Biological Psychiatry: Celebrating 50 Years

Commentary

Assortative Mating in Autism Spectrum Disorder: Toward an Evidence Base From DNA Data, but Not There Yet

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The term "assortative mating" always seems a bit distasteful when applied to humans, but it is the most succinct way to convey the concept of the consequences in children (and their descendants) associated with a consistent trend of phenotypic similarities between parents of heritable traits. Almost all phenotypes have some genetic contribution, and therefore children have trait values correlated with those of their parents. There are so many dimensions on which partner choice can be made that the genetic structure within future generations is not necessarily affected (Figure 1). In contrast, assortative mating implies a consistency across pairs of parents in the population in mate choice preferences associated with a trait. Height and educational attainment are perhaps the most easily identifiable candidates for assortative mating. Strong partner correlations are also reported for personality traits (1), consistent with the results of a comprehensive assessment of the co-occurrence of psychiatric disorders (2). The fundamental importance of assortative mating is the impact it may have in future generations through an increase in genetic variance and, for psychiatric disorders, an increase in prevalence over time (3). In this issue of *Biological Psychiatry*, Connolly *et al.* (4) used DNA data in an attempt to provide direct evidence for assortative mating in autism spectrum disorder (ASD). However, our evaluation suggests that strong evidence-based conclusions cannot yet be drawn.

Assortative mating, by definition, is placed in the context of a population. For example, Nordsletten *et al.* (2) provided the most comprehensive assessment of assortative mating for psychiatric disorders using complete national records of Sweden from 1973 to 2014. Their estimate for the phenotypic correlation between parents of ASD was 0.47 (sex-averaged). However, this correlation is not an estimate of spouse pair correlation in the population, because the estimate was made in a sample that was ascertained on the affected status of one of the parents. The estimate of the assortative mating from these data for the population as a whole, correcting for this ascertainment bias, was 0.28 (3). Similarly, Connolly *et al.* (4) do not consider a population sample but instead consider parents ascertained through the diagnosis of ASD in their child or children. ASD affects only approximately 1% of the general population, and therefore this is a highly ascertained group, particularly because the sample is enriched for multiplex families (i.e., those with more than one affected child).

Connolly *et al.* (4) approach the challenge of assessing assortative mating within this highly ascertained group by testing the hypothesis that if assortative mating is present, the spouse pairs will be genetically more similar to each other than between nonspouse pairs, where nonspouse pairs represent all possible pairings of male and female parents in the data set excluding the true spouse pairings. Using the method of Domingue *et al.* (5), Connolly *et al.* (4) provide a similarity measure estimate from the Autism Genome Project cohort of 1092 spouse pairs of 0.025 (95% confidence interval 0.011, 0.039), which is significantly different from zero. This result contrasts with a nonsignificant estimate from 101 spouse pairs from the International HapMap Project data 0.0176 (95% confidence interval −0.024, 0.057). Connolly *et al.* (4) conclude that there is evidence of assortative mating for ASD in the "population" of Autism Genome Project parents. However, when Domingue *et al.* (5) presented their similarity measure, they provided no guidelines for the expected value of this statistic. We have derived the mathematical relationship between their similarity measure and the classical genomic coefficient of relationship estimated from genome-wide association study single nucleotide polymorphism data (6). We show that even though contrasting genetic similarity between spouse and nonspouse pairs is intuitively appealing, in fact, millions of spouse pairs are required to detect assortative mating by this method (7). We believe that this study is underpowered for the method used, and our calculations suggest that the similarity statistic estimate is, in fact, implausibly high given best-guess assortative mating parameters.

A key question in analyses of assortative mating is how to distinguish the putative signal from population stratification. Connolly *et al.* (4) attempt to address this question. By using 101 International HapMap Project parent–offspring trios, they demonstrate that their method generates a massively significant test statistic when the ancestries of the trios (11 African American, 42 European, and 48 Yoruban) are ignored but becomes nonsignificant when the nonspouse pairs were restricted to within the ancestry groups. Based on this experience, the authors selected 1092 spouse pairs from the Autism Genome Project set (comprising ancestries defined as 782 European, 53 Mexican, 103 Tuscan Italian, 11 Gujarati Indian, 24 admixed Tuscan Italian/European, and 118 European/Tuscan Italian) and conducted comparisons of spouse pairs and nonspouse pairs within these groups. Given our experience of working with

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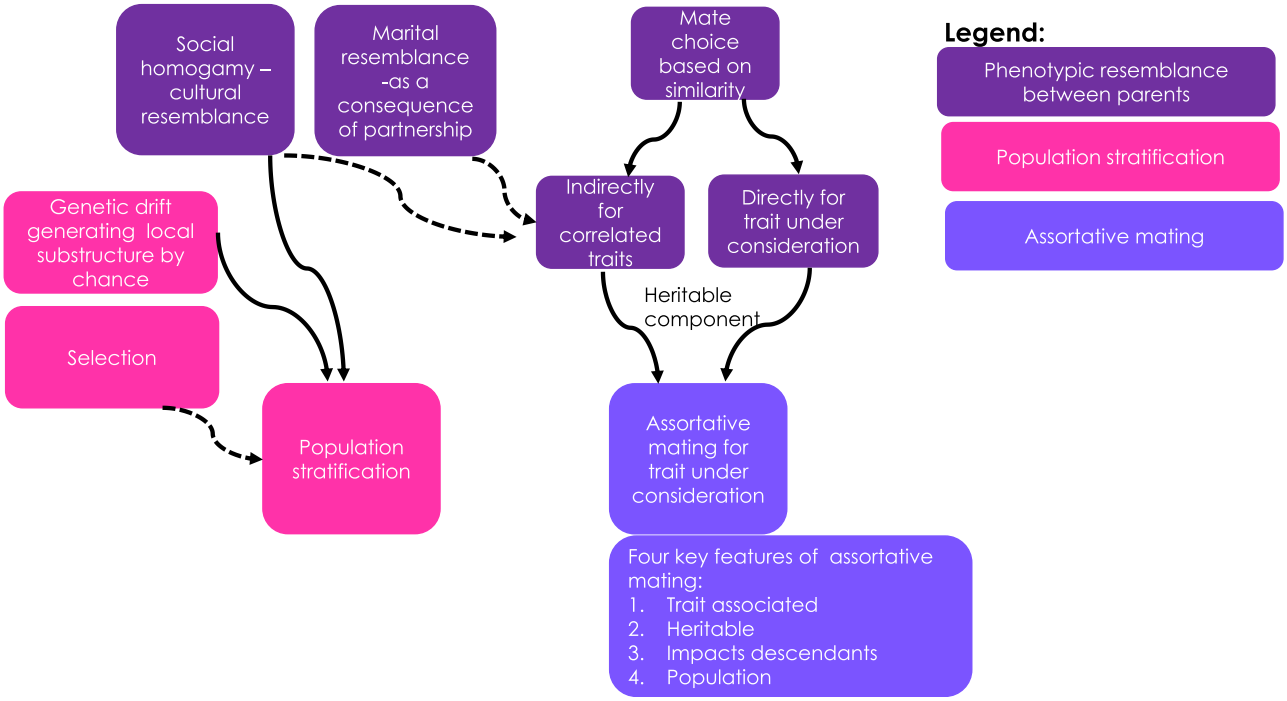

Figure 1. Factors generating assortative mating and population stratification.

genetic data, it is hard to imagine that residual population stratification does not remain within these groups, where spouse pairs are more likely to come from the same population substrata than nonspouse pairs.

It is important to be clear on the difference between population stratification and assortative mating. Population stratification reflects the genetic substructure associated with genetic drift that is trait independent. In contrast, assortative mating is genetic substructure associated with trait-associated alleles. While Connolly *et al.* (4) demonstrated evidence for strong phenotypic correlation between spouses based on item responses from the Broad Autism Phenotype Questionnaire and the Social Responsive Scale–Adult version, their analyses did not provide evidence that the higher coefficient of genetic similarity between spouse pairs was associated with genetic risk alleles associated with ASD traits.

Connolly *et al.* (4) acknowledge the limitations of their study and note that an approach we have developed (8) would be desirable in the future. We agree that data are currently limiting to draw strong conclusions using our approach, but nonetheless it is of value to discuss the method with a view to the data and analyses that will be needed to draw strong evidence-based conclusions. Briefly, we used UK Biobank data to investigate assortative mating. While this cohort of approximately 400,000 individuals of British European ancestry also has recognized ascertainment biases (white individuals, those who are well-educated, and those who are female are all overrepresented compared with the census UK population), it is much more representative of a general population than a sample based on proband ascertainment. Here, we did not have parent–offspring trios but used DNA data from unrelated individuals to assess a signature of assortative mating, given than each individual's chromosomes are a combination of the chromosomes of their parents. We demonstrated through simulation that our method could separate a signature of assortative mating from a signature of population stratification. In the absence of assortative mating, the number of risk alleles for disease (or trait-increasing alleles for a quantitative trait) would be scattered across the genome randomly; if the genome was split randomly, say into odd and even chromosomes, then the number of trait-associated alleles found in each half would be expected to be random. In contrast, assortative mating generates a correlation structure in the genome (linkage phase disequilibrium) such that random halves of the genome will be correlated for the number of disease- or trait-associated alleles. In our analyses, we contrasted odd and even chromosomes for their polygenic risk scores for a range of traits. We showed by simulation that twice the correlation between chromosomes should equal the correlation between polygenic risk scores of spouses, and verified this relationship in real data (using approximately 19,000 spouse pairs in the UK Biobank independent from the primary analysis). We found strong evidence for assortative mating for height and educational attainment (Table 1). This is not a surprising result for two reasons. First, there has long been strong evidence for phenotypic correlation between parents for these highly heritable traits. Second, the genome-wide association studies from which the polygenic risk scores are taken have much larger sample sizes than for many other traits—their power evidenced by the number of genome-wide significant

Table 1. An Extract of Assortative Mating Results[a]

Trait	Correlation of Trait Polygenic Risk Score Between Spouses (SE)	p	Twice Within-Individual Correlation Between Polygenic Risk Score on Odd and Even Chromosomes (SE)	p
Height	0.059 (0.008)	9.8×10^{-14}	0.064 (0.003)	6.5×10^{-89}
Educational Attainment	0.061 (0.009)	7.3×10^{-11}	0.054 (0.004)	6.0×10^{-46}
Autism Spectrum Disorder	0.022 (0.007)	.003	0.014 (0.003)	.88
Schizophrenia	0.020 (0.008)	.006	−0.0002 (0.003)	.59

[a]Data from Yengo *et al*. (8) show through simulation and theory that under many generations of assortative mating, both 1) the correlation in polygenic risk score for a trait between spouses and 2) twice the with-individual correlation of polygenic risk score between odd and even chromosomes should generate estimates of assortative mating. Using approximately 19,000 spouse pairs and within-individual correlation of odd and even chromosomes from approximately 400,000 people of European ancestry, we found highly significant estimates of assortative mating for height and educational attainment that were consistent across the two independent methods. For autism spectrum disorder and schizophrenia, the estimates of between-spouse pair correlation, while suggestive for assortative mating, did not survive correction for the multiple testing in our study (requiring $p < .001$ to declare statistical significance). Nonetheless, it is interesting that the estimates from between-spouse pairs are higher than the correlation between odd and even chromosomes, the former representing assortative mating among the parents of the current individuals and the latter representing the cumulative signal among parents through generations.

loci identified for these traits (697 for height and 74 for educational attainment). In contrast, the ASD genome-wide association study has identified only 5 genome-wide significant loci (9). Nonetheless, we found a suggestive trend for assortative mating in this study, but the estimate did not pass our multiple testing correction given the number of traits we studied (Table 1).

In conclusion, evidence for assortative mating for ASD would contribute to understanding of the disorder for its role in increasing rates of ASD over time. There is strong phenotypic evidence for correlation between spouses in ASD-related traits, both in the general population and within parents of ASD children, and this would be expected to generate genetic consequences implied by assortative mating because the traits are heritable. Analyses using DNA should provide a direct evidence-base for assortative mating. Connolly *et al.* (4) have started that process, but their analyses and the data available to them are limited. They report evidence for assortative mating, but it seems to us that their signal may be contaminated with unidentified population stratification. Moreover, the key aspect of assortative mating is that the genetic correlation is associated with the trait under consideration. The evidence reported by Connolly *et al.* (4) could equally fit assortment based on height, educational attainment, or other compatibility traits that may or may not be correlated with ASD. Lastly, the consequences of assortative mating must be considered for a population, not for highly ascertained groups. All in all, a step in the right direction, but more to do!

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Article Information

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References

1. Youyou W, Stillwell D, Schwartz HA, Kosinski M (2017): Birds of a feather do flock together. Psychol Sci 28:276–284.
2. Nordsletten AE, Larsson H, Crowley JJ, Almqvist C, Lichtenstein P, Mataix-Cols D (2016): Patterns of nonrandom mating within and across 11 major psychiatric disorders. JAMA Psychiatry 73:354–361.
3. Peyrot WJ, Robinson MR, Penninx BW, Wray NR (2016): Exploring boundaries for the genetic consequences of assortative mating for psychiatric traits. JAMA Psychiatry 73:1189–1195.
4. Connolly S, Anney R, Gallagher L, Heron EA (2019): Evidence of assortative mating in autism spectrum disorder. Biol Psychiatry 86:286–293.
5. Domingue BW, Fletcher J, Conley D, Boardman JD (2014): Genetic and educational assortative mating among US adults. Proc Natl Acad Sci U S A 111:7996–8000.
6. Yengo L, Sidari M, Verweij KJH, Visscher PM, Keller MC, Zietsch BP (2019): No evidence for social genetic effects or genetic similarity among friends beyond that due to population stratification: A reappraisal of Domingue et al (2018) [published online ahead of print May 21]. bioRxiv.
7. Robinson MR, Kleinman A, Graff M, Vinkhuyzen AAE, Couper D, Miller MB, *et al.* (2017): Genetic evidence of assortative mating in humans. Nat Hum Behav 1:0016.
8. Yengo L, Robinson MR, Keller MC, Kemper KE, Yang Y, Trzaskowski M, *et al.* (2018): Imprint of assortative mating on the human genome. Nat Hum Behav 2:948–954.
9. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al.* (2019): Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51:431–444.