A Report on "A Rigorous Measure of Genome-Wide Genetic Shuffling That Takes into Account Crossover Positions and Mendel's Second Law" by Veller et al. (2019)

Reviewer 2

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v2

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> I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.
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> Plato, *The Apology of Socrates*, 21d

> To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Veller, C., Kleckner, N., and Nowak, M. A. (2019). A Rigorous Measure of Genome-Wide Genetic Shuffling That Takes into Account Crossover Positions and Mendel's Second Law. *Proceedings of the National Academy of Sciences*, Vol. 116, No. 5, pp. 1659–1668.

Abstract Summary: Traditional measures of genetic shuffling, which only count the average number of crossovers, are inadequate because they fail to account for crossover positions and independent assortment. The authors develop a rigorous measure, r, defined as the probability that alleles at two randomly chosen loci are shuffled during gamete production, which can be decomposed into contributions from crossover number/position and independent assortment.

Key Methodology: Mathematical and statistical development of the measure r and its decomposition, followed by application to human male and female cytological and sequence data.

Research Question: How can a rigorous measure of genome-wide genetic shuffling be developed that accounts for crossover positions and Mendel's second law (independent assortment)?

Editor's Note

Version 2 of this report has been written by an improved model of Reviewer 2.

Summary

Is It Credible?

Veller et al. present a methodological critique of how evolutionary genetics has traditionally quantified genetic shuffling. They argue that standard metrics—specifically crossover frequency and map length—are "qualitatively inadequate" because they fail to account for two critical factors: the specific genomic positions of crossovers and the independent assortment of homologous chromosomes (p. 1659). To remedy this, the authors derive a new metric, $\bar{r}$, defined as "the probability that the alleles at two randomly chosen loci are shuffled during gamete production" (p. 1659). By applying this metric to human cytological and sequence data, they claim to demonstrate that total genome-wide shuffling in humans is near its maximum possible value of 0.5 and is driven overwhelmingly by independent assortment rather than crossing over.

The mathematical derivation of $\bar{r}$ appears rigorous and logically sound. By decomposing the metric into intrachromosomal (crossover-driven) and interchromosomal (independent assortment-driven) components, the authors provide a transparent framework for evaluating the relative contributions of these mechanisms. The application of this metric to human data yields robust results; the authors cross-validate their findings using cytological analysis of pachytene chromosomes, single-gamete sequencing, and linkage maps, with all methods converging on similar values for $\bar{r}$ (pp. 1664–1665). The conclusion that independent assortment is the dominant force in human genetic shuffling is particularly well-supported. The data show that the interchromosomal component contributes approximately 30 times more to the total shuffling rate than the intrachromosomal component (p. 1659). This finding effectively challenges the crossover-centric view often found in discussions of the adaptive value of sexual reproduction.

However, the credibility of the authors' evolutionary interpretations is strained regarding the function of crossover interference. The article demonstrates mathematically that spacing crossovers evenly—a consequence of interference—maximizes the intrachromosomal component of $\bar{r}$ (p. 1662). Based on this, the authors suggest a "possible selective advantage" for interference, proposing it may have evolved to enhance shuffling (p. 1666). While the mathematical relationship between spacing and shuffling is valid, the biological significance of this effect is debatable given the magnitude of the numbers involved.

The authors' own data indicate that while interference increases the intrachromosomal component by about 15% in human males, this component is a minute fraction of the total (p. 1666). Consequently, the absolute increase in total genome-wide shuffling attributable to interference is negligible. In spermatocytes, where the total $\bar{r}$ is approximately 0.473, the boost from interference raises the total rate by only roughly 0.002. It is difficult to accept that such a marginal increase in shuffling would provide a selection pressure strong enough to drive the evolution of a mechanism as complex as crossover interference. The authors frame this as an alternative to mechanical explanations for interference, citing organisms like fission yeast that segregate chromosomes successfully without interference (p. 1666). However, while they successfully argue that interference is not strictly necessary for segregation in all species, they do not adequately explain why a trivial gain in aggregate shuffling would be the selected alternative. To be fair, the authors do note that aggregate measures might mask the importance of shuffling for specific tightly linked loci, but the primary argument relies on the maximization of genome-wide shuffling (p. 1666).

Despite this specific overinterpretation, the core contributions of the article remain credible. The validation of physical axis length as a proxy for genomic length is supported by analysis across diverse species, strengthening the methodological basis of their cytological work (pp. 1663, S18). The definition of $\bar{r}$ successfully integrates Mendel's Second Law into the quantitative measurement of shuffling, offering

a more accurate picture of gametic diversity than crossover counts alone.

The Bottom Line

The proposed metric, $\bar{r}$, is a credible and rigorous tool that successfully corrects deficiencies in traditional measures of genetic shuffling. The authors convincingly demonstrate that independent assortment, rather than crossing over, is the primary driver of shuffling in humans. However, the hypothesis that crossover interference evolved specifically to maximize this shuffling is weak, as the quantitative gain provided by interference is negligible in the context of the total genome-wide rate.

Potential Issues

Proposed adaptive function of crossover interference: The article suggests that positive crossover interference, which promotes the even spacing of crossovers, may confer a selective advantage by increasing the amount of genetic shuffling (pp. 1662, 1666). The authors present this cautiously as a "possible selective advantage" and a "possibility," framing it as an alternative to existing mechanical explanations for interference (p. 1666). The article acknowledges and argues against these mechanical hypotheses, such as those related to bivalent stability or homolog segregation, by citing organisms that lack interference but segregate chromosomes successfully (p. 1666). However, while the article's evolutionary hypothesis is presented as a plausible alternative, its biological significance is debatable given the small magnitude of the effect. The authors calculate that interference increases the intrachromosomal component of shuffling by approximately 15% in human males (p. 1666). While the article consistently acknowledges that this component is a minor fraction of total shuffling—which is dominated by independent assortment—it does not fully grapple with the implications of this fact (pp. 1659, 1664). Using the article's own data for human males, the 15% increase in the minor intrachromosomal component (0.0143, p. 1664) translates to an absolute increase in the total genome-wide shuffling rate of only about 0.002. This marginal change raises the total rate from approximately 0.471 to 0.473, a small optimization of a value already near its theoretical maximum of 0.5. The article does not provide a strong argument for why such a small increase in aggregate shuffling would be sufficient to drive the evolution and maintenance of a complex biological mechanism like crossover interference. Therefore, while the article correctly identifies a consequence of interference and situates it within the existing literature, its proposed adaptive function remains speculative.

Future Research

Testing the adaptive value of interference: Future work could evaluate the plausibility of the interference-for-shuffling hypothesis by modeling the selection coefficients required to maintain interference solely for its shuffling benefits. This could be coupled with comparative genomics to analyze species with varying chromosome numbers; if the hypothesis holds, one might expect stronger interference in species with fewer chromosomes, where the relative contribution of crossovers to total shuffling is higher and the "diminishing returns" of independent assortment are less pronounced.

Implementation of functional genomic weighting: The authors identify that the current calculation of $\bar{r}$ treats all genomic regions as equally important, and they propose future extensions to account for gene density and heterozygosity (p. 1666). Future research should operationalize this proposal by weighting the probability of shuffling against maps of functional density (e.g., exome density) and population-level heterozygosity. This would transition the metric from a measure of "potential" shuffling to "effective" shuffling, providing a more direct link to evolutionary theories regarding the maintenance of sex.

High-resolution loop mapping: The validity of using physical axis length as a proxy for genomic length relies on the assumption of constant chromatin packing ratios. While the article provides aggregate evidence for this, future studies using high-resolution, sequence-based chromatin conformation capture (Hi-C) or similar technologies on single meiotic cells could map loop sizes with greater precision. This would verify whether local variations in packing density (e.g., near telomeres or centromeres) introduce systematic biases into the cytological estimates of $\bar{r}$.

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