Chromosome Res (2025) 33:22
https://doi.org/10.1007/s10577-025-09779-x

REVIEW

The dynamic centromere

Angela Enriquez · Yael Nechemia-Arbely

Received: 4 May 2025 / Revised: 15 August 2025 / Accepted: 26 August 2025 / Published online: 16 October 2025

Abstract Centromeres are fundamental chromosomal structures that ensure accurate chromosome segregation during cell division. Despite their conserved and essential role in maintaining genomic stability, centromeres are subject to rapid evolutionary change. At the heart of centromere identity is the histone H3 variant CENP-A, an epigenetic mark that defines and propagates active centromeres and is essential for their function. Recent evidence supports a rapid evolution of centromere DNA sequences but also suggests a certain degree of flexibility in CENP-A deposition and propagation. The phenomenon of centromere drift, recently observed in humans, highlights how the dynamic repositioning of CENP-A and associated epigenetic environment over time maintains a regulated equilibrium, ensuring centromere function despite positional variation. Understanding these processes is crucial for unraveling centromere dynamics and their broader implications for genome stability and evolution.

Responsible Editor: Bungo Akiyoshi

A. Enriquez · Y. Nechemia-Arbely (✉)
UPMC Hillman Cancer Center, Pittsburgh, PA 15232, USA
e-mail: arbelyy@upmc.edu

A. Enriquez · Y. Nechemia-Arbely
Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA 15213, USA

Keywords Centromeres · CENP-A · Chromatin · Mitosis · Epigenetics · Evolution

Introduction

Faithful chromosome segregation is essential for ensuring genome integrity. As cells divide, their genetic material must be precisely replicated and distributed between two daughter cells (Novák et al. 2018). Centromeres are chromosomal regions of condensed chromatin that provide the foundation for kinetochore assembly and correct spindle microtubule attachment and are essential for enabling faithful sister chromatid segregation during mitosis (Cleveland et al. 2003).

While different species share a conserved role for centromeres, their centromere DNA sequences and organization differ markedly, giving rise to 'The Centromere Paradox' (Malik and Henikoff 2001). Highly and moderately repetitive DNA elements are a hallmark of most centromeres in plants, animals, and fungi; however, many exceptions exist, including the point centromeres of budding yeast, the holocentric chromosomes of *Caenorhabditis elegans* (*C. elegans*) (Eichler 1999), and non-repetitive evolutionary new centromeres (ENCs) (observed in horses, orangutans, and chickens) (Fukagawa and Earnshaw 2014). Among eukaryotes, human centromeres are the most complex, and are composed of tandemly repeated arrays of α-satellite DNA sequences that are further

organized into Higher Order Repeat (HOR) arrays (Willard and Waye 1987). Some of these α-satellite DNA sequences contain a 17 bp DNA binding motif, termed the CENP-B box, that bind the CENP-B protein, making it the only centromeric protein known to recognize and bind a specific centromeric DNA sequence (Muro et al. 1992). Interestingly, CENP-B is thought to have originated from a pogo-like transposase, a type of DNA-transposing element, and this domestication, where a transposase becomes part of a host's cellular machinery, has happened independently in three different lineages: mammals, fission yeast and holocentric insects (Mateo and González 2014). The presence and conservation of CENP-B boxes vary across species. In humans, CENP-B boxes are found in all autosomes and the X chromosome but are absent from the Y chromosome. The CENP-B box is found also in great apes and certain New World monkeys, but not in all primate groups (Kugou et al. 2016; Suntronpong et al. 2016). In Equids (horses, zebras, etc.) CENP-B is expressed but does not bind most satellite-based centromeres, or the satellite-free ones, while it is localized at several ancestral inactive centromeres (Cappelletti et al. 2025). Thus, CENP-B's evolutionary journey from a transposase to a centromeric protein, along with the varying presence and function of its binding site, highlights the dynamic and multifaceted nature of centromere evolution (Gamba and Fachinetti 2020).

Paradoxically, despite the conservation of repetitive DNA elements at centromeres across species, centromere identity is not defined by a specific DNA sequence. Instead, centromeres are epigenetically defined by the presence of a histone H3 variant, centromere protein A (CENP-A), which propagates centromere epigenetic identity and marks their location (Earnshaw and Rothfield 1985; Palmer et al. 1987; Sekulic and Black 2012; Fachinetti et al. 2013). Thus, the ultimate genetic locus responsible for genome inheritance is epigenetically defined.

Histones are essential architectural proteins that package the DNA of eukaryotic organisms into a compact and organized structure. They form octameric nucleosome cores around which the DNA double helix wraps tightly, creating the fundamental units of chromatin (Malik and Henikoff 2003). Typically, each nucleosome consists of eight histone proteins, two copies each of H2A, H2B, H3, and H4 (Yoda et al. 2000). The nature and composition of CENP-A-containing chromatin has been debated with multiple models proposed: an octameric nucleosome with two molecules of CENP-A (Hasson et al. 2013; Miell et al. 2013; Padeganeh et al. 2013; Nechemia-Arbely et al. 2017), a heterotypic nucleosome containing one molecule of CENP-A and one molecule of H3 (Lacoste et al. 2014), a tetrasome with only CENP-A and H4 (Yoda et al. 2000), a hemisome with only one molecule each of CENP-A, H4, H2A and H2B (Dalal et al. 2007; Dimitriadis et al. 2010; Henikoff et al. 2014; Walkiewicz et al. 2014) and even an oscillating structure transitioning from an octameric nucleosome in S-phase to a hemisome in G2/M/G1 cell cycle phases (Bui et al. 2012; Walkiewicz et al. 2014). However, a series of studies have led to a general agreement that CENP-A is assembled into an octameric nucleosome with two CENP-A molecules replacing histone H3, and paired with histones H4, H2A, and H2B (Hasson et al. 2013) across the cell cycle (Nechemia-Arbely et al. 2017) at all active centromeres (Fachinetti et al. 2013). This unique octamer is characterized by flexible DNA ends at the entry and exit points of the nucleosome that are not tightly bound (Conde E Silva et al. 2007; Tachiwana et al. 2011; Yatskevich et al. 2022). This transient DNA unwinding of the CENP-A nucleosome is mediated by the CENP-A shorter N-terminal tail and CENP-A Targeting Domain (CATD) (Tachiwana et al. 2011; Nechemia-Arbely et al. 2017), and results in it wrapping less DNA (110–150 bp) compared to H3 nucleosomes (147 bp), in in vivo ChIP-MNase-seq studies (Hasson et al. 2013; Lacoste et al. 2014; Nechemia-Arbely et al. 2017). This chromatin feature that differentiates CENP-A- from H3-containing chromatin is thought to be important for binding of the constitutive centromere associated network (CCAN) of proteins (Ali-Ahmad et al. 2019; Tian et al. 2022), a complex made of 16 centromeric proteins that forms the inner kinetochore (Foltz et al. 2006), and is essential for kinetochore assembly and mitotic fidelity (Roulland et al. 2016; Pesenti et al. 2022).

The fact that human centromeres are epigenetically defined is supported by the discovery of neocentromeres, where centromeres emerge at new chromosomal locations lacking α-satellite DNA (Amor and Choo 2002), highlighting that centromere identity is not dictated by a DNA sequence but rather by an epigenetic mechanism (Earnshaw and Migeon 1985; Amor and Choo 2002). Additionally, while previous

efforts to generate human artificial chromosomes (HACs) showed that centromeres can form de novo only on α-satellite DNA sequences with intact binding motifs for the CENP-B protein (Ikeno et al. 1998; Ohzeki et al. 2002), recent efforts have demonstrated that seeding of CENP-A alone through artificial tethering via HJURP is sufficient to establish a functional centromere, even in the absence of α-satellite DNA (Logsdon et al. 2019; Gambogi et al. 2024), questioning the requirement of a universal repetitive element for centromere function.

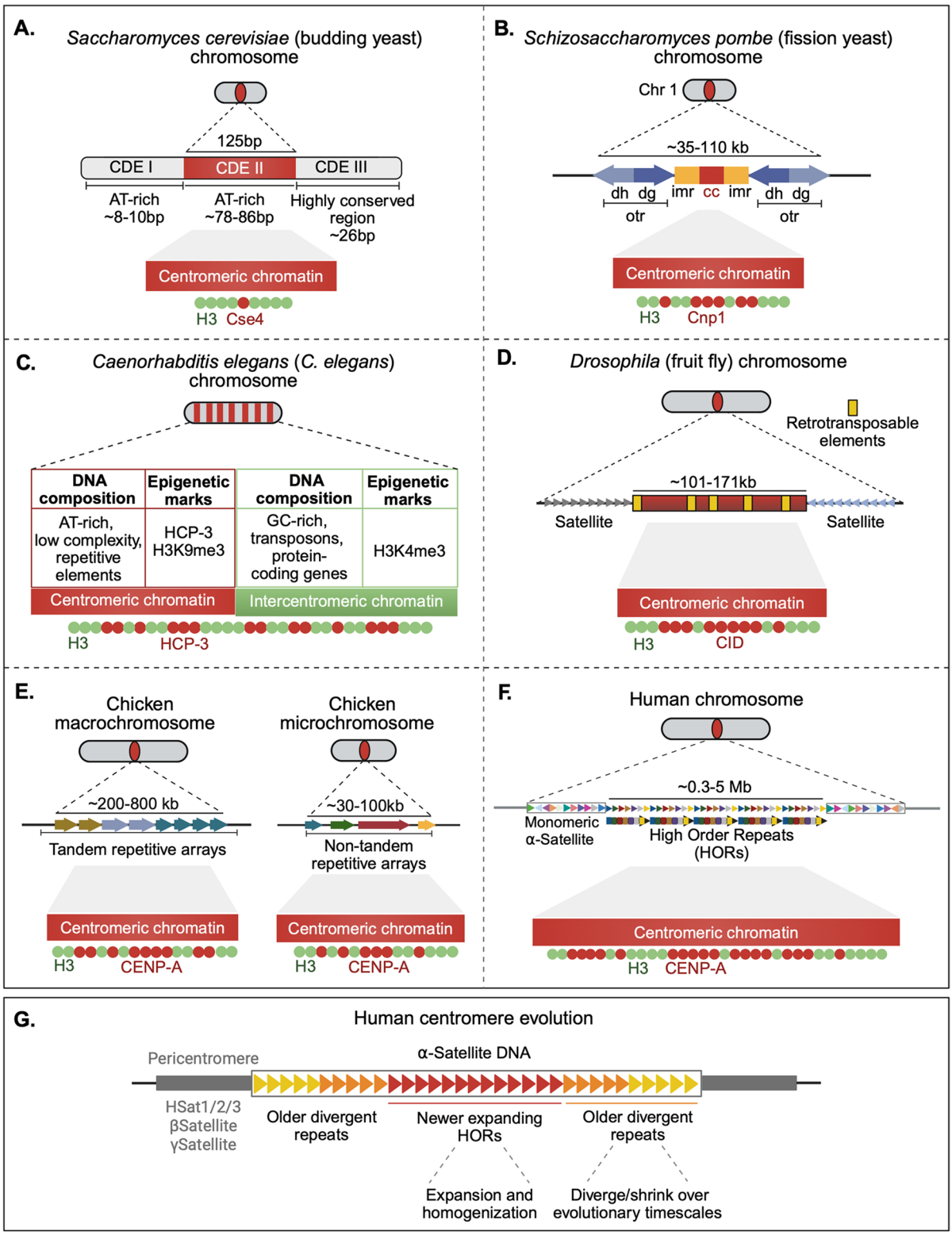
Evidence of centromere drift, characterized by sliding of CENP-A nucleosomes within a specific genomic region, further highlights the dynamic nature of centromeres. Positional movement of CENP-A observed across species and cell types, including fission yeast, chicken, horse, and now human, reveal that CENP-A positioning is dynamic in evolutionary timescales, undergoing movement over cellular proliferation while maintaining a critical threshold of CENP-A nucleosomes that is essential for centromere function (Fachinetti et al. 2013; Bodor et al. 2014; Hoffmann et al. 2016). Heterochromatin modifications have been implicated in serving as centromere boundaries (Lam et al. 2006; Ohzeki et al. 2012, 2016; Mckinley and Cheeseman 2016) and may also constrain CENP-A drift and domain size (Jansen et al. 2007; Carty et al. 2025; Mahlke et al. 2025) linking CENP-A position to the larger centromere epigenetic environment.

In this review, we focus on centromere plasticity by exploring the evolution of centromeric DNA sequences and CENP-A maintenance. Furthermore, we discuss the phenomenon of centromere drift in humans, highlighting the dynamic repositioning of CENP-A and its implications.

Centromere sequence evolution – from species to individual variation

The evolutionary history of centromeres is marked by significant plasticity, as evidenced by the substantial divergence in centromere sequence and location among species (Warburton et al. 1996; Amor et al. 2004). *Saccharomyces cerevisiae* (budding yeast) represents a unique case in which centromeres function rely on a defined non-repetitive 125 bp DNA sequence that wraps a single CENP-A (Cse4) containing nucleosome (Henikoff and Henikoff 2012; Henikoff et al. 2014). The highly conserved 125 bp sequence is composed of three distinct elements (CDE I, CDE II, and CDE III), with Cse4 deposition occurring at the AT-rich CDE II region (Fig. 1A). This sharply contrasts with the organization of centromeres in *Schizosaccharomyces pombe* (fission yeast) that share key features with those of higher eukaryotes consisting of a central core, where CENP-A (Cnp1) is deposited, flanked by inner repeats (imr) which vary in sequence between centromeres, and outer repeats (Birney et al. 2007) which contain conserved dg and dh repetitive elements (Fig. 1B) (Cleveland et al. 2003; Gonzalez and Li2012; Yang and Li 2017). Centromeres in *C. elegans* and *Drosophila* also exhibit unique structural adaptations suited to their chromosomal organization. The holocentric centromeres of *C. elegans* are characterized by the distribution of CENP-A (HCP-3) along the entire chromosome length rather than at a single locus, and do not rely on large arrays of repetitive sequences (Kuo et al. 2023) (Fig. 1C). Meanwhile, *Drosophila* centromeres are composed of large blocks of repetitive satellite DNA interspersed with transposable elements (Fig. 1D) (Sun et al. 1997; Cleveland et al. 2003; Chang et al. 2019). Studies using chromatin immunoprecipitation of CENP-A combined with long-read sequencing technologies achieved the complete assembly of all *Drosophila* centromeres, revealing that CENP-A is enriched over islands of complex DNA sequences (101–171 kb), which are flanked by blocks of simple satellite repeats and enriched for the non-LTR retrotransposable element G2/Jockey-3 (Fig. 1D) (Chang et al. 2019). For example, the *Drosophila* minichromosome Dp1187 contains a 420 kb region that serves as the centric heterochromatin. This region is primarily composed of AATAT and AAGAG satellite repeats with minimal sequence variation, while transposable elements are interspersed within AATAT but absent from AAGAG sequences. Deletions in this region lead to chromosome instability, emphasizing the role of satellite DNA and transposable elements in *Drosophila* centromere structure and function (Sun et al. 1997; Kyriacou and Heun 2023).

Vertebrates' centromeres typically consist of repetitive DNA arrays of varying sequence composition and organization. Chicken macrochromosomes contain large tandem repeat arrays that span hundreds of kilobases (~200–800 kb) (Fig. 1E). Satellite motifs, such as CR-1, CR1-C, and GGXHOI contribute variably to centromeric repeat content, ranging from 41% in Cen1 to 100% in Cen4 (Shang et al. 2010). In


A.
Saccharomyces cerevisiae (budding yeast) chromosome
125bp
CDE I
CDE II
CDE III
AT-rich ~8-10bp
AT-rich ~78-86bp
Highly conserved region ~26bp
Centromeric chromatin
H3 Cse4
B.
Schizosaccharomyces pombe (fission yeast) chromosome
Chr 1
~35-110 kb
dh dg imr cc imr dh dg
otr otr
Centromeric chromatin
H3 Cnp1
C.
Caenorhabditis elegans (C. elegans) chromosome
DNA composition
Epigenetic marks
DNA composition
Epigenetic marks
AT-rich, low complexity, repetitive elements
HCP-3 H3K9me3
GC-rich, transposons, protein-coding genes
H3K4me3
Centromeric chromatin
Intercentromeric chromatin
H3 HCP-3
D.
Drosophila (fruit fly) chromosome
Retrotransposable elements
~101-171kb
Satellite
Satellite
Centromeric chromatin
H3 CID
E.
Chicken macrochromosome
~200-800 kb
Tandem repetitive arrays
Chicken microchromosome
~30-100kb
Non-tandem repetitive arrays
Centromeric chromatin
H3 CENP-A
Centromeric chromatin
H3 CENP-A
F.
Human chromosome
~0.3-5 Mb
Monomeric α-Satellite
High Order Repeats (HORs)
Centromeric chromatin
H3 CENP-A
G.
Human centromere evolution
Pericentromere
α-Satellite DNA
HSat1/2/3
βSatellite
γSatellite
Older divergent repeats
Newer expanding HORs
Older divergent repeats
Expansion and homogenization
Diverge/shrink over evolutionary timescales

◂**Fig. 1** Comparative organization of centromeres across species. **(A)** Centromere organization in *Saccharomyces cerevisiae* (budding yeast). The centromere consists of a ~ 125 bp DNA region divided into three conserved elements: CDE I (~ 8–10 bp, AT-rich), CDE II (~ 78–86 bp, AT-rich), and CDE III (~ 26 bp, highly conserved region). The CDE II region serves as the primary site for CENP-A (Cse4) nucleosome deposition. **(B)** Schematic representation of the centromere structure in *Schizosaccharomyces pombe* (fission yeast), highlighting the arrangement of distinct repeat elements and the central core region. Each centromere consists of an inner core region (imr) flanked by outer repeat elements (dg and dh), which are essential for heterochromatin formation. The central core (cc) is the site of CENP-A (Cnp1) nucleosome deposition. **(C)** Centromere organization in *C. elegans*. The panel illustrates a chromosome with dispersed centromeric regions (red bands) along its length, reflecting the holocentric nature of *C. elegans* chromosomes. Tables show the underlying DNA composition and epigenetic landscape of centromeric chromatin versus intercentromeric chromatin. Centromeric chromatin is enriched for the histone variant CENP-A (HCP-3). **(D)** Schematic representation of a *Drosophila* centromere composed of a central CENP-A (CID) enriched island (101–171 kb in length), flanked by large blocks of simple satellite DNA (light gray and blue chevrons) that make up the surrounding pericentromeric heterochromatin. The island contains complex DNA sequences, including G2/Jockey-3 non-LTR retrotransposable elements (yellow rectangles), which are interspersed throughout the region. While each centromere has a unique sequence composition, the overall structure of satellite-rich flanks and a retroelement-enriched core is conserved across chromosomes. **(E) Left panel:** The centromere of a chicken macrochromosome, which consists of chromosome-specific, homogeneous tandem repetitive arrays spanning several hundred kilobases. The arrangement of these sequences varies among centromeres, with different lengths and homology regions. Below these centromere sequences, CENP-A deposition is shown in red, indicating the establishment of a functional centromere. **Right panel:** The centromere of a chicken microchromosome consisting of non-tandem repetitive sequences. Despite the absence of extensive tandem repeats, these centromeres remain functional, as indicated by CENP-A deposition (red) below the region. **(F)** Representation of human centromere organization. Human centromeres are composed of α-satellite DNA, which includes monomeric repeat units further organized into higher order repeat (HOR) structures that form chromosome specific arrays. The schematic illustrates the clustering of CENP-A (red) within the active HOR, marking the location of the functional active centromere. **(G)** Evolutionary layering expansion of centromeric α-satellite DNA. Older, more divergent HOR arrays are concentrated at the periphery of the centromere (yellow and orange chevrons), representing ancestral repeat units. In contrast, newer and evolutionary younger, more homogeneous HORs are expanding at the center, reflecting ongoing centromeric sequence evolution and array renewal over time (red chevrons)

contrast, centromeres in chicken microchromosomes 5, 27, and Z harbor non-tandem repetitive sequences (Fig. 1E). Studies that used ChIP-sequencing to determine DNA sequences bound by CENP-A revealed that the major CENP-A-associated region spans approximately ~ 30 kb on chromosomes 5, Z, and 27, but all are entirely devoid of tandem repeats (Shang et al. 2010). Despite the vast difference in chromosome lengths, with chromosome Z being 75 Mb in comparison to chromosome 27 (~ 5 Mb), the size of the centromere and kinetochore do not scale with chromosome size. Rather, similar levels of constitutive centromere proteins are present across all chicken chromosomes (Shang et al. 2010; Huang et al. 2023). In humans, centromeres are primarily composed of α-satellite DNA, a type of non-coding tandemly repeated 171 bp DNA monomer arranged into higher-order repeat (HOR) array structures (Fig. 1F). HORs are chromosome-specific, with each chromosome having a unique pattern of repeating α-satellite DNA monomers. While divergent monomeric α-satellite DNA is more abundant adjacent to flanking pericentromeric heterochromatin, uniform HORs are strongly associated with active centromeres that recruit CENP-A (Fig. 1F) (Pironon et al. 2010; Sullivan et al. 2017). Collectively, despite their shared role in ensuring accurate chromosome segregation (Cleveland et al. 2003), centromeres vary widely across species in both sequence composition and structural organization, pointing towards their evolution and suggesting that different species have evolved diverse solutions for maintaining centromere stability and function (Thakur et al. 2021; Piras et al. 2022).

Comparative analyses of centromeric satellite DNA in humans, non-human apes, and other primates reveal that satellite DNA evolves rapidly through mutational events including insertions, deletions, and gene conversion, driving high sequence divergence within and between species (Charlesworth et al. 1994; Haaf and Willard 1997; Shepelev et al. 2009; Logsdon and Eichler 2023). In humans, centromeric sequences are especially dynamic, showing differences across populations (Sullivan and Sullivan 2020; De Lima et al. 2021) and individuals (Logsdon et al. 2024). Studies using digital droplet PCR (ddPCR) assay to measure centromeric HOR length, measured the size of five centromeric HOR arrays (DXZ1, D18Z1, D11Z1, D7Z2, and D6Z1), and found up to tenfold variation in the length of the same array and

up to 50-fold length variation across different centromeric arrays between individuals from China, the UK, and the US (De Lima et al. 2021). Notably, D6Z1, D11Z1, and DXZ1 arrays exhibited significant length differences between individuals from China and those from the UK/US, suggesting population-specific haplotypes. Additionally, when applying this assay to four different types of cancer (head and neck, breast, medulloblastoma, and acute lymphoblastic leukemia) to examine centromeric sequence evolution, an elevated instability and changes in HOR copy number were observed in primary cancer samples, especially pediatric cancers, compared to normal tissue (De Lima et al. 2021).

While α-satellite DNA is the defining feature of all human centromeres, the composition and arrangement of other satellite families vary across centromeres of different chromosomes. Recent advances in long-read sequencing have revealed for the first time, the complete linear assembly of human centromere sequences in the CHM13 cell line (a hydatidiform mole cell line with a nearly homozygous genome), and uncovered the evolution of human centromeres, enabling detailed sequence comparisons (Altemose et al. 2022a, b). Human satellites 2 and 3 (HSat2 and HSat3) were found to be the largest contiguous satellite DNA arrays, primarily composed of the (CATTC)n simple repeat (Altemose et al. 2022a, b). They are predominantly located in pericentromeric regions but are absent from certain centromeres, such as centromeres of chromosomes 6 and 8, while chromosome 9 contains the largest HSat3 array (Altemose et al. 2022a, b; Showman et al. 2024). Other key satellite families include HSat1A (enriched on chromosomes 3, 4, and 13), HSat1B (primarily on chromosome Y and some acrocentric chromosomes), β-satellite (bSat, abundant on chromosome 1 and acrocentric chromosomes), and γ-satellite (γSat, a smaller family spanning 630 kb genome-wide) (Altemose et al. 2022a, b). While these non-alpha satellite families are abundant, they are typically located in pericentromeric regions, do not generally form HORs, and are not directly involved in forming the functional centromeric core where CENP-A is localized (Fig. 1G). However, they may contribute to the overall architecture of pericentric heterochromatin (Lehnertz et al. 2003; Altemose et al. 2022a, b). These advances in our understanding of human centromeric DNA sequence and organization, have revealed that centromeric DNA evolves through a dynamic process of layered expansions, where newer α-satellite variants can arise and expand through tandem duplications, while older sequences shrink and diverge (Fig. 1G). Recent efforts completed Telomere-to-Telomere (T2T) assemblies for additional human cell lines, including CHM1 (Logsdon et al. 2024), RPE-1 (Volpe et al. 2023) and HG002 (Garg et al. 2021; Jarvis et al. 2022) and provide a more comprehensive view of human centromeric variation. The comparison between CHM13 and CHM1 assemblies reveal accelerated variation in centromeric α-satellite HORs (Logsdon et al. 2024). Similarly, a fully phased assembly of the diploid RPE-1 cell line (RPE-1v1.0) reveals significant variation in human centromere sequence and size between chromosomal haplotypes, emphasizing centromere complexity and heterogeneity (Volpe et al. 2023).

Collectively, these latest efforts of T2T sequencing of human centromeres revealed that centromere sequences are subject to unique evolutionary pressures resulting in them exhibiting some of the most rapid sequence evolution in the genome as reviewed in (Balzano and Giunta 2020). Despite this rapid evolution of centromere sequences, some genomic characteristics of α-satellite sequences are maintained through evolution, including them being repetitive, AT-rich, and containing the CENP-B Box in many species (Gamba and Fachinetti 2020; Thakur et al. 2021). The fact that these genomic features of α-satellite sequences are maintained within the rapidly evolving centromeres indicate a selective pressure to preserve these features, while the exact nucleotide sequences per se might not be important to preserve centromere function.

Stability and precision in propagation of the centromere epigenetic identity

Maintenance of CENP-A at the centromeres is critical for proper chromosome segregation during cell division, as it defines centromere identity and serves as foundation for kinetochore recruitment (Sekulic and Black 2012). CENP-A homologs are found in almost all species: Cse4 in budding yeast (Camahort et al. 2007), Cnp1 in fission yeast (Williams et al. 2009), HCP-3 in *C. elegans* (Kitagawa 2009), and CID in *Drosophila* (Heun et al. 2006). While species-specific variants of CENP-A have a conserved role

in ensuring faithful chromosome segregation, some show significant amino acid divergence throughout evolution compared to other highly conserved histone proteins (De Rop et al. 2012). Thus, not only the DNA sequences at the centromere are evolving, but also the amino-acid sequence of the major epigenetic mark that defines centromere's identity. In *Arabidopsis* and *Drosophila* CENP-A is under positive selection particularly in the Loop1 region, a structurally distinct segment within the histone fold domain of histone proteins, that is important for DNA binding, histone dimerization or tetramerization, and overall nucleosome stability (Malik and Henikoff 2001; Talbert et al. 2002; Vermaak et al. 2002; Cooper and Henikoff 2004), suggesting that CENP-A is evolving rapidly in these organisms, likely in response to selective pressures acting on centromere composition and function (Malik and Henikoff 2001). In contrast, mammals and budding yeasts such as *S. cerevisiae* show no evidence of positive selection acting on CENP-A, indicating different evolutionary dynamics of centromeric proteins across eukaryotes. These differences may reflect the distinct centromere structures, modes of chromosome segregation, or the influence of additional regulatory proteins such as chaperones in mammals that constrain CENP-A evolution as reviewed in (Malik 2009; Drinnenberg et al. 2014; Kursel and Malik 2017).

Despite this variability in CENP-A amino acid sequence, CENP-A is consistently preserved throughout the cell cycle, safeguarding genome integrity through a process that is tightly regulated (Jansen et al. 2007; Fachinetti et al. 2013; Nechemia-Arbely et al. 2019; Mahlke et al. 2023). New CENP-A deposition occurs at exit of mitosis (Jansen et al. 2007) through a stepwise process that includes PLK1-dependent phosphorylation of the Mis18 complex (Mckinley and Cheeseman 2014; Conti et al. 2024; Parashara et al. 2024) that activates it and licenses the deposition of CENP-A by its chaperone, HJURP (Dunleavy et al. 2009; Foltz et al. 2009), ensuring centromere epigenetic maintenance and propagation across the cell cycle (Fachinetti et al. 2013), as reviewed in detail by Jansen and colleagues in this issue (Rowley and Jansen 2025). Interestingly, some CENP-A is deposited ectopically at non-centromeric sites (Lacoste et al. 2014; Nechemia-Arbely et al. 2019) and this ectopic deposition is increased in correlation with CENP-A expression levels (Nechemia-Arbely et al. 2019). During DNA replication, CENP-A is distributed to daughter centromeres resulting in 50% dilution of CENP-A at centromeres (Jansen et al. 2007). The reassembly of CENP-A onto the daughter centromeres during S-phase occurs through an interaction of CENP-A with both HJURP (Zasadzinska et al. 2018) and MCM2 (Zasadzinska et al. 2018; Nechemia-Arbely et al. 2019), and requires CENP-C and the CCAN (Nechemia-Arbely et al. 2019). The combined interaction of CENP-A with HJURP, MCM2, and the CCAN during DNA replication enables the reassembly of CENP-A onto the same centromeric sequences it was loaded on in early G1. Meanwhile, the passage of the DNA replication machinery strips off CENP-A from ectopic sites on the chromosome arms, thereby restricting CENP-A to the centromeres only and reinforcing epigenetic centromere identity (Nechemia-Arbely et al. 2019).

The crucial roles of CENP-A's inheritance and its stability from one generation to the other are emphasized by the stable retention of CENP-A nucleosomes in the mouse female germline. Studies in mouse oocytes show that once incorporated before prophase I arrest, CENP-A remains stable and functional for over a year, marking centromeres throughout oocyte development (Smoak et al. 2016). Unlike CENP-A, H3.3 is actively deposited during prophase I arrest to maintain chromatin structure, gene expression, and oocyte viability (Swartz et al. 2019; Toyama et al. 2019). This remarkable stability of centromeric chromatin, despite ongoing nucleosome turnover in other regions, reflects the durability and stability of CENP-A nucleosomes (Smoak et al. 2016). Such retention is particularly notable given the prolonged meiotic arrest in humans, which can last decades. However, in some species, low-level transcription during meiotic arrest, as seen in starfish oocytes, can lead to gradual erosion of CENP-A nucleosomes (Swartz et al. 2019). This suggests that CENP-A stability is subject to species-specific regulation, influenced by chromatin environment and germline challenges (Swartz et al. 2019; Mitra et al. 2020).

Additional centromeric proteins like CENP-B and CENP-C provide additional layers of stability and functionality at centromeres (Gamba and Fachinetti 2020). As mentioned above, CENP-B is the only centromeric protein known to bind a specific centromeric DNA sequence, known as the CENP-B box (Muro

et al. 1992). Despite this unique characteristic of CENP-B and its implications in centromere evolution (Gamba and Fachinetti 2020), studies of CENP-B null mice showed that these mice remain viable, demonstrating the dispensability of CENP-B at centromeres (Hudson et al. 1998; Perez-Castro et al. 1998). Moreover, human neocentromeres and the Y chromosome, as well as non-repetitive ENCs, are lacking CENP-B boxes and binding of CENP-B, further demonstrate the fact that CENP-B may not be essential for centromere function and identity (Voullaire et al. 1993; Gamba and Fachinetti 2020; Cappelletti et al. 2025). In species such as mice and humans where CENP-B is present, CENP-B helps maintain centromeres by establishing a "memory" system that ensures stable CENP-A deposition (Hoffmann et al. 2020). CENP-B binding to centromeric DNA and its dimerization was recently shown to promote centromeric DNA compaction by forming DNA loops, with knockdown of CENP-B during constant microtubule pulling resulting in increased centromere fragility (Chardon et al. 2022). Thus, CENP-B promotes secondary DNA structure that is important for maintenance of centromere integrity. Furthermore, CENP-B serves as a backup mechanism to stabilize CENP-A (Fachinetti et al. 2015; Otake et al. 2020). Using a mutant version of CENP-A that lacks the C-terminal tail required for binding CENP-C, CENP-A can still be incorporated at centromeres, but only in the presence of CENP-B (Fachinetti et al. 2015). This suggests that CENP-B helps stabilize CENP-C at centromeres independently of direct CENP-A interaction, and that this stabilized CENP-C, in turn, supports the loading of CENP-A. Thus, CENP-B binding to CENP-B boxes at α-satellite DNA forms a feedback loop that promotes CENP-C retention, which in turn enables CENP-A incorporation. This backup pathway for CENP-A deposition is important when direct CENP-A–CENP-C interaction is compromised (Fachinetti et al. 2015; Hoffmann et al. 2020).

CENP-C is an inner kinetochore protein that is highly conserved across species from yeast to higher eukaryotes (Przewloka et al. 2011). Unlike CENP-B, CENP-C is essential and depletion of CENP-C leads to a significant decrease in CENP-A retention at centromeres (Falk et al. 2015; Nechemia-Arbely et al. 2019), disruption of kinetochore structure and function (Tomkiel et al. 1994; Carty et al. 2021), defective mitosis characterized by accumulation of prometaphase cells, chromosome missegregation, and cell death (Kwon et al. 2007). CENP-C is regarded as the blueprint for kinetochore assembly (Klare et al. 2015), providing structural stability by directly binding the C-terminal tail of CENP-A (Carroll et al. 2010; Guse et al. 2011; Fachinetti et al. 2013) and recruiting essential KMN network components such as KNL1, Spc105, the Mis12 complex, and the Ndc80 complex (Foltz et al. 2006; Milks et al. 2009; Przewloka et al. 2011). CENP-C recognizes CENP-A nucleosomes via its conserved central motif, which interacts with the hydrophobic C-terminal tail of CENP-A and the acidic patch on the H2A/H2B dimer (Song et al. 2002; Kato et al. 2013).

CENP-C also facilitates new CENP-A deposition at exit of mitosis by recruiting the Mis18 complex to the centromere, a complex that further licenses CENP-A deposition (Dambacher et al. 2012; Hoffmann et al. 2020; London et al. 2023). Depletion of CENP-C in Xenopus egg extract assays demonstrated reduced centromeric Mis18 Binding Protein 1 (M18BP1) levels, and reduced CENP-A deposition (Moree et al. 2011). In human cells, CENP-C depletion reduces HJURP localization at centromeres, and M18BP1 depletion disrupts HJURP recruitment, indicating that M18BP1 is essential for HJURP targeting to centromeres. Thus, CENP-C plays a central role, not only in stabilizing CENP-A, but also in new CENP-A deposition through the recruitment of the essential CENP-A deposition factors M18BP1 and HJURP to centromeres during mitosis (Fujita et al. 2007; Moree et al. 2011). Interestingly, in some holocentric insects lacking CENP-A, CENP-C is also absent, suggesting that CENP-C's primary conserved function may be the recognition of CENP-A nucleosomes, rather than binding directly to DNA or functioning independently (Drinnenberg et al. 2014). These findings again highlight CENP-A as the primary protein responsible for centromere identity.

The epigenetic environment at human centromeres

CENP-A-containing chromatin is interspersed within canonical histone H3 (Fig. 1F) (Blower et al. 2002). These neighboring histone H3 are predominantly marked by epigenetic marks associated with active transcription, including H3K4me2 and H3K36me2/3 (Blower et al. 2002; Sullivan and Karpen 2004; Bergmann et al. 2011; Mckinley and Cheeseman 2016),

that contribute to the euchromatic state of centromeric chromatin, promoting transcription and potentially influencing kinetochore assembly and stability (Liu et al. 2015; Perea-Resa et al. 2020; Chen et al. 2022). Additionally, CENP-A nucleosomes contain modified H4K20me1 that is directly linked to kinetochore assembly (Hori et al. 2014). Notably, while centromeres are generally highly methylated, the most recently expanded centromeric α-satellite repeats preferentially interact with CENP-A at regions of low CpG methylation, known as centromere dip regions (CDRs), together defining the "active HORs" and highlighting a link between satellite repeat expansion, kinetochore positioning, and DNA hypomethylation (Altemose et al. 2022a, b; Gershman et al. 2022; Logsdon et al. 2024). Thus, CENP-A is embedded within a unique epigenetic environment. This unique organization supports the transcription of centromeric DNA, generating centromere-derived RNAs that have been implicated in the establishment and maintenance of centromere identity as well as in the proper assembly of centromere and kinetochore proteins (Chan et al. 2012; Naughton et al. 2022; Chabot et al. 2024).

Flanking the centromeric chromatin are pericentromeric regions composed of constitutive heterochromatin enriched in H3K9me3 (Sullivan and Karpen 2004; Lam et al. 2006; Logsdon et al. 2021; Gershman et al. 2022), a heterochromatic mark proposed to function as centromere boundaries (Peters et al. 2003; Rice et al. 2003; Sidhwani and Straight 2023) by suppressing CENP-A assembly (Ohzeki et al. 2012, 2016) and stabilizing CENP-A positioning (Slee et al. 2012). The pericentromeric heterochromatin is also enriched in the repressive modifications H3K27me3 (Martins et al. 2016), as well as H4K20me3, the regulation of which is important for cohesin binding and for maintaining chromatin compaction (Hahn et al. 2013; Agredo and Kasinski 2023). The pericentromeric heterochromatin is highly methylated and disruptions in this methylation pattern is linked to the human ICF (Immunodeficiency, Centromeric instability, Facial anomalies) syndrome with mutations in four genes: *DNMT3B, ZBTB24, CDCA7* and *HELLS*, being linked to the disease (Maison and Almouzni 2004; Vukic and Daxinger 2019; Scelfo et al. 2024). Interestingly, DNA methyltransferase 1 (DNMT1) directly binds H4K20me3, and disruption of that binding leads to DNA hypomethylation within H4K20me3 enriched regions (Ren et al. 2021). Thus, H4K20me3 may be involved in generating DNA hypermethylation at pericentromeric heterochromatin, through its binding to DNMT1 (Agredo and Kasinski 2023). Yet, little is known about how the different centromeric components contribute to establish and maintain DNA methylation patterns at centromeric and pericentromeric regions (Scelfo et al. 2024).

Maintenance of CENP-A within an evolving locus: stability vs. drift and expansion

CENP-A has been observed as a stable, long-lived nucleosome that is inherited indefinitely and precisely to maintain and propagate centromere identity (Fachinetti et al. 2013; Ross et al. 2016; Smoak et al. 2016; Nechemia-Arbely et al. 2019; Mahlke et al. 2023). Nevertheless, CENP-A must be maintained within the highly evolving nature of centromeric HOR α-satellite arrays (Altemose et al. 2022a, b; Logsdon et al. 2024). While CENP-A is preferentially enriched within the evolutionary younger repeats of the centromeric array, there is also evidence for epigenetic variation in CENP-A positioning, where CENP-A is enriched in different parts of HORs of the same centromere in different human cell lines. For example, while CENP-A is enriched in the evolutionary younger repeats of the centromere of chromosome X in CHM13 and PD-NC4 fibroblasts cells, it is enriched in the evolutionarily older parts of the same centromere array in HeLa, RPE-1 and HuREF cells (Mahlke et al. 2023). Moreover, positions of CENP-A enrichment and kinetochore attachment vary by hundreds of kilobases across CHM13 and CHM1 cell lines that represent different individuals (Logsdon et al. 2024) and between the haplotypes of RPE-1 (Volpe et al. 2023).

These differential CENP-A placements at the same centromere between human populations and individuals suggest movement of CENP-A domains across evolution. Movement of CENP-A position can occur as part of complete centromere relocation as in the process of de novo neocentromere formation (Sart et al. 1997; Carty and Dunleavy 2021; Murillo-Pineda et al. 2021; Renaud-Pageot et al. 2022) and through drift or “sliding” of CENP-A domains at non-repetitive centromeres within a specific genomic region that has been observed between maize species, yeast strains, horse generations, and also within a single population of chicken cells (Allshire et al.

1994; Purgato et al. 2015; Gent et al. 2017; Hori et al. 2017), as we discuss in detail below. These phenomena showcasing different types of CENP-A movement may explain the ability of CENP-A to be maintained within a highly evolving locus.

Neocentromeres are formed by the relocation of the entire CENP-A domain to a new chromosomal location that can lack typical α-satellite DNA (Fukagawa and Earnshaw 2014), and they can form in all human chromosomes (Warburton et al. 2000; Marshall et al. 2008). Neocentromeres show capability to conserve their essential centromere function while adapting to new chromosomal loci. Their identification serves as evidence for the epigenetic identity of human centromeres. Because neocentromeres are functional and heritable, human cell lines that harbor neocentromeres serve as important cellular models for studying de novo centromere formation, function, and maintenance (Bassett et al. 2010; Hasson et al. 2013; Nishimura et al. 2019).

The phenomena of centromere drift and CENP-A domain expansion emphasizes the dynamic nature of centromere positioning, and their ability to evolve over time (Hori and Fukagawa 2020). Centromere drift refers to the dynamic movement or "sliding" of CENP-A nucleosomes within a specific genomic region (Ross et al. 2016; Hori et al. 2017; Sundararajan and Straight 2022). Centromere drift has been observed across a range of species. In fission yeast, the positioning of CENP-A (Cnp1) nucleosomes within the centromeric core varies among genetically identical cells, showing flexibility in centromere chromatin organization, without affecting cell growth or chromosome segregation fidelity (Yao et al. 2013). Studies in non-repetitive centromeres in chicken DT40 cells revealed positional variability of CENP-A, showing that centromere position remains stable within subclones (following approximately 50 cell divisions), but drift over a 16.8-kb region during cell proliferation following several months of cell culture. Depletion of CENP-U and CENP-S further accelerated centromere drift, indicating that chicken CENP-U and CENP-S proteins have a role in stabilizing the positioning of CENP-A nucleosomes (Hori et al. 2017). In horses, CENP-A nucleosomes on chromosome 11 exhibit dynamic movement resembling a diffusion-like process where CENP-A nucleosomes slides within a ~ 500 kb region in different individual horses, giving rise to positional alleles (Purgato et al. 2015). Further examination revealed that the horse centromere is localized in the same region in several tissues of the same horse, suggesting that the position of the centromeric domain is maintained during development (Cappelletti et al. 2023).

A recent study from our laboratory using several human cell lines that each harbor a neocentromere reveals that CENP-A position at native centromeres and at neocentromeres is heterogenous within the bulk population (Mahlke et al. 2025). This study demonstrates that human CENP-A position is differential at the same centromere between otherwise identical cells and that CENP-A position at a specific centromere in the bulk population represents a mix of heterogenous CENP-A positions within single-cells (Fig. 2A) (Mahlke et al. 2025). Each single-cell pattern of CENP-A position maintained a similar number of CENP-A molecules, and similar length of CENP-A domain. Using CENP-A Directed Methylation with Long-read sequencing (DiMeLo-seq), a novel method used to determine target occupancy on long stretches of chromatin (Altemose et al. 2022a, b), coupled with mapping of the long reads to a matched diploid chromosome assembly, this study further showed that each heterogenous single-cell CENP-A position was accompanied by DNA methylation CDRs that were inversely correlated with CENP-A and that changed in correlation with CENP-A position (Fig. 2B). While neocentromeres had individual DNA methylation CDRs inversely correlated to CENP-A peaks, at native centromeres CENP-A peaks were encapsulated within a single wide CDR (Fig. 2B). While CENP-A position was precisely maintained at both native centromeres and neocentromeres for at least ~ 40 cell cycles (Fig. 2A), it naturally evolved through drift, expansion, and shrinkage over prolonged proliferation spanning ~ 280 cell cycles (Fig. 2A) (Mahlke et al. 2025). Evolution of CENP-A position at native centromeres over prolonged proliferation occurred within a stable single DNA methylation CDR (Fig. 2A). In contrast, at the neocentromere prolonged proliferation (~ 280 cell cycles) was accompanied by loss of inverse correlation between DNA methylation and CENP-A peaks, that is, the CDR was decoupled from CENP-A enrichment. Moreover, the neocentromere showed increased heterogeneity in CENP-A position, and increased rates of chromosome missegregation following prolonged cellular proliferation (Fig. 2A). Thus, DNA methylation CDRs create centromeric boundaries that confine CENP-A position and may be

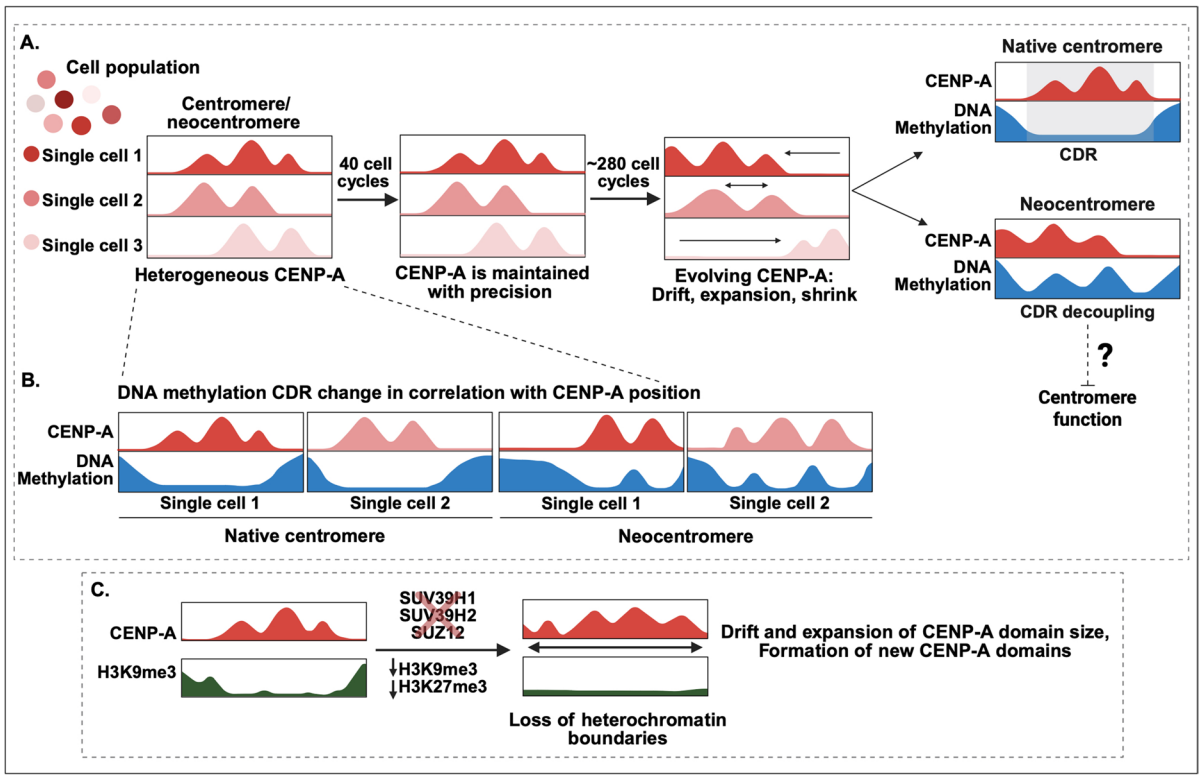


Fig. 2 Maintenance of CENP-A within an evolving locus. Model of potential drivers of centromeric drift and instability. **(A)** Schematic representation of single-cell heterogeneity of CENP-A position at centromeres and neocentromeres, within otherwise identical cells. CENP-A (shades of red) is maintained with precision at both native centromeres and neocentromeres, for at least ~ 40 cell cycles. Following prolonged proliferation for ~ 280 cell cycles, representing several generations' time scale, CENP-A evolves through drift, expansion and shrinkage of the CENP-A domain. While CENP-A evolves within a stable DNA methylation CDR at native centromeres, the DNA methylation CDR at neocentromeres is decoupled and lost over prolonged proliferation which may affect centromere function. **(B)** Single-cell CENP-A positions are accompanied by inversely correlated DNA methylation CDR that change in correlation with CENP-A enrichment. **(C)** Loss of heterochromatin marks such as H3K9me3, as a result of knocking out SUV39H1, SUV39H2 and SUZ12, disrupts the centromeric heterochromatin boundaries, resulting in CENP-A domain drift and expansion, as well as formation of new additional CENP-A domains

important for centromere function. These results indicate that native centromeres have greater long-term epigenetic stability, compared to neocentromeres (Mahlke et al. 2025). Further studies are needed to determine how the DNA methylation CDR is established and maintained at centromeres and its importance to centromere function. Since most human cells divide 40–60 times during development (Hayflick 1965; Childs et al. 2015), these findings suggest that for most human cells CENP-A position will be precisely maintained throughout their lifespan. However, cell types with high mitotic indexes, such as gut and tumor cells, are more likely to show evolution in CENP-A position.

Further evidence for centromere drift in humans and the role of heterochromatin boundaries in stabilizing CENP-A position and domain size comes from another recent study by Jansen and colleagues that used a CRISPR-based system to induce neocentromere formation on chromosome 4 (Neo4p13) in human RPE-1cells and assessed the positional stability of Neo4p13 over 100 days of cell proliferation (Carty et al. 2025). Although CENP-A domains exhibited positional drift over time, their overall size remained stable, fluctuating between 90–100 kb, again suggesting that maintaining an optimal number of CENP-A molecules is critical to preserve neocentromere function, regardless

of positional drift (Carty et al. 2025; Mahlke et al. 2025). Ultra-long-read DiMeLo-seq to detect CENP-A and H3K9me3 occupancy at Neo4p13 and at native centromeres revealed stable heterochromatin dips that shape centromeres' architecture. While H3K9me3 was enriched in pericentric regions, it was notably depleted within active HORs and CENP-A domains, mirroring DNA methylation dips at CDRs (Fig. 2C). Knocking out SUV39H1 and SUV39H2, methyltransferases responsible for depositing the repressive histone mark H3K9me3, and loss of SUZ12, a component of the Polycomb Repressive Complex 2 (PRC2) involved in regulating H3K27me3, led to significant CENP-A drift of 20–150 kb, as well as a twofold expansion of the CENP-A domain. Thus, H3K9me3 and H3K27me3 act as functional boundaries that regulate CENP-A positioning and restrict CENP-A domain size (Fig. 2C). These findings highlight the role of H3K9me3 and H3K27me3 in maintaining centromere integrity by establishing functional boundaries that confine CENP-A positioning and prevent uncontrolled expansion (Carty et al. 2025). Besides drift and expansion, loss of heterochromatin marks led to the formation of new CENP-A domains distal to the primary centromere (Fig. 2C), resulting in distinct double centromeric CENP-C loci and the creation of functional dicentric chromosomes (Carty et al. 2025).

These recent studies demonstrate that CENP-A drift occurs also at human centromeres. They emphasize the remarkable flexibility and adaptability of the centromeric epigenetic environment and highlight the nature of CENP-A positioning: precise maintenance across the cell cycle, but with a certain degree of flexibility across evolutionary timescale. They also demonstrate that stable DNA methylation CDR and heterochromatin boundaries are essential for restricting movement and size of the CENP-A domain. Prolonged cellular proliferation and reduced H3K9me3 and H3K27me3 levels lead to disruption of the DNA methylation CDR and loss of heterochromatin marks, respectively, and to drift and expansion of the CENP-A domain (Fig. 2). This interplay between CENP-A positioning, DNA methylation patterns, and heterochromatin modifications introduces another layer of complexity in the epigenetic propagation of centromere identity within the evolving DNA sequence.

Final thoughts and open questions

To summarize, increasing evidence supports multiple dynamic and evolving layers at centromeres: centromere DNA sequence, CENP-A amino acid sequence, and CENP-A position all evolve in evolutionary timescale while maintaining stable function. Despite the varying layers within the dynamic centromere, maintaining a stable number of CENP-A nucleosomes in parallel to the maintenance of certain genomic characteristics of α-satellite sequences, appear to be important for centromere function. Epigenetic factors such as DNA methylation and heterochromatin dynamics help strengthen, stabilize and confine the position of CENP-A nucleosomes, suggesting that centromere identity is preserved through a finely tuned balance between flexibility and epigenetic reinforcement. Future studies aimed at understanding the mechanisms establishing the pattern of DNA methylation at centromeres and at pericentromeric heterochromatin, and the CDR at the active HORs, are needed to define their role in confining CENP-A position and their importance for centromere function. Better understanding of the interplay between CENP-A and DNA methylation dynamics, as well as the possible contribution of additional centromeric and pericentromeric post-translational epigenetic modifications to this interplay, will be crucial in elucidating how centromeres maintain stability while allowing for plasticity, ultimately providing insights into centromere function and evolution.

Acknowledgements Many important contributions could not be cited due to space constraints, and we apologize to our colleagues for any relevant exclusion. We thank members of the Nechemia-Arbely laboratory for their valuable suggestions during the review writing.

Author Contribution A.E. and YN-A. wrote the main manuscript and A.E. prepared figures. Both authors reviewed and edited the manuscript.

Funding This work was supported by a grant from the National Institute of General Medical Sciences to YN-A. (R35GM142717), and by a diversity supplement (R35GM142717-04S1) to A.E.

Data Availability No datasets were generated or analysed during the current study.

The authors declare no competing interests.

References

Agredo A, Kasinski AL (2023) Histone 4 lysine 20 tri-methylation: a key epigenetic regulator in chromatin structure and disease. Front Genet 14:1243395

Ali-Ahmad A, Bilokapić S, Schäfer IB et al (2019) CENP-C unwraps the human CENP-A nucleosome through the H2A C-terminal tail. EMBO reports 20:e48913

Allshire RC, Javerzat J-P, Redhead NJ et al (1994) Position effect variegation at fission yeast centromeres. Cell 76:157–169

Altemose N, Logsdon GA, Bzikadze AV et al (2022) Complete genomic and epigenetic maps of human centromeres. Science 376:eabl4178

Altemose N, Maslan A, Smith OK et al (2022) Dimelo-seq: a long-read, single-molecule method for mapping protein-DNA interactions genome wide. Nat Methods 19:711–723

Amor DJ, Choo KH (2002) Neocentromeres: role in human disease, evolution, and centromere study. Am J Hum Genet 71(4):695–714

Amor DJ, Bentley K, Ryan J et al (2004) Human centromere repositioning "in progress." Proc Natl Acad Sci U S A 101:6542–6547

Balzano E, Giunta S (2020) Centromeres under pressure: evolutionary innovation in conflict with conserved function. Genes. https://doi.org/10.3390/genes11080912

Bassett EA, Wood S, Salimian KJ et al (2010) Epigenetic centromere specification directs Aurora B accumulation but is insufficient to efficiently correct mitotic errors. J Cell Biol 190:177–185

Bergmann JH, Rodríguez MG, Martins NM et al (2011) Epigenetic engineering shows H3K4me2 is required for HJURP targeting and CENP-A assembly on a synthetic human kinetochore. EMBO J 30:328–340

Birney E, Stamatoyannopoulos JA, Dutta A et al (2007) Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 447:799–816

Blower MD, Sullivan BA, Karpen GH (2002) Conserved organization of centromeric chromatin in flies and humans. Dev Cell 2:319–330

Bodor DL, Mata JF, Sergeev M et al (2014) The quantitative architecture of centromeric chromatin. Elife 3:e02137

Bui M, Dimitriadis EK, Hoischen C et al (2012) Cell-cycle-dependent structural transitions in the human CENP-A nucleosome in vivo. Cell 150:317–326

Camahort R, Li B, Florens L et al (2007) Scm3 is essential to recruit the histone H3 variant Cse4 to centromeres and to maintain a functional kinetochore. Mol Cell 26:853–865

Cappelletti E, Piras FM, Sola L et al (2023) The localization of centromere protein A is conserved among tissues. Commun Biol 6:963

Cappelletti E, Piras FM, Biundo M et al (2025) CENP-A/CENP-B uncoupling in the evolutionary reshuffling of centromeres in equids. Genome Biol 26:23

Carroll CW, Milks KJ, Straight AF (2010) Dual recognition of CENP-A nucleosomes is required for centromere assembly. J Cell Biol 189:1143–1155

Carty BL, Dunleavy EM (2021) Truly epigenetic: A centromere finds a "neo" home. J Cell Biol. https://doi.org/10.1083/jcb.202101027

Carty BL, Dattoli AA, Dunleavy EM (2021) *CENP-C* functions in centromere assembly, the maintenance of *CENP-A* asymmetry and epigenetic age in *Drosophila* germline stem cells. PLoS Genet 17:e1009247

Carty BL, Dubocanin D, Murillo-Pineda M et al (2025) Heterochromatin boundaries maintain centromere position, size and number. bioRxiv 635667. https://doi.org/10.1101/2025.02.03.635667

Chabot BJ, Sun R, Amjad A et al (2024) Transcription of a centromere-enriched retroelement and local retention of its RNA are significant features of the CENP-A chromatin landscape. Genome Biol 25:295

Chan FL, Marshall OJ, Saffery R et al (2012) Active transcription and essential role of RNA polymerase II at the centromere during mitosis. Proc Natl Acad Sci U S A 109:1979–1984

Chang CH, Chavan A, Palladino J et al (2019) Islands of retroelements are major components of Drosophila centromeres. PLoS Biol 17:e3000241

Chardon F, Japaridze A, Witt H et al (2022) CENP-B-mediated DNA loops regulate activity and stability of human centromeres. Mol Cell 82:1751-1767.e8

Charlesworth B, Sniegowski P, Stephan W (1994) The evolutionary dynamics of repetitive DNA in eukaryotes. Nature 371:215–220

Chen Y, Zhang Q, Liu H (2022) An emerging role of transcription in chromosome segregation: ongoing centromeric transcription maintains centromeric cohesion. Bioessays 44:e2100201

Childs BG, Durik M, Baker DJ et al (2015) Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat Med 21:1424–1435

Cleveland DW, Mao Y, Sullivan KF (2003) Centromeres and kinetochores: from epigenetics to mitotic checkpoint signaling. Cell 112:407–421

Conde E Silva N, Black BE, Sivolob A et al (2007) CENP-A-containing nucleosomes: easier disassembly versus exclusive centromeric localization. J Mol Biol 370:555–573

Conti D, Verza AE, Pesenti ME et al (2024) Role of protein kinase PLK1 in the epigenetic maintenance of centromeres. Science 385:1091–1097

Cooper JL, Henikoff S (2004) Adaptive evolution of the histone fold domain in centromeric histones. Mol Biol Evol 21:1712–1718

Dalal Y, Wang H, Lindsay S et al (2007) Tetrameric structure of centromeric nucleosomes in interphase Drosophila cells. PLoS Biol 5:e218

Dambacher S, Deng W, Hahn M et al (2012) CENP-C facilitates the recruitment of M18BP1 to centromeric chromatin. Nucleus 3:101–110

De Lima LG, Howe E, Singh VP et al (2021) PCR amplicons identify widespread copy number variation in human centromeric arrays and instability in cancer. Cell Genom. https://doi.org/10.1016/j.xgen.2021.100064

De Rop V, Padeganeh A, Maddox PS (2012) CENP-A: the key player behind centromere identity, propagation, and kinetochore assembly. Chromosoma 121:527–538

Dimitriadis EK, Weber C, Gill RK et al (2010) Tetrameric organization of vertebrate centromeric nucleosomes. Proc Natl Acad Sci U S A 107:20317–20322

Drinnenberg IA, Deyoung D, Henikoff S et al (2014) Recurrent loss of CenH3 is associated with independent transitions to holocentricity in insects. Elife. https://doi.org/10.7554/eLife.03676

Dunleavy EM, Roche D, Tagami H et al (2009) HJURP is a cell-cycle-dependent maintenance and deposition factor of CENP-A at centromeres. Cell 137:485–497

Earnshaw WC, Migeon BR (1985) Three related centromere proteins are absent from the inactive centromere of a stable isodicentric chromosome. Chromosoma 92:290–296

Earnshaw WC, Rothfield N (1985) Identification of a family of human centromere proteins using autoimmune sera from patients with scleroderma. Chromosoma 91:313–321

Eichler EE (1999) Repetitive conundrums of centromere structure and function. Hum Mol Genet 8:151–155

Fachinetti D, Diego Folco H, Nechemia-Arbely Y et al (2013) A two-step mechanism for epigenetic specification of centromere identity and function. Nat Cell Biol 15:1056–1066

Fachinetti D, Han JS, Mcmahon MA et al (2015) DNA sequence-specific binding of CENP-B enhances the fidelity of human centromere function. Dev Cell 33:314–327

Falk SJ, Guo LY, Sekulic N et al (2015) Chromosomes. CENP-C reshapes and stabilizes CENP-A nucleosomes at the centromere. Science 348:699–703

Foltz DR, Jansen LET, Black BE et al (2006) The human CENP-A centromeric nucleosome-associated complex. Nat Cell Biol 8:458–469

Foltz DR, Jansen LE, Bailey AO et al (2009) Centromere-specific assembly of CENP-a nucleosomes is mediated by HJURP. Cell 137:472–484

Fujita Y, Hayashi T, Kiyomitsu T et al (2007) Priming of centromere for CENP-A recruitment by human hMis18alpha, hMis18beta, and M18BP1. Dev Cell 12:17–30

Fukagawa T, Earnshaw WC (2014) Neocentromeres. Curr Biol 24:R946–R947

Gamba R, Fachinetti D (2020) From evolution to function: Two sides of the same CENP-B coin? Exp Cell Res 390:111959

Gambogi CW, Birchak GJ, Mer E et al (2024) Efficient formation of single-copy human artificial chromosomes. Science 383:1344–1349

Garg S, Fungtammasan A, Carroll A et al (2021) Chromosome-scale, haplotype-resolved assembly of human genomes. Nat Biotechnol 39:309–312

Gent JI, Wang N, Dawe RK (2017) Stable centromere positioning in diverse sequence contexts of complex and satellite centromeres of maize and wild relatives. Genome Biol 18:121

Gershman A, Sauria MEG, Guitart X et al (2022) Epigenetic patterns in a complete human genome. Science 376:eabj5089

Gonzalez M, Li F (2012) DNA replication, RNAi and epigenetic inheritance. Epigenetics 7:14–19

Guse A, Carroll CW, Moree B et al (2011) In vitro centromere and kinetochore assembly on defined chromatin templates. Nature 477:354–358

Haaf T, Willard HF (1997) Chromosome-specific α-satellite DNA from the centromere of chimpanzee chromosome 4. Chromosoma 106:226–232

Hahn M, Dambacher S, Dulev S et al (2013) Suv4-20h2 mediates chromatin compaction and is important for cohesin recruitment to heterochromatin. Genes Dev 27:859–872

Hasson D, Panchenko T, Salimian KJ et al (2013) The octamer is the major form of CENP-A nucleosomes at human centromeres. Nat Struct Mol Biol 20:687–695

Hayflick L (1965) The limited in vitro lifetime of human diploid cell strains. Exp Cell Res 37:614–636

Henikoff S, Henikoff JG (2012) "Point" centromeres of Saccharomyces harbor single centromere-specific nucleosomes. Genetics 190:1575–1577

Henikoff S, Ramachandran S, Krassovsky K et al (2014) The budding yeast centromere DNA element II wraps a stable Cse4 hemisome in either orientation in vivo. Elife 3:e01861

Heun P, Erhardt S, Blower MD et al (2006) Mislocalization of the *Drosophila* centromere-specific histone CID promotes formation of functional ectopic kinetochores. Dev Cell 10:303–315

Hoffmann S, Dumont M, Barra V et al (2016) CENP-A is dispensable for mitotic centromere function after initial centromere/kinetochore assembly. Cell Rep 17:2394–2404

Hoffmann S, Izquierdo HM, Gamba R et al (2020) A genetic memory initiates the epigenetic loop necessary to preserve centromere position. EMBO J 39:e105505

Hori T, Fukagawa T (2020) Artificial generation of centromeres and kinetochores to understand their structure and function. Exp Cell Res 389:111898

Hori T, Shang WH, Toyoda A et al (2014) Histone H4 Lys 20 monomethylation of the CENP-A nucleosome is essential for kinetochore assembly. Dev Cell 29:740–749

Hori T, Kagawa N, Toyoda A et al (2017) Constitutive centromere-associated network controls centromere drift in vertebrate cells. J Cell Biol 216:101–113

Huang Z, Xu Z, Bai H et al (2023) Evolutionary analysis of a complete chicken genome. Proc Natl Acad Sci U S A 120:e2216641120

Hudson DF, Fowler KJ, Earle E et al (1998) Centromere protein b null mice are mitotically and meiotically normal but have lower body and testis weights. J Cell Biol 141:309–319

Ikeno M, Grimes B, Okazaki T et al (1998) Construction of YAC-based mammalian artificial chromosomes. Nat Biotechnol 16:431–439

Jansen LE, Black BE, Foltz DR et al (2007) Propagation of centromeric chromatin requires exit from mitosis. J Cell Biol 176:795–805

Jarvis ED, Formenti G, Rhie A et al (2022) Semi-automated assembly of high-quality diploid human reference genomes. Nature 611:519–531

Kato H, Jiang J, Zhou BR et al (2013) A conserved mechanism for centromeric nucleosome recognition by centromere protein CENP-C. Science 340:1110–1113

Kitagawa R (2009) Key players in chromosome segregation in *Caenorhabditis elegans*. Front Biosci (Landmark Ed) 14:1529–1557

Klare K, Weir JR, Basilico F et al (2015) CENP-C is a blueprint for constitutive centromere-associated network assembly within human kinetochores. J Cell Biol 210:11–22

Kugou K, Hirai H, Masumoto H et al (2016) Formation of functional CENP-B boxes at diverse locations in repeat units of centromeric DNA in New World monkeys. Sci Rep 6:27833

Kuo Y-T, Câmara AS, Schubert V et al (2023) Holocentromeres can consist of merely a few megabase-sized satellite arrays. Nat Commun 14:3502

Kursel LE, Malik HS (2017) Recurrent gene duplication leads to diverse repertoires of centromeric histones in *Drosophila* species. Mol Biol Evol 34:1445–1462

Kwon MS, Hori T, Okada M et al (2007) CENP-C is involved in chromosome segregation, mitotic checkpoint function, and kinetochore assembly. Mol Biol Cell 18:2155–2168

Kyriacou E, Heun P (2023) Centromere structure and function: lessons from Drosophila. Genetics. https://doi.org/10.1093/genetics/iyad170

Lacoste N, Woolfe A, Tachiwana H et al (2014) Mislocalization of the centromeric histone variant CenH3/CENP-A in human cells depends on the chaperone DAXX. Mol Cell 53:631–644

Lam AL, Boivin CD, Bonney CF et al (2006) Human centromeric chromatin is a dynamic chromosomal domain that can spread over noncentromeric DNA. Proc Natl Acad Sci U S A 103:4186–4191

Lehnertz B, Ueda Y, Derijck AA et al (2003) Suv39h-mediated histone H3 lysine 9 methylation directs DNA methylation to major satellite repeats at pericentric heterochromatin. Curr Biol 13:1192–1200

Liu H, Qu Q, Warrington R et al (2015) Mitotic transcription installs Sgo1 at centromeres to coordinate chromosome segregation. Mol Cell 59:426–436

Logsdon GA, Eichler EE (2023) The dynamic structure and rapid evolution of human centromeric satellite DNA. Genes 14:92

Logsdon GA, Gambogi CW, Liskovykh MA et al (2019) Human artificial chromosomes that bypass centromeric DNA. Cell 178:624-639.e19

Logsdon GA, Vollger MR, Hsieh P et al (2021) The structure, function and evolution of a complete human chromosome 8. Nature 593:101–107

Logsdon GA, Rozanski AN, Ryabov F et al (2024) The variation and evolution of complete human centromeres. Nature 629:136–145

London N, Medina-Pritchard B, Spanos C et al (2023) Direct recruitment of Mis18 to interphase spindle pole bodies promotes CENP-A chromatin assembly. Curr Biol 33:4187-4201.e6

Mahlke MA, Lumerman L, Ly P et al (2023) Epigenetic centromere identity is precisely maintained through DNA replication but is uniquely specified among human cells. Life Sci Alliance. https://doi.org/10.26508/lsa.202201807

Mahlke MA, Lumerman L, Nath P et al (2025) Evolution and instability of human centromeres are accelerated by heterochromatin boundary loss and CENP-A overexpression. bioRxiv 636285. https://doi.org/10.1101/2025.02.03.636285

Maison C, Almouzni G (2004) HP1 and the dynamics of heterochromatin maintenance. Nat Rev Mol Cell Biol 5:296–305

Malik HS (2009) The centromere-drive hypothesis: a simple basis for centromere complexity. Prog Mol Subcell Biol 48:33–52

Malik HS, Henikoff S (2001) Adaptive evolution of Cid, a centromere-specific histone in *Drosophila*. Genetics 157:1293–1298

Malik HS, Henikoff S (2003) Phylogenomics of the nucleosome. Nat Struct Mol Biol 10:882–891

Marshall OJ, Chueh AC, Wong LH et al (2008) Neocentromeres: new insights into centromere structure, disease development, and karyotype evolution. Am J Hum Genet 82(2):261–282

Martins NM, Bergmann JH, Shono N et al (2016) Epigenetic engineering shows that a human centromere resists silencing mediated by H3K27me3/K9me3. Mol Biol Cell 27:177–196

Mateo L, González J (2014) Pogo-like transposases have been repeatedly domesticated into CENP-B-related proteins. Genome Biol Evol 6:2008–2016

Mckinley KL, Cheeseman IM (2014) Polo-like kinase 1 licenses CENP-A deposition at centromeres. Cell 158:397–411

Mckinley KL, Cheeseman IM (2016) The molecular basis for centromere identity and function. Nat Rev Mol Cell Biol 17:16–29

Miell MD, Fuller CJ, Guse A et al (2013) CENP-A confers a reduction in height on octameric nucleosomes. Nat Struct Mol Biol 20:763–765

Milks KJ, Moree B, Straight AF (2009) Dissection of CENP-C-directed centromere and kinetochore assembly. Mol Biol Cell 20:4246–4255

Mitra S, Srinivasan B, Jansen LET (2020) Stable inheritance of CENP-A chromatin: inner strength versus dynamic control. J Cell Biol. https://doi.org/10.1083/jcb.202005099

Moree B, Meyer CB, Fuller CJ et al (2011) CENP-C recruits M18BP1 to centromeres to promote CENP-A chromatin assembly. J Cell Biol 194:855–871

Murillo-Pineda M, Valente LP, Dumont M et al (2021) Induction of spontaneous human neocentromere formation

and long-term maturation. J Cell Biol. https://doi.org/10.1083/jcb.202007210
Muro Y, Masumoto H, Yoda K et al (1992) Centromere protein B assembles human centromeric alpha-satellite DNA at the 17-bp sequence, CENP-B box. J Cell Biol 116:585–596
Naughton C, Huidobro C, Catacchio CR et al (2022) Human centromere repositioning activates transcription and opens chromatin fibre structure. Nat Commun 13:5609
Nechemia-Arbely Y, Fachinetti D, Miga KH et al (2017) Human centromeric CENP-A chromatin is a homotypic, octameric nucleosome at all cell cycle points. J Cell Biol 216:607–621
Nechemia-Arbely Y, Miga KH, Shoshani O et al (2019) DNA replication acts as an error correction mechanism to maintain centromere identity by restricting CENP-A to centromeres. Nat Cell Biol 21:743–754
Nishimura K, Komiya M, Hori T et al (2019) 3D genomic architecture reveals that neocentromeres associate with heterochromatin regions. J Cell Biol 218:134–149
Novák B, Heldt FS, Tyson JJ (2018) Genome stability during cell proliferation: a systems analysis of the molecular mechanisms controlling progression through the eukaryotic cell cycle. Curr Opin Syst Biol. https://doi.org/10.1016/j.coisb.2018.02.004
Ohzeki J, Nakano M, Okada T et al (2002) CENP-B box is required for de novo centromere chromatin assembly on human alphoid DNA. J Cell Biol 159:765–775
Ohzeki J, Bergmann JH, Kouprina N et al (2012) Breaking the HAC barrier: histone H3K9 acetyl/methyl balance regulates CENP-A assembly. EMBO J 31:2391–2402
Ohzeki J, Shono N, Otake K et al (2016) KAT7/HBO1/MYST2 regulates CENP-A chromatin assembly by antagonizing Suv39h1-mediated centromere inactivation. Dev Cell 37:413–427
Otake K, Ohzeki JI, Shono N et al (2020) CENP-B creates alternative epigenetic chromatin states permissive for CENP-A or heterochromatin assembly. J Cell Sci. https://doi.org/10.1242/jcs.243303
Padeganeh A, Ryan J, Boisvert J et al (2013) Octameric CENP-A nucleosomes are present at human centromeres throughout the cell cycle. Curr Biol 23:764–769
Palmer DK, O'day K, Wener MH et al (1987) A 17-kD centromere protein (CENP-A) copurifies with nucleosome core particles and with histones. J Cell Biol 104:805–815
Parashara P, Medina-Pritchard B, Abad MA et al (2024) PLK1-mediated phosphorylation cascade activates Mis18 complex to ensure centromere inheritance. Science 385:1098–1104
Perea-Resa C, Bury L, Cheeseman IM et al (2020) Cohesin Removal Reprograms Gene Expression upon Mitotic Entry. Mol Cell 78:127-140.e7
Perez-Castro AV, Shamanski FL, Meneses JJ et al (1998) Centromeric protein B null mice are viable with no apparent abnormalities. Dev Biol 201:135–143
Pesenti ME, Raisch T, Conti D et al (2022) Structure of the human inner kinetochore CCAN complex and its significance for human centromere organization. Mol Cell 82:2113-2131.e8
Peters AH, Kubicek S, Mechtler K et al (2003) Partitioning and plasticity of repressive histone methylation states in mammalian chromatin. Mol Cell 12:1577–1589
Piras FM, Cappelletti E, Santagostino M et al (2022) Molecular dynamics and evolution of centromeres in the genus *Equus*. Int J Mol Sci. https://doi.org/10.3390/ijms23084183
Pironon N, Puechberty J, Roizès G (2010) Molecular and evolutionary characteristics of the fraction of human alpha satellite DNA associated with CENP-A at the centromeres of chromosomes 1, 5, 19, and 21. BMC Genomics 11:195
Przewloka MR, Venkei Z, Bolanos-Garcia VM et al (2011) CENP-C is a structural platform for kinetochore assembly. Curr Biol 21:399–405
Purgato S, Belloni E, Piras FM et al (2015) Centromere sliding on a mammalian chromosome. Chromosoma 124:277–287
Ren W, Fan H, Grimm SA et al (2021) DNMT1 reads heterochromatic H4K20me3 to reinforce LINE-1 DNA methylation. Nat Commun 12:2490
Renaud-Pageot C, Quivy JP, Lochhead M et al (2022) CENP-A regulation and cancer. Front Cell Dev Biol 10:907120
Rice JC, Briggs SD, Ueberheide B et al (2003) Histone methyltransferases direct different degrees of methylation to define distinct chromatin domains. Mol Cell 12:1591–1598
Ross JE, Woodlief KS, Sullivan BA (2016) Inheritance of the CENP-A chromatin domain is spatially and temporally constrained at human centromeres. Epigenetics Chromatin 9:20
Roulland Y, Ouararhni K, Naidenov M et al (2016) The flexible ends of CENP-A nucleosome are required for mitotic fidelity. Mol Cell 63:674–685
Rowley G, Jansen LET (2025) A brief historical perspective on cell cycle control of CENP-A assembly and inheritance. Chromosom Res 33:15
Sart DD, Cancilla MR, Earle E et al (1997) A functional neocentromere formed through activation of a latent human centromere and consisting of non-alpha-satellite DNA. Nat Genet 16:144–153
Scelfo A, Angrisani A, Grillo M et al (2024) Specialized replication mechanisms maintain genome stability at human centromeres. Mol Cell 84:1003-1020.e10
Sekulic N, Black BE (2012) Molecular underpinnings of centromere identity and maintenance. Trends Biochem Sci 37:220–229
Shang WH, Hori T, Toyoda A et al (2010) Chickens possess centromeres with both extended tandem repeats and short non-tandem-repetitive sequences. Genome Res 20:1219–1228
Shepelev VA, Alexandrov AA, Yurov YB et al (2009) The evolutionary origin of man can be traced in the layers of defunct ancestral alpha satellites flanking the active centromeres of human chromosomes. PLoS Genet 5:e1000641
Showman S, Talbert PB, Xu Y et al (2024) Protocol to measure centromeric array size changes using droplet digital PCR-based quantification of higher-order repeats. STAR Protoc 5:103218
Sidhwani P, Straight AF (2023) Epigenetic inheritance and boundary maintenance at human centromeres. Curr Opin Struct Biol 82:102694

Slee RB, Steiner CM, Herbert BS et al (2012) Cancer-associated alteration of pericentromeric heterochromatin may contribute to chromosome instability. Oncogene 31:3244–3253

Smoak EM, Stein P, Schultz RM et al (2016) Long-term retention of CENP-A nucleosomes in mammalian oocytes underpins transgenerational inheritance of centromere identity. Curr Biol 26:1110–1116

Song K, Gronemeyer B, Lu W et al (2002) Mutational analysis of the central centromere targeting domain of human centromere protein C, (CENP-C). Exp Cell Res 275:81–91

Sullivan BA, Karpen GH (2004) Centromeric chromatin exhibits a histone modification pattern that is distinct from both euchromatin and heterochromatin. Nat Struct Mol Biol 11:1076–1083

Sullivan LL, Sullivan BA (2020) Genomic and functional variation of human centromeres. Exp Cell Res 389:111896

Sullivan LL, Chew K, Sullivan BA (2017) α satellite DNA variation and function of the human centromere. Nucleus 8:331–339

Sun X, Wahlstrom J, Karpen G (1997) Molecular structure of a functional *Drosophila* centromere. Cell 91:1007–1019

Sundararajan K, Straight AF (2022) Centromere identity and the regulation of chromosome segregation. Front Cell Dev Biol 10:914249

Suntronpong A, Kugou K, Masumoto H et al (2016) CENP-B box, a nucleotide motif involved in centromere formation, occurs in a New World monkey. Biol Lett 12:20150817

Swartz SZ, Mckay LS, Su KC et al (2019) Quiescent Cells Actively Replenish CENP-A Nucleosomes to Maintain Centromere Identity and Proliferative Potential. Dev Cell 51:35-48.e7

Tachiwana H, Kagawa W, Shiga T et al (2011) Crystal structure of the human centromeric nucleosome containing CENP-A. Nature 476:232–235

Talbert PB, Masuelli R, Tyagi AP et al (2002) Centromeric localization and adaptive evolution of an Arabidopsis histone H3 variant. Plant Cell 14:1053–1066

Thakur J, Packiaraj J, Henikoff S (2021) Sequence, chromatin and evolution of satellite DNA. Int J Mol Sci. https://doi.org/10.3390/ijms22094309

Tian T, Chen L, Dou Z et al (2022) Structural insights into human CCAN complex assembled onto DNA. Cell Discov 8:90

Tomkiel J, Cooke CA, Saitoh H et al (1994) CENP-C is required for maintaining proper kinetochore size and for a timely transition to anaphase. J Cell Biol 125:531–545

Toyama BH, Arrojo EDR, Lev-Ram V et al (2019) Visualization of long-lived proteins reveals age mosaicism within nuclei of postmitotic cells. J Cell Biol 218:433–444

Vermaak D, Hayden HS, Henikoff S (2002) Centromere targeting element within the histone fold domain of Cid. Mol Cell Biol 22:7553–7561

Volpe E, Corda L, Tommaso ED et al (2023) The complete diploid reference genome of RPE-1 identifies human phased epigenetic landscapes. bioRxiv 565049. https://doi.org/10.1101/2023.11.01.565049

Voullaire LE, Slater HR, Petrovic V et al (1993) A functional marker centromere with no detectable alpha-satellite, satellite III, or CENP-B protein: activation of a latent centromere? Am J Hum Genet 52:1153–1163

Vukic M, Daxinger L (2019) DNA methylation in disease: immunodeficiency, centromeric instability, facial anomalies syndrome. Essays Biochem 63:773–783

Walkiewicz MP, Dimitriadis EK, Dalal Y (2014) CENP-A octamers do not confer a reduction in nucleosome height by AFM. Nat Struct Mol Biol 21:2–3

Warburton PE, Haaf T, Gosden J et al (1996) Characterization of a chromosome-specific chimpanzee alpha satellite subset: evolutionary relationship to subsets on human chromosomes. Genomics 33:220–228

Warburton PE, Dolled M, Mahmood R et al (2000) Molecular cytogenetic analysis of eight inversion duplications of human chromosome 13q that each contain a neocentromere. Am J Hum Genet 66:1794–1806

Willard HF, Waye JS (1987) Hierarchical order in chromosome-specific human alpha satellite DNA. Trends Genet 3:192–198

Williams JS, Hayashi T, Yanagida M et al (2009) Fission yeast Scm3 mediates stable assembly of Cnp1/CENP-A into centromeric chromatin. Mol Cell 33:287–298

Yang J, Li F (2017) Are all repeats created equal? Understanding DNA repeats at an individual level. Curr Genet 63:57–63

Yao J, Liu X, Sakuno T et al (2013) Plasticity and epigenetic inheritance of centromere-specific histone H3 (CENP-A)-containing nucleosome positioning in the fission yeast. J Biol Chem 288:19184–19196

Yatskevich S, Muir KW, Bellini D et al (2022) Structure of the human inner kinetochore bound to a centromeric CENP-A nucleosome. Science 376:844–852

Yoda K, Ando S, Morishita S et al (2000) Human centromere protein A (CENP-A) can replace histone H3 in nucleosome reconstitution in vitro. Proc Natl Acad Sci U S A 97:7266–7271

Zasadzinska E, Huang J, Bailey AO et al (2018) Inheritance of CENP-A Nucleosomes during DNA Replication Requires HJURP. Dev Cell 47(348–362):e7