Application number/Title: 45624 - Combined impact of genetic variants that physically interact in the 3D genome on disease susceptibility

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Keywords provided by the Applicant PI to describe the research project:
3d genome, gene regulation, genetic risk, pathogenic cell types

Application Lay Summary:

Genetic variation enables the vast diversity observed in the human population, but genetic variation is also what defines our predisposition to disease. One of the primary goals in the field of genetics is to identify which genetic variants contribute to disease in order to learn more about how a disease works and affects the body. Ultimately, understanding these genetic risk factors can help inform patient diagnosis, treatment, and preventative care. However, identifying these genetic variants, is only the first step toward these goals. In order to identify new insights into the pathogenesis of human disease, we must first understand why a particular genetic variant puts one at risk of developing the disease.

There are two critical steps toward understanding why a particular genetic variant contributes to disease. The first is to determine the gene that is affected by the genetic variant and secondly, to determine where in the body this effect impact takes place. These questions are often challenging because many genetic risk factors do not fall within genes. Rather, these genetic variants can be found in "regulatory elements" which do not encode for proteins. These regulatory elements vary across the different cell types in the human body and play an important role in controlling which genes are made into proteins and how much protein is made in any given tissue.

In this study, we leverage new insights about the function of regulatory elements to help determine what tissue is affected by the genetic risk factor. We have previously applied this approach to multiple sclerosis, which is both an autoimmune and neurodegenerative disease. We identified MS genetic risk

factors that impact immune cell function in the blood, as well as genetic factors that impact the function of neuron-protecting cells in the brain. Using the UKbiobank, we will apply this approach to the study of neuropsychiatric diseases, in particular substance use disorders. We will integrate results from our analysis of the UKbiobank data with experimental data that measures regulatory element function in different brain cell types and regions. This will enable us to evaluate which cell types in the brain are affected by genetic variation that increases one's susceptibility to these traits. This study will enable us to generate new information as to why a given genetic variant contributes to disease and will reveal new insights into how a given disease progresses within the body.