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Dear Editor,

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Please find the attached manuscript, entitled “Haploid selection, sex ratio bias, and transitions between sex-determination systems”, which we submit to you for consideration for publication in *PLoS Biology*.

In this manuscript, we develop and thoroughly analyse models to show what conditions favour the evolution of new sex-determination systems. Evolutionary transitions between sex-determination systems are an active research focus due to the surprising diversity and lability of sex determination systems, which is becoming increasingly apparent (Bachtrog et al. 2014, *PLoS Biology*). Transitions in such a fundamental trait of large effect warrant evolutionary explanation; our results suggest several new scenarios under which new sex-determining systems are favoured, which could help to explain why the evolution of sex-determining systems is so dynamic.

Previous modelling studies include Muralidhar and Veller (2018, *Nature Ecology and Evolution*), and van Doorn and Kirkpatrick (2007, *Nature*; 2010, *Genetics*), which have shown that a new sex determining allele can be favoured if it arises in linkage with sexually-antagonistic loci. One novel feature of our models is that we explicitly consider selection on loci that are very tightly linked to the ancestral sex-determining region. Surprisingly, under various forms of selection, the unusual inheritance pattern of sex-linked loci can give rise to cases where the ancestral-X carries suboptimal alleles for females and/or the ancestral-Y carries female-beneficial alleles. This, in turn, can favour new sex-determining alleles that have weaker linkage with the loci under selection, which has not been predicted by previous theory.

It has been suggested that selection to balance the sex ratio is a dominant force driving transitions between sex-determining systems. Our models include haploid selection (meiotic drive or gametic competition), which can cause zygotic-sex ratios to become biased. In addition, haploid selection is usually sex-specific (occurring in either males or females only). Consequently, we find that haploid selection can cause transitions analogous to those caused by sexually-antagonistic selection, eliminating the need for differences in selection between male and female diploids. Unexpectedly, we do not find that selection to balance the sex ratio is overwhelming; transitions during which sex ratio biases increase or decrease are equally likely to evolve under a wide range of conditions. Furthermore, we find that looser linkage with the sex-determining region more often evolves when there is haploid selection,

increasing the potential for lability in sex-determination. We conclude that haploid selection should be considered as a pivotal factor driving transitions between sex-determining systems.

Overall, we have developed an extensive set of models that explore the forces driving transitions between sex determination systems, an important aspect of diversity. Of particular interest, we find several results (e.g., looser linkage and sex ratio biases evolving) that are surprising, given previous theory. We hope you agree that this work is of broad interest to the readership of *PLoS Biology* and we eagerly anticipate your response.

Sincerely,

Michael Scott, Matthew Osmond, Sarah Otto