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TITLE:

Local genetic correlation analysis reveals heterogeneous etiologic sharing of autism spectrum disorder and cognitive performance

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ABSTRACT:

Local genetic correlation quantifies the genetic similarity of complex traits in specific genomic regions, which could shed unique light on etiologic sharing and provide additional mechanistic insights into the genetic basis of complex traits compared to global genetic correlation. However, accurate estimation of local genetic correlation remains challenging, in part due to extensive linkage disequilibrium in local genomic regions and pervasive sample overlap across studies. We introduce SUPERGNOVA, a unified framework to estimate both global and local genetic correlations using summary statistics from genome-wide association studies. Through extensive simulations and analyses of 30 complex traits, we demonstrate that SUPERGNOVA substantially outperforms existing methods and identifies 150 trait pairs with significant local genetic correlations. In particular, we show that the positive, consistently-identified, yet paradoxical genetic correlation between autism spectrum disorder and cognitive performance could be explained by two etiologically-distinct genetic signatures with bidirectional local genetic correlations. We believe that statistically-rigorous local genetic correlation analysis could accelerate progress in complex trait genetics research.

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