

## Rethinking the nature of “genotype”: Indexing by copy number variation reveals previously undiscovered genome-wide significant SNP associations in expression quantitative trait loci analysis

Lea K. Davis

University of Chicago, USA

Current analysis methodologies used in genome-wide association studies (GWAS) collapse the homozygous (i.e., A/A), hemizygous (i.e., A/0) and duplicative (i.e., A/A/A) genotype states at any given autosomal locus. This approach assumes that these classes of genotype are equivalent and treats the genotype variable itself as irreducible or unaltered by other co-occurring forms of genetic (e.g., structural) variation. However, our understanding of common, genome-wide copy number variation (CNV) clearly suggests that the construct of genotype may belie the enormous complexity of the genome. We provide here compelling evidence demonstrating the effect of co-occurring genetic variants on GWAS. We describe a new approach to association mapping, which we call copy number indexed GWAS (cni-GWAS). We show that properly accounting for allelic dosage can dramatically increase power to detect associations in genome-wide analysis of expression quantitative trait loci (eQTLs). A comprehensive study of trait-associated SNPs identified by GWAS shows them to be enriched, relative to allele frequency matched SNPs, for loci where allelic content is subject to altered dosage due to loss of chromosomal material. These findings have important implications for the analysis of all phenotypes and suggest that some portion of the “missing” heritability may be recovered by indexing SNPs according to copy number status.

### Biography

Lea K. Davis completed her Ph.D., research in human genetics at the University of Iowa in 2009 focusing on the role of copy number variation in human disease. From 2009 to 2011 she conducted research as a postdoctoral associate at University of Illinois in Chicago with Dr. Ed Cook. From 2011-2013 she has worked with Dr. Nancy Cox at The University of Chicago. She is now a Research Associate (Assistant Professor) at the University of Chicago and has over 20 papers published or in press in journal such as *Human Genetics*, *American Journal of Medical Genetics*, and *Molecular Psychiatry*.

[lea.k.davis@gmail.com](mailto:lea.k.davis@gmail.com)