Why Mendelian segregation?

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Abstract

The discovery of alleles that are able to distort segregation during meiosis in their favour raises the question why Mendelian segregation is the rule and segregation distortion the exception. Previous research on this topic was limited by an unrealistic assumption: equal segregation in the two sexes. Úbeda and Haig [(2005) Genetics **170**, 1345–1357] provide a new model allowing sex-specific segregation distortion. This model shows that natural selection favours departure from Mendelian expectations. The evolutionary instability of Mendelian segregation under more realistic assumptions requires a new paradigm that explains its ubiquity.

Inspired by Mendel's work on the segregation of characters in peas, geneticists formalized the law of equal transmission: alleles at a heterozygous locus are transmitted with equal probability. Though Mendel's first law described, in principle, a fundamental constraint on genetics systems, Hiraizumi proved that no such limitation exists by finding loci where one of the alleles is able to distort the segregation process in its favour (see [1]). This observation motivated geneticists to model the evolution of segregation, using a main locus under viability selection and a modifier locus that determined the segregation of alleles at the main locus. The effort revealed that in the absence of perfect recombination between main and modifier locus, the modifier alleles are selected to distort fair segregation [2–4]. These modifiers gain fitness through preferential association with the allele that has segregation advantage. If the segregation process can be distorted and distorters have a selective advantage, then why is Mendelian segregation the rule and segregation distortion the exception, rather than the other way round?

Eshel [5] offered an elegant explanation to this conundrum. He found that with perfect recombination between main and modifier locus, alleles taking segregation away from Mendelian expectations are selected against. Those taking segregation closer to fair expectations, however, are selected in favour. With perfect recombination, modifiers cannot gain fitness through preferential association with any allele because they have the same probability of association with one allele or the other. Instead, they gain advantage by maximizing population mean fitness and it is through Mendelian segregation that this process occurs [6]. Considering that most of the loci in the genome are unlinked to any particular locus, Mendelian segregation would be maintained by mutual policing in the 'parliament of genes' [7].

The above results relied on the simplifying assumption that a modifier allele has the same effect on transmission during male and female gametogenesis. However, this assumption does not correspond to reality. A detailed review of all genetics systems where deviation from Mendelian expectation has been observed fails to provide a single case when segregation distortion is equivalent in males and females [8,9]. This is not surprising since mechanisms underlying male and female gametogenesis are extremely different [10]. The work of Úbeda and Haig [9] overcomes this limitation by allowing sex-specific segregation distortion. They, also, consider the most general viability scheme, which allows for differential viability of reciprocal heterozygotes as might arise, for example, from genomic imprinting [11].

Consider a population at equilibrium where alleles at a polymorphic main locus segregate with equal probability (this requires heterozygote advantage for non-frequency-dependent viability schemes). Úbeda and Haig [9] found that allowing for differential segregation distortion in male and female gametogenesis, Mendelian segregation lacks evolutionary genetic stability [12] even in the most favourable case of perfect recombination. Though fair segregation shows evolutionary instability both for differential and identical viability of reciprocal heterozygotes, there are significant differences between both segregation schemes. Specifically, for differential viability of reciprocal heterozygotes, the pair of male and female segregation schemes that can invade Mendelian segregation is much broader, independent of the viability of homozygotes with respect to heterozygotes (Figure 1), and the invasion rate is much faster. In addition, Úbeda and Haig [9] demonstrate that all-and-none segregation schemes (those in which one allele shows perfect drive in one sex while the opposite allele shows perfect drive in the other sex) not only can invade Mendelian segregation but also show evolutionary genetic stability.

The result of Úbeda and Haig [9] can be interpreted in a similar way Eshel's result [5] was viewed. With perfect recombination, modifiers cannot gain fitness through preferential association with any allele and they are selected to maximize population mean fitness. If segregation distortion is forced to be equal between males and females, Mendelian segregation maximizes the population mean fitness. The population mean fitness, however, can increase when

Figure 1 | **Evolutionary genetic stability of Mendelian segregation**

In each Figure, the horizontal axis represents the segregation ratio in favour of allele A_i (as opposed to allele A_j) during male meiosis, while the vertical axis represents the segregation ratio in favour of the same allele during female meiosis. Mendelian segregation (MS) is susceptible to invasion by segregation schemes that map on to the shaded area. (**a**) Differential viability of reciprocal heterozygotes. (**a.1**) Viability of genotype A_jA_i is greater than the viability of genotype A_iA_j. (**a.2**) Viability of genotype A_iA_j is greater than the viability of genotype A_jA_i. All-and-none segregation (A&N) cannot be invaded by any other segregation scheme. Solid circles represent segregation schemes showing evolutionary genetic stability. (**b**) Identical viability of reciprocal heterozygotes. (**b.1**) Heterozygotes are 60% more than homozygotes. (**b.2**) Lethal homozygotes.

Differential Viability of Reciprocal Heterozygotes
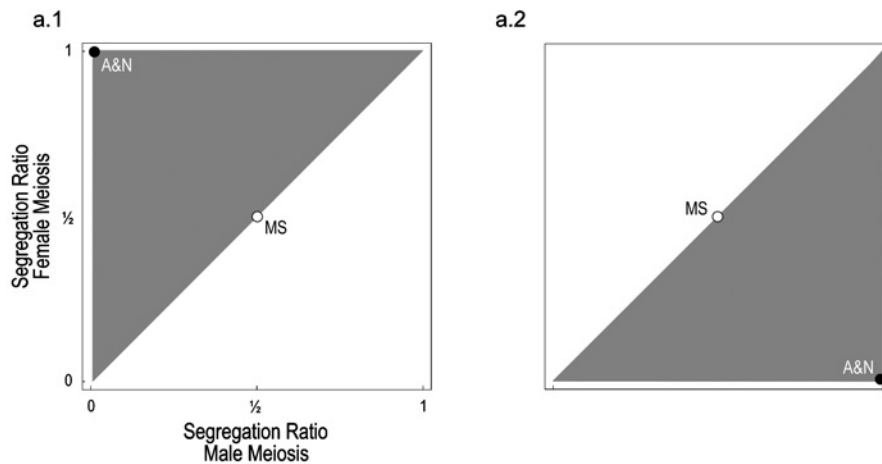
Identical Viability of Reciprocal Heterozygotes
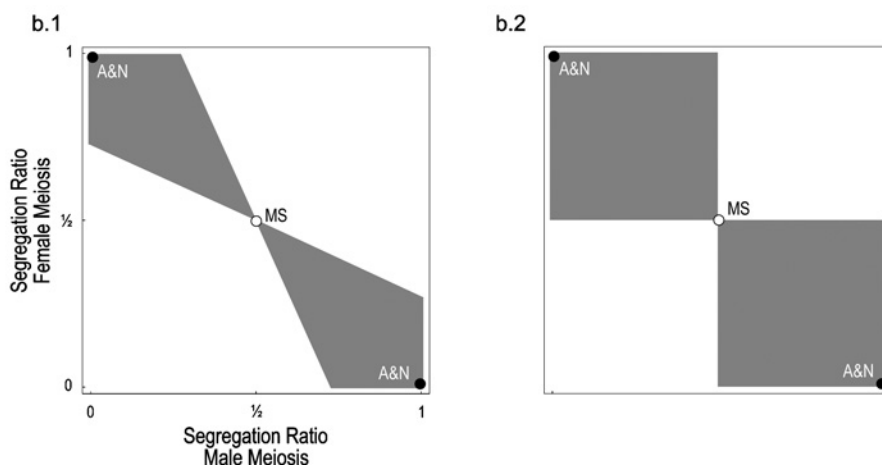
considering segregation schemes with different segregation distortion in males and females. Particularly, all-and-none segregation schemes maximize the population mean fitness [6] by allowing the production of the fittest heterozygote and suppressing the production of the less fit homozygotes, that is, eliminating what Crow [13] called segregation or balance genetic load.

The work of Úbeda and Haig [9] bring the argument on the evolution of Mendelian segregation back to square zero. The authors are not questioning that Mendelian segregation is the rule in Nature; they are drawing attention on

the need for a satisfactory explanation to why Mendelian segregation is the rule. What might be concluded from their work is that perfect recombination (at least by itself) is not the answer.

Úbeda and Haig [9] suggest four possible ways in which Mendelian segregation can regain evolutionary genetic stability: (i) Segregation distortion requires a balanced polymorphism at the main locus. Such balanced polymorphism, however, might be rare enough to prevent the evolution of modifiers. (ii) With identical viability of reciprocal heterozygotes, a modifier successful in driving the system away from

Mendelian segregation must convey a segregation advantage of one allele in one sex but a segregation disadvantage of the same allele in the opposite sex. If differential viability of reciprocal heterozygotes is rare, the requirement for co-ordinated change in male and female meiosis might be a major constraint on the evolution of non-Mendelian segregation schemes. (iii) Modifiers that induce a co-ordinated change in male and female meiosis result in the preferential transmission of one allele through one of the sexes and the opposite allele through the other sex. This might have some adverse consequences due to the accumulation of other genes whose expression is beneficial for males (or females) but detrimental for females (or males) even if costs outweigh benefits. As a result, all-and-none segregation schemes generate a collateral conflict that may result in the extinction of such systems. This consideration becomes irrelevant for self-fertilization systems because each allele depends on the maintenance of male and female functions in a single individual. (iv) In general, segregation distortion in males is linked to a reduction in the number of functional sperms produced by a particular male. This may translate in a reduction in male fertility in mating systems where sperm competition happens. Reduction in male fertility might be enough to stabilize Mendelian segregation.

To conclude, the prevailing explanation to the evolutionary puzzle that Mendelian segregation is does not hold when the artificial constraint of equal segregation in males and females is relaxed. It is all-and-none and not Mendelian segregation that shows evolutionary genetic stability. While the pre-eminence of Mendelian segregation in natural populations is not questioned, it can no longer be explained by perfect recombination between main and modifier loci. Four alternative explanations are provided for future research to examine the validity of each one of them.

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