
**Insights into the genetic architecture of neuropsychiatric disorders through the lens of
genome structural instability**

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Abstract:

Human neurodevelopmental disorders have a strong genetic underpinning. Genome structural changes, particularly those involving complex alterations, are key drivers of these disorders. Complex structural variations (cxSVs), which are localized rearrangements of multiple DNA segments, are often overlooked in human genome analyses due to detection challenges. We developed Automated Reconstruction of Complex Structural Variations, a probabilistic and machine-learning method that enables the characterization of cxSVs on a population scale with unprecedented accuracy using standard whole-genome sequencing. By analyzing genomes spanning all continental populations, we observed that cxSVs—especially those that are rare in the human population (i.e., with signatures of negative selection)—are particularly enriched, more so than other variant types, in neural genes and loci that underwent rapid human-specific evolution, including those regulating human-specific corticogenesis. Through integrative analyses of postmortem brains, including those from individuals with schizophrenia and bipolar disorder, our results implicate cxSVs as a previously unrecognized contributing factor in the complex genetic architecture of human neuropsychiatric disorders.

Reading List:

- <https://www.pnas.org/doi/10.1073/pnas.2322834121>
- <https://med.stanford.edu/news/all-news/2024/10/complex-genomic-variants-psychiatric-diseases.html>
- <https://www.sciencedirect.com/science/article/pii/S0092867424010328?via%3Dihub>