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Heterochromatin state and cell cycle separate the deposition of H2A and H2A.Z.

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Histone variant distribution contributes to the definition of distinct chromatin states, and genome-wide alterations in this chromatin landscape represent one of the hallmarks of cancer. What dictates the local incorporation of histone variants is a major unresolved question. Here, by focusing on the centromere, a region where chromatin organization is critical for ensuring chromosomal segregation, we address how the deposition of two H2A variants, canonical H2A and H2A.Z, is controlled to mark this locus in a distinct manner. To this end, we exploit a strategy that distinguishes newly synthesized histones from the parental ones. With this strategy, while H2A and H2A.Z dynamics in euchromatin is indistinguishable, at pericentric heterochromatin we reveal two discrete waves of *de novo* deposition of H2A variants during the cell cycle. H2A is deposited at pericentric heterochromatin during mid-late S phase in a replication-dependent manner. In contrast, H2A.Z incorporation is strictly limited to G1 phase. Notably, this cell cycle-regulated incorporation is lost when the heterochromatin features of the pericentromeric domain are altered. We can then observe cells with aberrant accumulation of H2A.Z due to unscheduled incorporation. Remarkably, normal pattern of H2A variant localization of at pericentric heterochromatin can be restored as soon as the normal heterochromatin state itself is re-established. We propose that the heterochromatic nature of the locus is key for the receptivity for H2A.Z incorporation. We discuss how the interplay between cell cycle and heterochromatin dynamics determines distinct cell-cycle deposition of H2A and H2A.Z histone variants at pericentric heterochromatin, and how this mechanism offers a potential regulatory means for defining chromatin states during development and in pathological situations.