contributions to disease incomplete. My laboratory uses a combination of human genetics, model systems, and computational approaches to dissect the genetic architecture of autism and intellectual disability disorders. I will present examples of our work on each of these aspects, to make a case for how genetic interactions can explain the missing heritability of complex disorders.

Educational Objects: Upon completion, participants should be able to:
● Appreciate the complexity of understanding the genetic basis of human disorders.
● Understand how most disorders are non-Mendelian and are influenced by multiple genes.
● Appreciate the utility of model systems and their relevance to study core mechanisms of human disease.

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