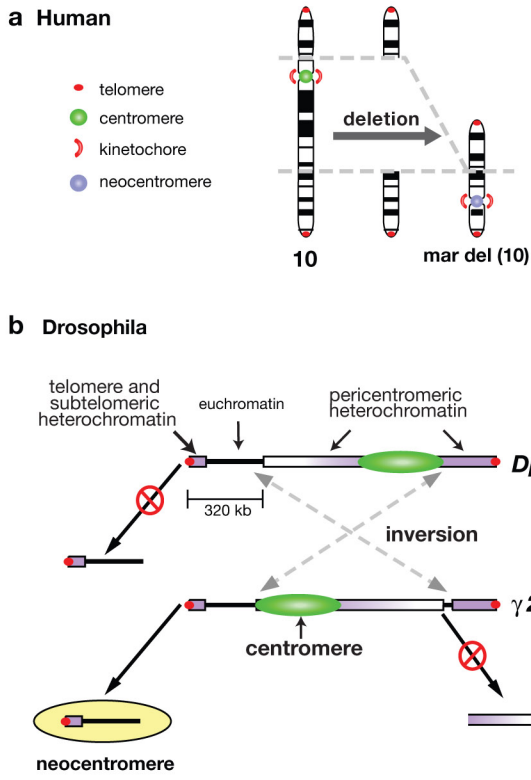

Figure 5. Neocentromere Formation in Humans and Flies

(*a*) Human chromosomes carrying neocentromeres, which exhibit centromere function/kinetochore formation in the absence of centromeric DNA, are usually associated with gross rearrangements (Amor and Choo 2002). In this classic example, a chromosome-10-derived neocentromere (mar(del)10), whose structure indicates formation via a large interstitial deletion that removed the endogenous centromere (*gray dotted lines*). Mar(del)10 was recovered in an individual whose karyotype also contained a ring chromosome (ring(del)10, not shown) that contains the DNA from the deleted region. The order of events for human neocentromeres is unclear; neocentromere formation could occur first, producing a dicentric chromosome that subsequently undergoes rearrangements, or neocentromere formation could occur after deletion of the endogenous centromere. (*b*) Neocentromeres can be generated experimentally in flies from a molecularly defined minichromosome. A 320-kb fragment of euchromatin and telomeric chromatin, which contains no centromeric DNA, can be separated from the rest of the minichromosome by irradiation. This fragment, which should be "acentric," can become a functional neocentromere that is propagated faithfully through mitosis and meiosis, and contains centromere and kinetochore proteins normally restricted to the endogenous centromere (Blower and Karpen 2001). However, neocentromere formation requires proximity to the endogenous centromere (420 kb), as in the inversion derivative *γ238;* furthermore, neocentromere formation does not occur on either side of the centromere when pericentric heterochromatin is present (Maggert and Karpen 2001). These results suggest that neocentromere formation occurs via epigenetic spreading of centromeric chromatin into adjacent euchromatin, followed by epigenetic propagation of centromere identity and function. The blocking of this process by heterochromatin is consistent with the observation that overexpressed CENP-A is incorporated ectopically into euchromatin but not heterochromatin (Heun et al. 2006) and suggests that the extent of centromeric chromatin is determined by two epigenetic processes: CENP-A loading and spreading, and heterochromatin formation/blocking.