Examining the patchwork of mutations contributing to bipolar disorder

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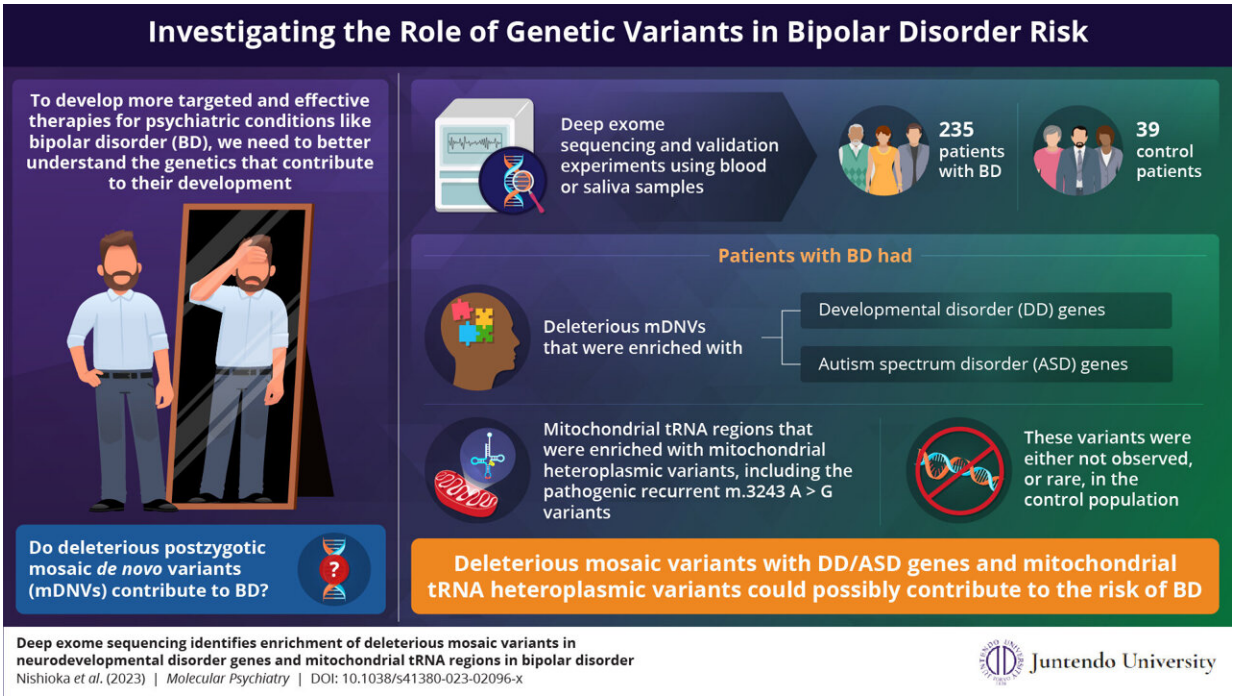

Japanese researchers showed that genes associated with developmental disorders and autism spectrum disorders are significantly enriched with deleterious mosaic mutations in patients with bipolar disorder (BD). Similarly, the mitochondrial tRNA region of these patients also showed significant enrichment of deleterious mosaic mutations. These findings help better understand the genetics and pathogenesis of BD. Credit: Masaki Nishioka from Juntendo University

Bipolar disorder (BD) is a major psychiatric condition that afflicts about

1% of people. Symptoms of BD include sudden onset of depressive mood with loss of interest which alternates with a manic state of hyperactivity. The suffering of the patients and societal cost of this disorder requires the use of continued therapeutic management.

Current medications—although vital for patients with BD—are not perfect solutions, given their potential side-effects and treatment resistance. This necessitates the development of better therapeutics for BD, including precision medicine. A major hindrance to this process, however, lies in our limited understanding of the underlying biological mechanisms of BD, i.e., its pathogenesis and the genetic architecture of people with BD.

Several studies have linked BD with hereditary mutations, but recent genomic studies are now focusing on somatic mosaic variants—new mutations occurring during developmental stages—as another possible mechanism behind psychiatric disorders like BD.

In a new study published in *Molecular Psychiatry* a team of researchers led by Associate Professor Masaki Nishioka of Juntendo University, Japan, investigated the association between mosaic variants and the risk of BD. The research team included Dr. Tadafumi Kato, also from Juntendo University, and Dr. Atsushi Takata from RIKEN Center for Brain Science.

"Most analyses exploring the genetic mechanisms of BD involve extracting information from mutations that are shared among all the cells of the patients. However, mosaic de novo mutations or somatic mutations, which arise during development, are not shared among all the cells. We know very little about how these mutations influence diseases like BD. Therefore, for our study, we hypothesized that deleterious mosaic de novo variants (mDNVs) in the genes associated with developmental disorders may have a role in BD's pathology," explains

Dr. Nishioka.

The team recruited 235 participants with BD and 39 control participants without psychiatric disorders. They collected blood or saliva samples from the participants and analyzed the DNA extracted from these samples using deep exome sequencing (DES) to detect mosaic variants that originated during early development.

Participants with BD had mosaic variants enriched in genes that are responsible for causing developmental disorders (DD) and autism spectrum disorder (ASD). Moreover, the proteins encoded by the DD/ASD genes with the proteins of the mosaic variants were closely linked and had more protein-protein interactions than expected.

Surprisingly, the team also found significant heteroplasmic mutations (another class of mosaic variants) in mitochondrial tRNA genes of participants with BD. For reference, some tRNA mutations are known to be pathogenic for other diseases.

In fact, two participants with mitochondrial tRNA mutations had recurrent m.3243 A > G variants, which are known to be major causal variants for mitochondrial diseases, MELAS, which is a serious neurodevelopmental disorder. This finding complements other studies that have found that patients with mitochondrial diseases often exhibit symptoms of bipolar disorder or schizophrenia.

Furthermore, both the sets of deleterious mosaic variants—mDNVs and mitochondrial tRNA variants—were either absent or rarely observed in the control participants. These results indicate that the molecular mechanisms underlying DD/ASD could also contribute to BD in a compromised way through mosaic mutations. Moreover, they suggest that mitochondrial tRNA variants could be associated with BD despite the patient showing no obvious symptoms of mitochondrial diseases.

With this study, the researchers demonstrate that mosaic mutations, particularly those in neurodevelopmental disorder genes and mitochondrial tRNA genes, may be involved in the pathophysiology of BD. Dr. Nishioka is encouraged by what their study's findings mean for scientists pursuing the research of molecular pathologies in neuropsychiatric diseases.

He concludes, "Our research sheds new light on the genetic architecture of BD and provides more insights into the pathological contribution of mosaic variants in human diseases. This could potentially pave the way and expedite new research for the development of more effective, precision medications for treating BD and other psychiatric disorders."

More information: Masaki Nishioka et al, Deep exome sequencing identifies enrichment of deleterious mosaic variants in neurodevelopmental disorder genes and mitochondrial tRNA regions in bipolar disorder, *Molecular Psychiatry* (2023). DOI: 10.1038/s41380-023-02096-x

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