

Genetics of Gene Expression and its effect on disease

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A steadily growing number of studies have identified and characterized expression and splicing quantitative trait loci (eQTLs) in human cell-lines, primary cells, and tissues. This class of genetic variation has been shown to play a role in complex traits, including disease. I will discuss how eQTLs in primary immune cells have accelerated the discovery of disease genes and functional mechanisms underlying complex traits. I will discuss how context-specificity of eQTLs is being characterized at an unprecedented scale and breadth, and how this informs on the intricacy of human genome function. I will present results from the ImmVar project demonstrating remarkable polarization of functional effects on innate immune function for Alzheimer's and Parkinson's disease. This observation represents an important advance that significantly refines the emerging narrative of the role of the myeloid cells in susceptibility to neurodegenerative diseases. I will also present results from a comprehensive study of mRNA gene expression and splicing from the transcriptome of over 1,000 Alzheimer's disease (AD) brains to demonstrate that AD susceptibility variants regulate the generation of aberrant mRNA splicing (sQTLs) through effects on RNA binding proteins, and that the splicing machinery is altered by the pathophysiology of AD. Together, these studies have important ramifications for elucidating function of genetic variants of interest, particularly for those contributing to neurodegenerative disease. These contributions provide a foundation for further mechanistic studies that will elucidate the drivers of disease, dissect the resulting causal chain leading to neurodegeneration and pave the way for future drug discovery efforts.