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HOT TOPICS

Mobile DNA and the brain

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Neuropsychopharmacology (2022) 47:411–412; https://doi.org/10.1038/s41386-021-01151-x

The genetic etiologies of many complex psychiatric conditions, neurodevelopmental defects, and neurodegenerative disorders are poorly understood. Although genome wide association studies (GWAS) have linked thousands of genetic loci with many brain disorders, most causal variants remain to be discovered. Mobile DNA, which comprises ~45% of the genome, consists of multiple copies of different types of transposable elements (TE; e.g., *LINE1, Alu, SVA, HERV*) and other repetitive sequences [1]. Traditionally labeled *Junk DNA*, TE induce germline, somatic DNA, and epigenetic changes that are strongly implicated in development, cancer, and other genetic diseases [2]. TE are highly active in the developing brain and expressed in specific brain tissues in adults under normal and disease states. However, they are understudied in neurological and neuropsychiatric conditions due to many challenges, including: differences between the germline and brain genomes within an individual; somatic mosaicism within the brain, which necessitates sequencing small numbers of cells from specific brain tissues; genomic sequencing limitations of repetitive DNA; and lack of inclusion in GWAS detection strategies [1]. Here we discuss evidence that TEs are emerging candidates for brain disorders.

Highly polymorphic *Alu* elements are disproportionately identified through GWAS [3]. Payer et al. tested the hypothesis that *Alu* elements modulate disease risk through co-opting mRNA splicing. They found an *AluY* insertion in *CD58* that is in strong linkage disequilibrium ($r2 > 0.9$) with a risk allele for multiple sclerosis [4]. The *AluY* insertion causes aberrant splicing of *CD58*, resulting in a frameshift. This data plausibly links *Alu* elements with disease risk, as reduced *CD58* expression is associated with increased risk for multiple sclerosis [4].

Human endogenous retroviruses (*HERV*), once thought to be inactive viral remnants, are proving to be important modulators that induce phenotypic consequences. Wang et al. [5], demonstrated that *HML2*, the most recently incorporated *HERVK* subtype, is necessary for embryonic and neurological development. The HML2 envelope protein is highly expressed on the surface of pluripotent stem cells, signaling through direct binding to CD98HC, which activates the mTOR and lysophosphatidylcholine acyltransferase signaling cascades. Wang et al. [5], further demonstrated that downregulation of the HML2 envelope protein dissociated stem cell colonies and drove differentiation down neuronal trajectories.

Zhu et al. [6] sought to understand the implications of somatic TE insertions in neurological disorders. They developed a machine learning approach, called RetroSom, to analyze *LINE1* and *Alu* insertions in sorted human neurons and glia. They found intronic *LINE1* insertions in two genes associated with neuropsychiatric disorders, *CNNM2* and *FRMD4A*. The insertion in *CNNM2* disrupted a potential regulatory element that is associated with schizophrenia in humans and mouse models. They also detected a TE that disrupts the coding region of *FRMD4A*, a gene associated with microcephaly and intellectual abilities. Enhanced GFP reporter assays in cell culture demonstrate that these insertions impaired endogenous gene expression.

These findings, along with others in the literature, provide evidence that TE could contribute to a variety of neurological and neuropsychiatric diseases. Developing tools and methods to better study TE may uncover new mechanisms underlying complex brain disorders.

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AUTHOR CONTRIBUTIONS

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Published online: 16 August 2021

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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