MS ID#: GENETICS/2014/167064

Dear Yaniv:

Please visit http://submit.genetics.org to view the comments of the reviewers of your submission, "Sperm should evolve to make female meiosis fair."

Both reviewers found the manuscript inventive and well-written. However, both have raised substantive issues that indicate that the interesting ideas presented need more development before consideration for publication.

The paper as written establishes that factors expressed in sperm should generally evolve to suppress drivers of meiotic drive in female meiosis. However, as Reviewer 1 points out, this is different from showing that factors expressed in females should evolve to delay completion of meiosis until after fertilization. There is general agreement that the argument needs to be completed so that it supports all conclusions and that the justification for study of the question be improved. Reviewer 2 has provided many valuable suggestions along these lines.

The format of this submission departs from the style of GENETICS (model description and analysis, literature citations, etc.). As a result, it is unclear whether GENETICS is the appropriate or even the intended forum for this work. I am recommending rejection of the present submission. A manuscript that addressed all concerns raised would essentially constitute a new work, and could be reviewed as a new submission.

Best wishes, Marcy

I regret to have to bring this unwelcome news. I hope you will continue to submit your best work for publication in the journal, and that I can bring more favorable news when you do.

Sincerely,

Marcy Uyenoyama

Associate Editor

Senior Editor

Reviewer 1 – Reviewer's Comments to Author ...

This manuscript uses simple population genetic models to evaluate the potential for sperm haplotype (or paternal genotype) to influence female meiotic drive. The models are quite straightforward and the results are very clearly explained. In that sense, the manuscript was a pleasure to read. This manuscript should be published somewhere but I am not sure it is enough of a sufficient advance to warrant publication in Genetics.

1. A major part of the motivation for the model seems to be to explain why, in animals, meiosis is typically suspended until fertilization occurs (providing the opportunity for males to influence female drive). This seems a poor motivation for the project because it would require a bizarre form of logic by which the evolution of this delay in meiosis evolved with the "foresight" that there would then be subsequent evolution of male influence on female drive. More directly, if the authors' interest is in the evolution of arrest in female meiosis, then it would be better to do a model that explicitly addressed that issue.

   Obviously, the authors can avoid this problem by simply saying, given that meiotic arrest occurs and provides the opportunity for males to influence drive, we want to see what will happen. However, it is misleading to present this model as though it addresses the issue of the evolution of meiotic arrest.

   We thank the reviewer for this comment, and have reworked our manuscript to focus around our major result – that sperm are expected to evolve to prevent female meiotic drive. We view this as an important point, and as the significant change in this new manuscript. As suggested by R1, we focus our discussion of the fertilization requirement to pointing out that it provides sperm an opportunity to influence female meiosis, and we only briefly point out that given the potential reasons for this delay, the threat of sperm collaboration in meiotic drive does not represent a selective force favoring the completion of meiosis before fertilization.

2. I did not feel that the authors made a convincing case that this is an important phenomenon in its own right. P. 5 has one short paragraph pointing to what seems like some rather indirect evidence of male influence on drive. Consequently, I find myself wondering whether this manuscript addresses a topic of sufficient importance for Genetics. The authors do make an interesting prediction regarding drive effects in hybrids but in the absence of any current evidence it is hard to know whether this is just an interesting idea that never really happens.

Reviewer 2 – Reviewer's Comments to Author ...

R2 Summary

The focus of the manuscript entitled "Sperm should evolve to make female meiosis fair" by Yaniv Brandvain and Graham Coop is to provide a theoretical foundation for two seemingly unrelated enigmatic observations: i) that it is common for female meiosis to arrested at an early stage and then complete the process only after the egg is fertilized, and ii) that there is evidence (i.e., a couple of established cases) that the strength of female meiotic drive can be influenced by the genotype of the sperm that fertilizes an egg. These two seemingly unrelated empirical patterns are functionally coupled by the authors by solving for the conditions under which different forms of sperm-mediated modifiers of female meiotic drive will be selectively favored. The authors show that "Greenbeard-effect" modifiers that bias female meiotic drive in favor of the allele found in the sperm evolve under a very restricted part of the total parameter space (and rapidly fix under these conditions) while those that prevent or reduce meiotic drive evolve under a much expanded parameter space (and are more likely to remain polymorphic). This asymmetry would be expected to lead to the evolution of sperm that suppress female meiotic drive, but only if most of the steps of female meiosis are delayed until after fertilization. So arrested meiotic progression (until fertilization) may be an adaptation that expands the ability of females to reduce the deleterious effects of meiotic drive by creating the opportunity for sperm to also suppress the trait.

Overall I found the paper to be well written and organized, and because of this, the theory that the authors describe will be accessible to a broad spectrum of the readership of Genetics – not just other theoreticians. Although I have not re-derived all of the equations used in the author's models, the special cases that I have worked through, and the logic used by the authors to motivate the models, suggest to me that they are sound. I would like to see the authors consider (but not necessarily follow) a few suggestions that I describe below.

R2 Primary suggestions

1. The importance of the wok hinges critically on the the degree to which: ***i)*** female meiotic drive operates in nature, and ***ii)*** sperm influence the level of female meiotic drive. In species like maize, where every chromosome has two or more established meiotic drivers ("chromosomal knobs"), the importance of meiotic drive is obvious, but in most species there is little or no evidence for the current operation of meiotic drive – although low levels of transmission ratio distortion (TRD) are becoming increasingly well established from genome-wide SNP studies. However, the rapid divergence of telomeric sequences among closely related species is certainly consistent with the widespread operation of transient episodes of meiotic drive via centromere drive. In the present manuscript, the prevalence and importance of female meiotic drive is quickly summarized by the terse statements "Meiotic drivers observed in both plants [5, 10, 9], and animals [1, 29, 21] highlight this conflict – the selfish benefits and the associated pleiotropic fitness costs of drive sustain a balanced polymorphism [24], and often generate ongoing evolutionary escalations of drive suppressors and enhancers [8, 9]." I think the paper would be far more convincing and appreciated if the authors put a tad more effort into convincing the reader that female meiotic drive is sufficiently common to be a widespread selective force.

2. To my knowledge, the evidence for sperm influencing the outcome of meiotic drive is restricted to the In and Om drive systems in mice and aster transfer by the sperm in C. elegans. These are clearly proof of process examples but I think that many readers will take issue with the assumed general ability of sperm to substantially influence the outcome of female meiotic drive. This skepticism is to be expected because the egg typically completes meiosis immediately after fertilization, at a time when the sperm pronucleus is decondensing and presumably not yet transcriptionally active. The more evidence that the authors can provide for sperm being capable of influencing female

meiotic drive, the better this paper will be received. The authors could bolster their case by briefly reviewing the recent evidence for extensive paternal effects via RNA and protein packaged in the sperm, delivered to the egg, and influencing subsequent early embryonic development.

3. Finally, female meiotic drive potentially can be suppressed by alleles expressed in the female (traditional models) or by alleles originating in the sperm and acting in the egg immediately after fertilization (the authors new model). It would be useful to compare the constraints for the evolution of both types of suppressors to evaluate if sperm-mediated suppression of female meiosis has some evolutionary advantage that make it easier to evolve or non-redundant to female-coded suppressors.

Minor Points:

1. On the top of page 7 the statement "This analytical approximation, derived from Equation (1) assuming Hardy-Weinberg", – precedes the introduction of Equation (1) in the Appendix. I suggest pointing out here that all equations described in the text are located in the Appendix (so the reader doesn't stop reading and start looking for them, thinking they somehow overlooked them in the body of the manuscript). We can relate to the confusion and frustration of struggling to find the relevant equation. We have therefore added the parenthetical comment – "*We note that Equation 1 and all equations discussed in the main text are presented in the appendix and derived in File S2*" – to the end of this paragraph.

2. There are 6 models described in the text but these are not described in any detail until the Appendix. The authors might consider placing a table in the main body of the text that tersely describes the 6 models.? We have added a Methods section, which introduces these six models, and makes our manuscript more in line with the GENETICS format.

3. On the bottom of page 14 the authors write "we predict that a lower opportunity for female meiotic drive, e.g. an animal lineage with a long history of high inbreeding or selfing, would often be accompanied by a relaxation of the requirement of fertilization for the completion of female meiosis." As I recall, species with a history if inbreeding or selfing are only at the tips of most phylogenetic trees (i.e., they do not persist over geological time and do not have a "LONG history of high inbreeding or selfing") so this prediction may be limited.

4. On the bottom of page 14, do you also predict that observed drive in species hybrids will depend on the direction (which male) is used in the backcross?

5. I think that equations like ($s < d - 1/2 + 3sh/2 - dsh$) need parentheses to be clear. To add clarity, we have surrounded longer in-text equations like the example above, with parentheses.