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Embracing Complexity: Supercomputing Enabled Systems Biology to Understand Complex Neurosystems

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Complex neuropsychological conditions, including substance use disorders, often show high heritability but many traditional approaches to find the underlying genetic architectures (e.g. GWAS) have only been able to explain small portions of heritability. The heritability of Autism Spectrum Disorder (ASD), based on more than two million children from 680,000 families and five countries, is estimated to be nearly 80%, yet we lack genetic markers that explain it. Major reasons may be the exclusion of structural variation (SV) in previous analyses plus the heterogeneous nature of the disorder. Here we use a new method to determine parent-child genotypes to generate a completely novel database of ASD SVs and validate them in a second set. Contrary to previous studies, using a SV and systems biology based approach we find highly penetrant SVs in ASD cases that disrupt genes that control dendritic spinogenesis, axon guidance, and chromatin modification. We further define fine-grained biological pathways at the molecular level that strongly implicate aberrant early development of the cerebellum and auditory processing in the disorder. In addition, we will discuss how these approaches can be used for research in substance use disorders