

# Meiosis: How Gambling Chromosomes Beat the Rules

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**Selfish centromeres exploit asymmetric female meiosis to drive non-Mendelian segregation in their favor. Using inherent differences in drive propensity between mouse chromosomes, a new study reveals how proteins that modify chromatin states and microtubule stability enable this selfish behavior.**

Centromeres are the chromosomal sites of microtubule attachment that coordinate chromosome segregation during cell division in eukaryotes. Despite their essential, conserved roles in cell division, centromeric DNA and proteins evolve rapidly. Centromere-drive was proposed to explain this ‘centromere paradox’ [1]. In the first step of centromere-drive, chromosomes compete via their centromeric DNA for inclusion into the egg rather than the polar bodies, which are evolutionary dead-ends, during female meiosis. A series of cell biological studies in mouse oogenesis has elegantly demonstrated many tenets of this step of centromere-drive. Centromeric satellite DNA expansions recruit more centromeric proteins [2], allowing them to out-compete homologs in female meiosis [3] and exploit an intrinsic asymmetry of the cytoskeletal spindle in oocytes [4, 5]. A recent study by Takashi Akera and colleagues [6] builds on these previous findings to discover the molecular mechanisms that allow chromosomes to exploit oocyte spindle asymmetries.

The authors of this study had previously demonstrated that ‘selfish’ larger centromeres make more unstable microtubule attachments when they orient towards the polar body (‘losing’) rather than egg (‘winning’) side of the oocyte [4] (Figure 1). Thus, larger centromeres can increase their likelihood of orienting towards the egg side by repeatedly detaching when they happen to be on the losing side by chance. Such a strategy is akin to a gambler who games the system by frequently getting new cards when dealt a losing hand. Based on the finding that microtubule detachment might be at the heart of cheating behavior, Akera and colleagues [6] investigated

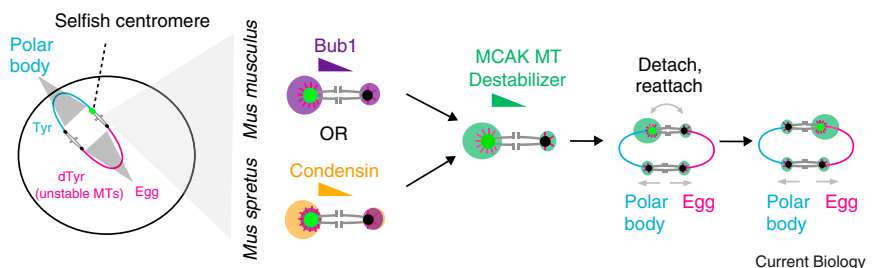
how centromeres may exploit preferential recruitment to achieve transmission bias.

To test the molecular basis of non-Mendelian transmission, the study’s authors took advantage of a previously described arena for centromere competition. F1 female hybrids between two strains of the house mouse (*Mus musculus*), CF1 and CHPO, have centromere asymmetries in strength, which correspond to different rates of meiotic transmission [3]. In the backdrop of this ‘driving test,’ Akera and colleagues [6] found that microtubule destabilizers like MCAK (mitotic centromere associated kinesin) exhibit asymmetric localization at pericentromeric heterochromatin, and the more destabilizers a centromere has, the more likely it will ‘win’ (Figure 1) [6].

Akera and colleagues [6] traced the pathway from increased centromere strength to MCAK recruitment. They show that increased recruitment of kinetochore proteins by larger centromeres ultimately leads to a proportional increase in the recruitment of the BUB1 kinase. Higher

BUB1 kinase activity leads to increased phosphorylation of histone H2A and Shugoshin recruitment to pericentromeric heterochromatin [7], ultimately increasing MCAK activity [8] specifically adjacent to larger centromeres (Figure 1). Thus, larger centromeres indirectly recruit higher MCAK activity to mediate centromere drive. Indeed, when the authors forced symmetry by bypassing centromere-mediated BUB1 recruitment, they successfully prevented asymmetries in MCAK activity and abrogated centromere drive. Furthermore, inhibiting BUB1 or MCAK activity also eliminated the asymmetries required for biased centromere orientation and transmission [2].

Next, Akera and colleagues [6] studied centromere drive in a different driving test, in interspecies F1 hybrids between *Mus musculus* and the related species *Mus spretus*. Surprisingly, although they saw clear evidence of centromere drive, they did not detect any differences in centromere strength or BUB1 recruitment. Instead, they found that differential recruitment of the condensin



**Figure 1. The molecular strategy of selfishness.**

Selfish centromeres exhibit transmission bias, preferentially segregating to the egg rather than the polar body. To ‘win’, selfish centromeres recruit more microtubule (MT) destabilizers (MCAK) relative to the homologous chromosome’s centromere. The resulting increased instability of microtubules allows for detachment and reattachment of the selfish centromere to the egg side, or ‘winning side’, of the cytoskeletal spindle. The increased MCAK recruitment is achieved either by recruiting more of the kinase BUB1 by higher numbers of kinetochore proteins (as in *Mus musculus*) or by recruiting more Condensin, which allows for increased H2A-phosphorylation (represented by pink marks) via the same amount of BUB1 kinase.



protein makes heterochromatic H2A more likely to be phosphorylated by the same level of BUB1 proteins in the vicinity of *M. spretus* centromeres (Figure 1). This H2A-phosphorylation results in increased Shugoshin and thereby MCAK recruitment, leading to drive by the *M. spretus* centromeres [6].

The findings of Akera and colleagues [6] recast centromere drive in molecular terms. First, they demonstrate that the asymmetry of microtubule destabilizers is the key to centromere drive. Microtubule-destabilizing proteins like MCAK play essential roles in the fidelity of chromosome segregation by facilitating the correction of incorrect MT attachments to centromeres. It appears that selfish genetic elements have usurped this act of quality control to manifest their selfishness. Second, the study demonstrates that centromeres in different *Mus* species rely on different mechanisms to achieve drive, potentially explaining the pervasive signatures of positive selection and gene turnover in kinetochore and condensin proteins in animal species [9, 10]. Even more opportunities to subvert meiosis likely exist based on other findings [11]. Finally, these studies highlight the unexpected role of time needed for the

detachment–reattachment mechanism of centromere-drive. In *Mus spretus*, a more rapid Anaphase I in meiosis leaves little time for selfish centromeres to flip to the egg side. However, artificially delaying anaphase enables centromere drive to take place. Thus, selective pressures to block centromere drive may have fundamentally shaped many aspects of the cell division apparatus and its regulation in animals.

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## Epileptic Seizures: Glia–Neuron Interactions For Better or For Worse

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Investigations of the mechanisms generating epileptic seizures have primarily focused on neurons. However, more systemic research of brain circuits has highlighted an important role of non-neuronal cells such as glia in the genesis and spreading of generalized seizures in the brain.

Epilepsy is the most common serious primary neurological disorder, and is characterized by recurrent, unforeseen and sudden changes in brain activity [1].

These epileptic seizures are marked by widespread neuronal hypersynchrony, generally in the context of an impaired excitation–inhibition balance. Clinically,

epileptic seizures are varied and often categorized according to their onset and spread (i.e. generalized, focal, or secondarily generalized). Understanding

