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The Missing Heritability of Complex Disorders: Structural Variants Hiding in Plain Site

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The heritability of substance abuse disorders is high, ranging from 40-70%, and yet genome-level interrogations have been unable to identify variants that underlie most cases. Proposed sources of this "missing heritability" include (1) interaction among variants (epistasis), (2) many hundreds of single nucleotide polymorphisms (SNPs), each of small effect, or (3) rare variants of large effect that are difficult to sample. We applied a novel method we developed to detect structural variation (SVs, genomic changes greater than 50 bp) to genotypes from individuals diagnosed with autism spectrum disorder (ASD) and instead find that a major source of this missing heritability is most likely cryptic SVs that are difficult to identify with current methods. Like addiction and substance abuse disorders, ASD is highly heritable neuropsychiatric phenotype (80%, based on 680,000 families and five countries) yet few genetic markers have been identified to adequately explain it. The genes harboring the SVs we discovered easily recapitulate the known molecular biology of ASD including dendritic spine development, axon guidance, and chromatin modification. Using independent RNA-Seq data from postmortem brain tissue we reveal that a frequent ASD-associated SV disrupts at splice site in the GRIK2 gene, and we further define biological pathways that strongly implicate aberrant early development of the cerebellum. Importantly, using these previously excluded variants, we identify the *ACMSD* gene in the kynurenine pathway as significantly associated with non-verbal cases of ASD and we then use an explainable artificial intelligence approach to define subgroups for future diagnosis and deployment of personalized medicine.