Paleoindian, and fishtail points previously provided a roadmap that archaeologists used to trace the spread of Paleoindians throughout the Americas. Such a roadmap is lacking for pre-Clovis sites. Assemblages with distinctive stemmed ("tanged") chipped-stone projectile points, crescents (lunate-shaped), and leaf-shaped bifaces found in Japan, northeast Asia, western North America, and South America (see the figure) have been proposed as potential markers of a pre-Clovis coastal dispersal (*14*) that seems generally consistent with genomic data, which suggest a northeast Asian origin for Native American ancestors some time in the past 20,000 years. But more data are needed to close substantial spatial and temporal gaps between these far-flung finds and trace a dispersal route from Asia to the Americas. Work on early coastal localities along the Pacific Coast from Alaska to Baja California (*8*), Peru (*10*), and Chile (*1*) is helping to fill these gaps.

If the first Americans followed a coastal route from Asia to the Americas, finding evidence for their earliest settlements will require careful consideration of the effects of sea level rise and coastal landscape evolution on local and regional archaeological records (*15*). Around the globe, evidence for coastal occupations between ~50,000 and 15,000 years ago are rare because of postglacial sea level rise, marine erosion, and shorelines that have migrated tens or even hundreds of kilometers from their locations at the LGM. Overcoming these obstacles requires interdisciplinary research focused on coastal areas with relatively steep offshore bathymetry, formerly glaciated areas where ancient shorelines have not shifted so dramatically, or the submerged landscapes that are one of the last frontiers for archaeology in the Americas. Methodological and analytical advances are moving us closer than ever toward understanding when, how, and why people first colonized the Americas. Coastal regions are central to this debate. ■

REFERENCES

1. T. D. Dillehay *et al.*, *PLOS ONE* **10**, e0141923 (2015).
2. M. W. Pedersen *et al.*, *Nature* **537**, 45 (2016).
3. J. J. Halligan *et al.*, *Sci. Adv.* **2**, e1600375 (2016).
4. D. L. Jenkins *et al.*, *Science* **337**, 223 (2012).
5. M. R. Waters *et al.*, *Science* **331**, 1599 (2011).
6. M. R. Waters *et al.*, *Science* **334**, 351 (2011).
7. L. Bourgeon, A. Burke, T. Higham, *PLOS ONE* **12**, e0169486 (2017).
8. L. Wade, *Science* **357**, 542 (2017).
9. J. M. Erlandson *et al.*, *J. Isl. Coast. Arch.* **2**, 161 (2007).
10. T. D. Dillehay *et al.*, *Sci. Adv.* **3**, e1602778 (2017).
11. B. Llamas *et al.*, *Sci. Adv.* **2**, e1501385 (2016).
12. S. R. Holen *et al.*, *Nature* **544**, 479 (2017).
13. T. J. Braje *et al.*, *PaleoAmerica* **3**, 200 (2017).
14. J. M. Erlandson, T. J. Braje, *Quatern. Int.* **239**, 28 (2011).
15. D. W. Fedje, H. Josenhans, *Geology* **28**, 99 (2000).

10.1126/science.aao5473

CELL BIOLOGY

Competing chromosomes explain junk DNA

Asymmetric modification of microtubules explains preferential inheritance of chromosomes

By **Francis J. McNally**

The vast majority of eukaryotes have two copies of each chromosome and reproduce sexually. Meiosis is a vital process that produces gametes (eggs and sperm) by reducing the number of chromosome copies to one; fertilization between egg and sperm restores the chromosome copy number to two. During female meiosis, one set of chromosomes is expelled into a tiny cell called a polar body, whereas the other is segregated into the egg. It is a fundamental tenet of genetics that there is a random, 50% chance for any particular chromosome to be segregated into the egg versus the polar body. However, cases in which one copy of a chromosome is inherited with greater than 50% frequency have been reported in many species (*1*), but the molecular mechanism of this preferential inheritance has remained obscure. Recent work has indicated that centromeres, the chromosomal regions that form attachments to microtubules that mediate chromosome segregation during meiosis, compete with each other for inheritance during female meiosis (*2*). Thus, the essential DNA sequences that mediate accurate chromosome segregation are actually "selfish" (or parasitic) genetic elements that have invaded our genome. On page 668 of this issue, Akera *et al.* (*3*) provide the most detailed molecular mechanism to date that explains how a parasitic DNA sequence has used the asymmetry of oocyte meiosis to ensure its own inheritance and therefore its spread through populations.

"...the essential DNA sequences that mediate accurate chromosome segregation are actually 'selfish' (or parasitic) genetic elements..."

Centromeric DNA is composed of more than 1000 copies of a very short (100 to 300 base pairs) sequence that evolves rapidly in both copy number and sequence (*4*). This has led to two very different ideas. There could be something about extremely repetitive short DNA sequences that is essential for function, or these short DNA sequences might be selfish and promote their own inheritance without any functional benefit for the host organism (*2*). This is remarkable because centromeric repeats are the most abundant class of noncoding DNA in our genome, and we do not know what they are for, if anything. Recent work has lent strong support to the idea of centromeres as selfish fragments of DNA.

Standard laboratory mouse strains have 20 different chromosomes, each with its centromere at one end (telocentric). In contrast, certain isolated populations of wild mice have 10 chromosomes, each formed by fusion of two telocentric chromosomes into one chromosome, with its centromere in the middle (metacentric). The female offspring of a cross between a telocentric strain and a metacentric strain exhibit a property called meiotic drive. Instead of transmitting a pair of telocentric chromosomes to 50% of their offspring and the homologous metacentric chromosome to 50% of their offspring, they preferentially transmit either telocentric or metacentric chromosomes (*5*). These findings have remained somewhat obscure because the phenomenon only explains why wild populations of mice tend to have all metacentric or all telocentric chromosomes, and the mechanism has been largely unknown. Recent work has shown that chromosomes that are preferentially transmitted to offspring have up to sixfold more copies of the centromeric repeat sequence (*6*) and load more kinetochore proteins (*5*, *6*) than do chromosomes that are less frequently inherited. The preferentially inherited centromeres with more copies of centromeric repeats and more kinetochore proteins have been called "strong" centromeres and are preferentially oriented toward the egg side of the meiotic spindle. "Weak" centromeres, with fewer copies of centromeric repeats, are preferentially oriented toward the plasma

Department of Molecular and Cellular Biology, University of California, Davis, Davis, CA, USA. Email: fjmcnally@ucdavis.edu

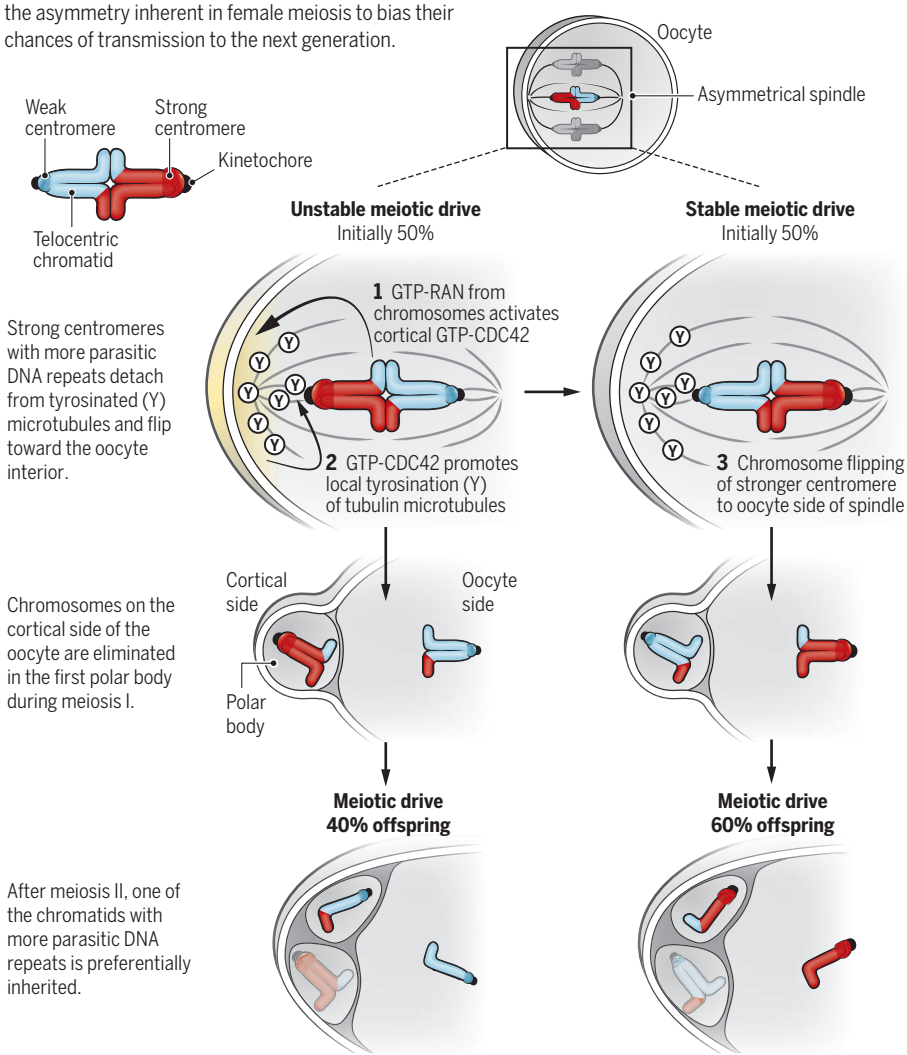
membrane, where they will be deposited in a polar body after chromosome segregation. The number of centromeric repeats influences the segregation preference even in the situation of two paired telocentric chromosomes derived from different strain backgrounds (*6*). This suggests that meiotic drive is occurring in every cross, not just in the rare cases of breeding between animals with different chromosome numbers.

Simply making one centromere stronger is not sufficient to explain preferential inheritance. Kinetochores are protein structures that assemble on centromeres; they have evolved to ensure that one of each pair of chromosomes binds to microtubules emanating from opposite sides of a bipolar spindle. Each kinetochore binds to the ends of microtubules in a manner that generates force and movement toward one pole of the spindle, at least in part, by coupling binding to the energy released by depolymerizing microtubules (which occurs to divide chromosomes) (*7*, *8*). If one kinetochore of a pair generated substantially more force, the pair of chromosomes could be pulled all the way to one side of the spindle before chromosomes separated. This occurs when both kinetochores of a pair of chromosomes attach to microtubules emanating from the same side of the spindle. If not corrected during female meiosis, this would lead to an egg with an extra copy of a chromosome, a situation that is typically lethal for the resulting embryo.

Akera *et al.* provide support for a more complex mechanism. The spindle assembles initially near the center of the egg, where the spindle is structurally symmetric, and strong and weak centromere pairs are randomly oriented toward each spindle pole. Migration of the spindle microtubules toward the plasma membrane brings the bound chromosomes into close proximity with the plasma membrane. A proximity-dependent signal from the chromosomes [guanosine triphosphate (GTP)–Ras-related nuclear protein (RAN)] locally activates a proximity-dependent signal at the plasma membrane [GTP–cell division control protein 42 homolog (CDC42)] (*9*). GTP-CDC42 then causes the microtubules closer to the plasma membrane to be more heavily tyrosinated than microtubules far from the plasma membrane. Attachments of kinetochores to heavily tyrosinated microtubules are more unstable, and the attachment of microtubules to strong kinetochores are more unstable than to weak kinetochores. As a result, attachments of membrane-proximal tyrosinated microtubules to strong kinetochores oriented toward the plasma membrane are stochastically broken more often, allowing the pair of kinetochores to "flip" and establish new, more stable attachments in the opposite orientation. The new orientation positions the strong kinetochore toward the interior of the egg, where it will be inherited by the embryo (see the figure).

Preferential inheritance during female meiosis

A parasitic DNA sequence in centromeric repeats exploits the asymmetry inherent in female meiosis to bias their chances of transmission to the next generation.



GRAPHIC: K. SUTLIFF/*SCIENCE*

This model is appealing because it parallels current thought on how pairs of kinetochores establish correct attachments to microtubules emanating from opposite poles. Attachments are made completely at random, incorrect attachments are preferentially broken, whereas correct attachments are stabilized (*7*, *8*). Future work is needed to understand this process further. First, it is unknown how GTP-CDC42 would locally increase tubulin tyrosination (or inhibit detyrosination). Second, it is not known how more heavily tyrosinated microtubules would have a higher rate of detachment from kinetochores, or why a strong kinetochore would have a higher rate of detachment from microtubules than that of a weak kinetochore. Tyrosinated tubulin is the preferred binding site for proteins with cytoskeleton-associated protein glycine-rich (CAP-Gly) domains (*10*, *11*), and recent work has shown that the motor protein, cytoplasmic dynein, preferentially initiates transport of cargo on tyrosinated microtubules (*12*, *13*). Thus, advances in our understanding of the post-translational modification of tubulin will allow us to understand how our genomes have been molded by selfish fragments of DNA. ■

REFERENCES

1. F. Pardo-Manuel de Villena, C. Sapienza, *Mamm. Genome* **12**, 331 (2001).
2. L. F. Rosin, B. G. Mellone, *Trends Genet.* **33**, 101 (2017).
3. T. Akera *et al.*, *Science* **358**, 668 (2017).
4. D. P. Melters *et al.*, *Genome Biol.* **14**, R10 (2013).
5. L. Chmátal *et al.*, *Curr. Biol.* **24**, 2295 (2014).
6. A. Iwata-Otsubo *et al.*, *Curr. Biol.* **27**, 2365 (2017).
7. A. Mussachio, A. Desai, *Biology* **6**, 5 (2017).
8. M. A. Lampson, E. L. Grishchuk, *Biology* **6**, 1 (2017).
9. M. Deng *et al.*, *Dev. Cell.* **12**, 301 (2007).
10. L. Peris *et al.*, *J. Cell Biol.* **174**, 839 (2006).
11. A. Weisbrich *et al.*, *Nat. Struct. Mol. Biol.* **14**, 959 (2007).
12. J. J. Nirschl *et al.*, *Cell Rep.* **14**, 2637 (2016).
13. R. J. McKenney *et al.*, *EMBO J.* **35**, 1175 (2016).

10.1126/science.aaq0200