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Assortative Mating—A Missing Piece in the Jigsaw of Psychiatric Genetics

Robert Plomin, PhD; Eva Krapohl, MSc; Paul F. O'Reilly, PhD

The topic of assortative (nonrandom) mating might seem esoteric or even salacious. For example, in lectures you have to point out to students that random mating is not about promiscuity. In this issue of *JAMA Psychiatry*, Nordsletten and colleagues¹ report the first



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general population study to date of assortative mating for psychiatric disorders, which may help to solve 3 puzzles in psychiatric genetics: Why are psychiatric disorders so highly heritable when they are associated with reduced fecundity? Why are some psychiatric disorders so much more highly heritable than others? Why is there so much genetic comorbidity across psychiatric disorders?

The research capitalizes on the powerful population registers in Sweden, which contain diagnostic information, including psychiatric diagnoses, on all individuals admitted to Swedish hospitals since 1973. The registers yield huge samples of cases (eg, more than 70 000 individuals diagnosed as having schizophrenia). Using other registers to track couples via their children, the investigators were able to measure assortative mating levels within and between 11 psychiatric disorders.

Although you can see assortative mating for physical traits, like height and weight, with your own eyes, the correlation between spouses is only approximately 0.20 for these traits. For personality, assortative mating is even lower at approximately 0.10. In contrast, Nordsletten and colleagues¹ find an amazing amount of assortative mating within psychiatric disorders. Spouse tetrachoric correlations are greater than 0.40 for attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and schizophrenia. The next highest spouse correlation emerged for substance abuse (range, 0.36-0.39). Assortative mating was significant but far less substantial for other disorders, such as affective disorders (range, 0.14-0.19).

These findings are intriguing in relation to the first 2 puzzles about heritability of psychiatric disorders. The significance of assortative mating for polygenic traits, such as psychiatric disorders, is that it increases additive genetic variance generation after generation until equilibrium is reached. Additive genetic variance refers to genetic effects that breed true from parents to offspring because they involve independent effects of alleles that “add up.” This additive variance is in contrast to nonadditive effects of dominance within a locus or epistasis across loci in which the effects of alleles or loci interact. Unlike inbreeding, which reduces heterozygosity across the genome, assortative mating is trait specific. That is, it increases additive genetic variance (changing genotypic frequen-

cies but not allelic frequencies) only for genes associated with the trait for which mates assort and other traits genetically correlated with that trait.

As a consequence, assortative mating increases the contribution of additive genetic variance (narrow heritability) for any trait on which it acts. This boost to heritability from assortative mating could help to explain why psychiatric disorders have such high heritability despite reduced fecundity.

Assortative mating could also contribute to the second question about why some psychiatric disorders—most notably, ADHD, ASD, and schizophrenia—are more heritable in twin studies than other disorders, such as the affective disorders. The answer from the article by Nordsletten and colleagues¹ could be that the former show twice as much assortative mating as the latter.

However, these solutions are not quite as clear cut as they may seem. The argument goes that the abundant assortative mating for ADHD, ASD, and schizophrenia increases additive genetic variance. However, twin studies suggest that nonadditive genetic influence is greater for these same 3 disorders than for other disorders in that dizygotic twins are much less than half as similar as monozygotic twins.² Most notably, concordance for ASD is approximately 60% for monozygotic twins and approximately 5% for dizygotic twins.² Nonetheless, it is possible that these 3 disorders are so highly heritable because they include injections of both additive genetic variance from assortative mating and unusually high nonadditive genetic variance. Without assortative mating, these disorders might show little additive genetic variance.

Another issue that needs to be resolved involves DNA-based heritability estimates, which only detect additive genetic variance. From the findings by Nordsletten and colleagues¹ alone, one would predict that DNA-based heritability estimates should be greater for ADHD, ASD, and schizophrenia than for affective disorders, but the results so far suggest otherwise.³ Nonetheless, the dust is yet to settle on the explosion of research estimating heritability using DNA alone. It is crucial to resolve this issue because genome-wide association studies typically only search for additive genetic effects. In other words, additive genetic variance is the ceiling both for DNA-based heritability estimates and for identifying DNA variants in genome-wide association studies. Understanding its extent and causes is key to psychiatric genetics research.

The third genetic puzzle is why there is so much genetic comorbidity across psychiatric disorders. A major discovery from genome-wide association studies is that genetic vari-

ants associated with one disorder (eg, schizophrenia) are usually also associated with other disorders. Genome-wide estimation of genetic correlations across psychiatric disorders supports the conclusion that many genetic effects are general across disorders. For example, genetic correlations are approximately 0.60 between schizophrenia and bipolar disorder and approximately 0.20 between schizophrenia and ASD.⁴

Assortative mating across psychiatric disorders could help to drive this genetic comorbidity. Nordsletten and colleagues¹ report that such cross-assortative mating is extensive. All of the spouse cross-correlations in Figure 1 in their article are significant. One of the highest spouse cross-correlations is 0.31 between schizophrenia and ASD, which could contribute to the genetic correlation of approximately 0.20 between these disorders in the population. An apparent contradiction is that the genetic correlation between schizophrenia and bipolar disorder is 0.60 but their cross-assortative mating is only 0.15. However, this finding might result from the low assortative mating for bipolar disorder (correlation, 0.15).

A nice touch in the article by Nordsletten and colleagues¹ is their reporting of 5 nonpsychiatric disorders (eg, diabetes mellitus and rheumatoid arthritis) that do not show these patterns of cross-assortative mating. This result suggests that the processes involved in cross-assortative mating and their effect on genetic architecture may be limited to psychiatric disorders.

The results by Nordsletten and colleagues¹ showing substantial assortative mating within and across psychiatric disorders correspond only to phenotypic (not genetic) correlations between spouses. Is it possible that assortative mating

is induced environmentally by convergence of spouses rather than genetically by assortment? For cognitive abilities—the other behavioral domain long known to show substantial assortative mating—assortative mating is due to initial selection of a mate (assortment) rather than by couples becoming more similar to each other after living together (convergence).⁴ Nordsletten and colleagues¹ cite literature suggesting a similar conclusion for psychiatric disorders.

Therefore, it will be intriguing to verify these phenotypic results for assortative mating using DNA. A study⁵ using genome-wide genotypes reported that spouses are more genetically similar than 2 individuals chosen at random from the population, although it is possible that population stratification contributed to this result.⁶ However, this finding was a general genome-wide estimate of genetic similarity between spouses that was not specific to psychiatric disorders. It is possible to assess the extent to which genome-wide similarity between spouses accounts for phenotypic assortative mating and cross-trait assortative mating by using univariate and bivariate extensions of DNA-based heritability estimates.⁷ However, very large samples of couples with genome-wide genotypes would be required for this analysis. An easier approach would be to examine the extent to which polygenic scores derived from genome-wide association studies for psychiatric disorders correlate between spouses.

Beyond genetics and genomics, assortative mating matters because it means that the person closest to an individual with a psychiatric disorder is also likely to have psychiatric problems, which could exacerbate problems for both spouses and their offspring.

ARTICLE INFORMATION

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