Differential Allele Expression Effects in the Brain Shape Genetic Architecture at the Cellular Level

Wei-Chao Huang[1], Elliott Ferris[1], Christopher Gregg[1]

1. Department of Neurobiology & Anatomy, University of Utah School of Medicine, Salt Lake City, Utah

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Several genomic studies revealed that loss-of-function heterozygous mutations, rather than recessive mutations, are involved in autism spectrum disorders as well as schizophrenia. We do not fully understand how heterozygous mutations contribute to complex disease. In a diploid genome, most genes have two copies and the healthy backup copy can reduce the impact of heterozygous mutations. However, if the mutated allele is the only allele expressed and the expression of the healthy allele is silenced, then a heterozygous mutation could have a stronger impact. Currently, the allele-specific effects best understood are genomic imprinting effects in which either the maternal or paternal allele is silenced for a small number of genes in the genome. Random monoallelic expression effects are also known to exist in the genome and impact genes on the X-chromosome in females, immune genes, and some autosomal genes. However, little is known about the prevalence of allele-specific effects in vivo for most genes in the genome.

We asked whether or not the maternal or paternal alleles are equally co-regulated for most genes in the genome. We developed a novel approach that analyzes maternal and paternal allele co-expression effects using RNASeq. Surprisingly, we discovered that thousands of genes in the genome differentially express their alleles. To determine the nature of genes with differential allele expression at the cellular level, we used a novel ultra-sensitive in-situ hybridization to detect allele-specific expression at the cellular level in tissue sections. The analysis revealed that genes with differential allele expression at the tissue level by RNASeq exhibit monoallelic expression in subpopulations of cells in vivo in the brain. Furthermore, we analyzed the cellular expression of the mutant lacZ allele versus the wildtype allele in vivo by using heterozygous mutant transgenic mice with a lacZ reporter gene inserted to disrupt the gene with differential allele expression to determine whether these novel effects impact the cellular expression of mutated and healthy alleles for inherited heterozygous mutations. We found some cells preferentially express the mutant allele, while other cells preferentially express the healthy allele. Overall, our new approach and discovery that many genes exhibit differential allele expression, and that these effects impact the cellular expression of heterozygous mutations, will improve our understanding of the genetic architecture of complex diseases.