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L1 Retrotransposons in Psychiatric and Substance Use Disorders

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Psychiatric and substance use disorders have substantial heritability. However, explanation of this heritability using common genetic variants, such as single nucleotide polymorphisms (SNPs) and copy number variants (CNVs), in genome wide association studies, has proven difficult. Long interspersed element 1 (L1) retrotransposons are a class of heritable genetic variants that are not detected by traditional studies of SNPs and CNVs, and literature evidence supports a role for L1 retrotransposons in psychiatric and substance use disorders. To investigate the role of L1 retrotransposons in the heritability of psychiatric and substance us disorders, we developed REBELseq (Restriction Enzyme Based Enriched L1 sequencing), a technique that allows for the identification of the number and location of L1 retrotransposons in the human genome. Using REBELseq, we have identified inherited polymorphic L1 retrotransposon insertions that are significantly associated with risk for Schizophrenia, Bipolar Disorder and Cocaine Use Disorder, a subset of which have now been validated in >6,800 samples. Additionally, biological pathway analysis suggests that intragenic L1 retrotransposon insertions may differentially affect biological pathways associated with Schizophrenia and Cocaine Use Disorder. Taken together, these results suggest that L1 retrotransposon may play a role in the heritability of psychiatric and substance use disorders, and that the overrepresentation of L1 retrotransposons in relevant biological pathways may help explain the disease etiology of psychiatric and substance use disorders.