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Satellite DNAs and human sex chromosome variation

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Abstract

Satellite DNAs are present on every chromosome in the cell and are typically enriched in repetitive, heterochromatic parts of the human genome. Sex chromosomes represent a unique genomic and epigenetic context. In this review, we first report what is known about satellite DNA biology on human X and Y chromosomes, including repeat content and organization, as well as satellite variation in typical euploid individuals. Then, we review sex chromosome aneuploidies that are among the most common types of aneuploidies in the general population, and are better tolerated than autosomal aneuploidies. This is demonstrated also by the fact that aging is associated with the loss of the X, and especially the Y chromosome. In addition, supernumerary sex chromosomes enable us to study general processes in a cell, such as analyzing heterochromatin dosage (i.e. additional Barr bodies and long heterochromatin arrays on Yq) and their downstream consequences. Finally, genomic and epigenetic organization and regulation of satellite DNA could influence chromosome stability and lead to aneuploidy. In this review, we argue that the complete annotation of satellite DNA on sex chromosomes in human, and especially in centromeric regions, will aid in explaining the prevalence and the consequences of sex chromosome aneuploidies.

Keywords

Satellite DNA; Centromere; Aneuploidy; X-inactivation; Sex chromosomes

1. Introduction

Large, multi-megabase sized arrays of tandem repeats, or satellite DNAs, are a common feature of eukaryotic genomes [1,2]. Although we do not yet fully understand their role in the cell, satellite DNA arrays are commonly associated with critical chromosomal structures that are important for cell viability, such as peri/centromeres, telomeres, and are found in close proximity to ribosomal DNA (rDNA) arrays [1,3]. These sites are enriched with

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densely, packaged constitutive heterochromatin, which are subject to specialized epigenetic regulation [4], replication timing [5], DNA repair [6,7], and transcriptional activity [8,9]. In contrast to our models that sequence conservation determines function [10,11], satellite DNAs in these regions are highly dynamic, turnover between closely related species, and present a substantial amount of sequence variation, often resulting in large, cytologically visible heteromorphisms [12,13]. It remains unclear how such large gains and losses of the underlying satellite repeats influence the local dosage of silencing factors, and/or contribute to epigenetic regulation and the stability of these regions. More broadly, we also do not fully understand how copy number variation of satellite-rich chromosomes, such as the loss and gain of the Y chromosome, alters the global heterochromatin dosage and influences epigenetic regulation in a cell [14,15]. We are only now, through the use of new genomic technologies, able to construct maps of these specialized regions to study their genomic organization, explore new models of sequence evolution, and study how genetic or epigenetic variation contribute to basic cellular processes [16–19].

Chromosomes X and Y, present a unique opportunity to study satellite DNA biology [20]. While long tracts of satellite DNAs are commonly observed on every chromosome in a genome, the lack of recombination between X and Y chromosomes (and between Z and W chromosomes in other species) has apparent consequences, typically leading to satellite accumulation on the Y/W [21]. For example, satellite DNAs are the predominant sequence on the human Yq-arm (distal-Yq heterochromatin ranges between 29% and 54% of the metaphase Y chromosome [22,23]), representing between one third and one half of the total DNA for the chromosome. The X chromosome, although less satellite-rich than the Y chromosome, undergoes chromosome-level epigenetic regulation during dosage compensation, which offers a unique context to study satellite DNA evolution and function [24,25]. In karyotypes of eutherian mammals where there are two or more X chromosomes, there is random inactivation of all but one [26]. The inactive X chromosome (Xi) is densely packaged, transcriptionally silent, and adopts an unusual 3D configuration in interphase, or Barr body [27,28]. Satellite DNAs on the Xi chromosome have unique chromatin organization and contribute to the long-range structural organization. For example, in humans and nonhuman primates, DXZ4, an X-linked macrosatellite, adopts opposite chromatin arrangements at the two alleles in response to X-chromosome inactivation, where the Xi is euchromatic and the Xa is heterochromatic [29]. Further, DXZ4 on Xi is positioned at a boundary that suppresses physical interactions between two large topologically associating domain (TAD)-depleted megadomains, and differentially associates with transcription factors (YY1 and CTCF) [30–32].

In addition to their unique genetic evolution and epigenetic regulation, chromosome-level variation in copy number (that is, the gain or loss of the entire X and Y chromosomes) are tolerated in cells (Table 1), as are large-scale rearrangements [33,34]. Sex chromosome aneuploidies (SCA), or karyotypes with an abnormal number of sex chromosomes, are prevalent in the general population (1:~500) [35], and are fairly benign. Affected individuals generally show reduced sexual development and fertility, but often have normal life spans, and many symptoms can be treated by hormone supplementation [33]. Remarkably, individuals can survive with as many as five sex chromosomes [36]. From the perspect of gene dosage, this tolerance most likely relates to both X inactivation and to the small

number of genes on the Y chromosome. However, from the perspective of chromosome biology and structure, such sex chromosome variations offer a unique opportunity to study the influence of heterochromatin dosage. In the extreme case of 49,XXXXY, this would mean that biological processes within the interphase nucleus are operating in the presence of three Xi Barr bodies and a large heterochromatic domain on Yq. Conversely, whereas cells are typically intolerant to the loss of chromosomes, the only viable human monosomy involving the X chromosome is a condition known as Turner's syndrome (45, X0), in which cells operate without an Xi or Yqh. Somatic monosomy is also common with sex chromosomes, as cells commonly lose the X or Y chromosome (Loss of X, LoX and Loss of Y, LoY) with age (Table 1). This tolerance of sex chromosome variation, both in early development and in somatic cells, presents a unique context to study the satellite DNAs genomic organization and the influence of sequence variation in cellular processes.

Since the first release of the human reference genome [37,38], satellite sequences (and large repeat-rich regions) on the sex chromosomes were incomplete, which limited studies of arrays' structure and function. However, with the recent advancements in long-read technologies [39,40] and assembly methods [17,41,42], we now have a more complete view of the satellite arrays across a complete, finished telomere-to-telomere, or "T2T" genome. Researchers are now able to confidently study base-level variation across satellite arrays [18], map CpG modifications [19], and explore chromatin structure [43,44]. Provided with this technological advance, we are now entering a new era where satellite arrays are available for detailed genetic and epigenetic study. These emerging maps in normal and abnormal karyotypes will broaden our understanding of the influence of centromeric satellite structure in chromosomal aneuploidies. Further, the ability to precisely map DNA-binding transcription factors, chromatin marks, and sites of transcription will allow us to explore how these sequences operate in normal cells, and how this regulation changes in the presence of sex chromosome variation.

Here, we provide a review of satellite DNA biology on human X and Y chromosomes. In doing so, we report what is known about the repeat content, array organization, and variation within normal genomes. Further, we explore how changes in genomic repeats and their epigenetic regulation could influence chromosome stability and lead to aneuploidy. Additionally, we present sex chromosome variation as a model for studying heterochromatin dosage in a cell and provide a perspective on the potential impact on cellular processes. We address the need to improve analyses of satellite DNAs in biomedical research and focus on how improving long-read based assays and T2T chromosome assemblies are an important step for addressing questions of structure and function.

2. Satellite DNAs on human X and Y chromosomes

Satellite arrays are commonly near-identical between diploid chromosomes, and therefore are a challenge to precisely phase sequence information to either the maternal or paternal haplotype. Human sex chromosomes, due to their nature of being haploid in male genomes, offer a unique opportunity to broaden sequence-based studies of satellite arrays on the X or Y chromosome. This technical advantage was critical to the release of complete assemblies of satellite arrays on X and Y chromosomes [45–47], as well as supported the

release of satellite assemblies in general in the first complete map of satellites in the XY pseudoautosomal regions (PAR1 and 2) in the T2T-CHM13 reference genome (where the assembly represents the duplicated paternal X chromosome and is effectively haploid) [17]. The emergence of accurate long-read data and assembly methods offers the possibility of the first comprehensive studies of satellite DNA organization across human sex chromosomes (Fig. 1), and broaden studies across high-resolution satellite assemblies [18].

2.1. PAR satellite DNAs

Satellite DNAs on the sex chromosomes are shared if located within the pseudoautosomal regions (PAR1,2), or the large sites of sequence homology between the X and Y at the ends of the chromosome (2.7 Mb and 320 kb, respectively) [48,49]. PARs are important to ensure the proper segregation of sex chromosomes during male meiosis [50,51]. Recombination is obligatory in PAR1, but not in PAR2 [52]. Deletion of PAR1, a 2.7 Mb region in the subtelomeric region of Xp [53], results in male sterility, and reduced recombination can lead to aneuploid sperm (0 and XY, thus resulting in X0 and XXY) [54–56]. Characterization of the PAR1 region in the T2T-CHM13 genome revealed at least two satellite arrays: *kalyke* (DXYS20, 61 bp tandem repeat, ~45 kb array) and *pasiphae* (55 bp tandem repeat, ~12 kb array), which map ~20 kbps from the X and Y short-arm telomeres [57,58] (Fig. 1). In the case of *kalyke*/DXYS20 the array length was determined to be highly polymorphic in the population [58]. Due to the requirement for a crossover in a very small portion of the chromosome, PAR1 is observed to have a 17-fold higher cross-over rate than the genome-wide average [56]. As a result, sequences in these regions are subject to extreme recombination and mutational processes [56]. Whereas the entire PAR1 region is prone to high recombination in male meiosis, this is not the case in female meiosis (where recombination in females is 10-fold less) [59]. However, female recombination rates are surprisingly similar to the rates seen in male meiosis in the subtelomeric region close to the most distal satellites (a 60-kb interval between DXYS20 and DXYS78 adjacent to the telomere) [59]. DNA methylation profiling over the two satellite arrays revealed that the two arrays are differentially regulated on the X chromosome, where *kalyke* had no detectable CpG methylation and *pasiphae* was observed to have high levels of methylation which is coincident with transcription (both satellites were observed to contain ~5 CpG sites per repeat unit) [57]. Future studies are needed to understand if satellites, or their genetic and epigenetic variability, in PAR1 influence the XY nondisjunction and meiotic recombination.

2.2. Satellite DNAs specific to the X chromosome

Outside of the PAR1,2, the largest satellite arrays on the X chromosome are found within the peri/centromeric regions [46]. The X centromeric satellite array (DXZ1) [60,61] is composed of an AT-rich primate-specific tandem repeat, known as alpha satellite [62], with a basic unit or ‘monomer’ length of ~171 bp [63,64]. The majority of alpha satellites on the X chromosome are organized into chromosome-specific ‘higher order repeats’ (HORs) [65], or a ~2 kb repeat unit composed of twelve monomers [60]. The DXZ1 array tends to be large and highly homogeneous (arrays can vary in length by a factor of 10 (range of 0.5–5 Mb), often containing thousands of nearly identical HOR units [47,61,66]. Assessment of array variation in the human population (sampling across male genomes in available 1000 genomes data) using shared centromere spanning linkage blocks (cenhaps), revealed

high centromere diversity in genomes sampled in Africa [18,67]. Further, the majority of individuals outside of Africa could be assigned to one of two large cenhaps groupings that differ in array length due to a large (greater than 100 kbps) internal duplication [18]. DXZ1 arrays can be further classified into HOR-haplotypes, or collections of HORs that share a set of sequence variants [68]. Phylogenetic dating of these haplotypes revealed symmetrical layering, with the evolutionarily younger repeats flanked by symmetric older HORs groups [18]. The oldest symmetric layers of alpha satellite on the X chromosome extend past the DXZ1 HOR array, and represent blocks of divergent, 'monomeric' blocks [61,69]. High-resolution studies of a panel of assembled DXZ1 arrays displayed that kinetochore proteins associate with only a subset of HOR units [18], and that the centromere location on the X chromosome varies genetically and epigenetically between different individuals [19]. On the human X chromosome, three different centromeric locations have been described recently [19], alluding to the possibility of such variability having consequences for the X chromosome segregation and aneuploidy.

Outside of alpha satellite, the pericentromeric region on Xp contains two satellite repeat classes: (1) HSat4, over 100 kbps of an ~35 bp [61, 70] repeat unit and enrichment of CATTC repeat, with interspersed Alu elements; and (2) gamma-satellite DNA (GSatX), a tandem array of ~40 kbps composed of 220-bp GC-rich repeats [70,71]. HSat4 is also represented in a very small array (~3 kb) in Xq27.2. The GSat array has a high proportion of mono-nucleosomes when compared to the other centromeric and pericentromeric regions on the X chromosome [19], supporting the organization of a euchromatic state. This is consistent with previous literature, where GSat is observed to have a dynamic chromatin structure characteristic of facultative heterochromatin with binding sites for Ikaros and CTCF [72,73]. The GSatX array is marked with elevated CpG methylation [19] in early development (CHM13) with a partial X inactivation. Similarly, increased CpG methylation is observed across the *sinpoe* satellite array (37 bp repeat unit, ~5 CpG sites) that marks the boundary of a 3.9 Mb block of Xq/Yp homologous region, *harpalyke* (54 bp, which overlaps gene annotation PWWP4 in an X-palindrome region [74], and the DXZ4 macrosatellite (localized at Xq23–24, consisting of 50–100 copies of a CpG-rich 3-kb monomer) known to be differentially regulated between Xa and Xi chromosomes [75].

DXZ4 is the longest macrosatellite repeat region outside of the peri/centromeric satellites. Previous studies have revealed that the DXZ4 array is packaged into distinct subtypes on the Xa (where DXZ4 is defined by constitutive heterochromatin, H3K9me3) and Xi chromosomes (where the array is packaged into euchromatin, H3K5me2 and H3k9Ac) [29]. Chromatin insulator protein, CTCF, and YY1 are bound to the Xi chromosome and act as a unidirectional insulator [76]. Further, DXZ4 (Dxz4 in the mouse genome) acts as a conserved boundary between two large TAD-depleted megadomains on Xi [77,78]. Overall, DXZ4 serves as an example of a satellite DNA array whose function (in terms of chromatin structure, transcription, DNA-bound complexes, and spatial organization in the nucleus) contributes to our understanding of Xi chromosome biology.

2.3. Satellite DNAs specific to the Y chromosome

The male-specifc region of the Y chromosome [79] is extremely repeat-rich, with satellite arrays interspersed within the peri/centromeric region, and with many smaller arrays interspersed with the X-transposed, X-degenerate, and ampliconic regions on both p-arm and q-arm. The Y centromere (DYZ3) has a 34-mer HOR (with a common repeat unit ~5.8 kb repeat unit) in human [45,80–82]. DYZ3 is the newest array in the genome and as such, is not positionally shared with great apes [45,83]. Intriguingly, it's also the only functional centromeric array in human that does not have a CENP-B box [84]. It has been suggested that the chromosomes without CENP-B box (including Y and neocentromere chromosomes) missegregate at elevated frequencies [85]. Indeed, the Y chromosome alpha satellite (DYZ3) does not efficiently form de-novo centromeres on human artificial chromosomes (HACs) [86,87], in contrast to the studied chromosomes 17 and 21 that were highly competent [87]. Similarly, mutated CENP-B boxes also did not readily form human HACs [88]. Therefore, studying the Y centromere is important to understand why it successfully assembles a functional centromere [89]. Several experimental systems have been set up to study missegregation systems for all but one human chromosome [90]. For example, the centromere on the Y chromosome (DYZ3) is typically much smaller (yet still observed in the range ~200 kb to ~2 Mb [47,92]) than other human centromeric arrays, and the inactivation of the Y centromere leads to a spectrum of both simple and complex genomic rearrangements [91].

Previous analysis [79] characterized three large heterochromatic sequence blocks on Yq: DYZ17 (GGAAT unit repeat; HSat3A3, [23]), DYZ18 (GGAAT unit repeat; organized in a larger nested repeat, 2.8 kb; Yq12), and DYZ19 (125 bp tandem repeat; Yq11.22). Yp-arm had been previously shown to contain beta-satellite sequence based on the experimental hybridization-based studies [93].

The large heterochromatic region on Yq is comprised of an interspersed mixture of DYZ1 (HSat3A6, 3.6 kb repeat unit) and DYZ2 (HSat1B, 2.4 kb repeat unit) [23,94,95]). Estimates of the length of the DYZ1 array had predicted that the satellites represented more than half the length of the Y chromosome [96], with evidence of variation in satellite abundance across ~400 individuals sampled geographically to represent diverse Y-haplogroups in the human populations [23,97]. These early estimates of DYZ1 array size variation revealed that the satellite could vary between individuals over an order of magnitude (7–98 Mb) with different distributions within each distinct Y haplogroup. Large heterochromatic variants have been scored cytogenetically (with heteromorphisms of Yq labeled as Yqh+ and Yqh−) and have been associated with both infertility (Yq−) and recurrent abortion (Yqh+) [98]. Further, partial Y-deleted mice exhibited heightened anxiety and depression, reduction in hippocampal neurogenesis, and altered expression of neurogenesis markers, compared to matched normals in stress tests [99]. Overall, improved genetic and epigenetic maps of Yqh (in human and other species) will help identify a complete catalog of sequences, and support new large-scale structural variation comparative studies and disease association.

3. Sex chromosome aneuploidy and defects in satellite array architecture

Sex chromosome aneuploidies (Turner syndrome 45, X0, trisomy X 47, XXX, Jacobs syndrome 47, XYY syndrome, Klinefelter syndrome 47, XXY) collectively constitute the most common class of chromosome abnormality in human livebirths [33]. Further, sex chromosomes are observed to undergo mosaic events more frequently than autosomes even in individuals born 46 XX or XY, which could have implications for understanding the underlying mechanisms of mosaic events and their possible contribution to risk for chronic diseases [100]. In contrast to autosomal aneuploidies which arise during maternal meiosis, the majority of SCAs are paternal in origin: 6% of 47, XXX; 50% of 47, XXY; 80% of 45, X0; and 100% of 47, XYY cases [101–104]. Typically, maternal age is an etiological factor linked to chromosomal trisomies, however there is no evidence for a significant maternal age effect on sex chromosome aneuploidies [105]. Rather, the incidence of XY, YY and XX disomic sperm was identified to be significantly elevated among older men [106]. Mechanistically, SCAs are thought to be largely due to nondisjunction which occurs during meiosis I, meiosis II, or during the early stages of postzygotic development, and varies based on the abnormal SCA condition [107]. The relationship between maternal age, recombination and non-disjunction appears to be highly chromosome specific (that is, the X and Y chromosomes have their own set of associated risk factors). Many different mechanisms are associated with sex chromosome non-disjunction (reviewed [107] and [33]), here we provide a focused review on the potential influence of peri/centromeric genetic and epigenetic architecture in SCA conditions.

Could genetic and epigenetic variation in satellite DNA arrays on the X and Y chromosome contribute to sex chromosome aneuploidies? Meiosis I errors involving sex chromosomes are often associated with aberrant recombination [108], such as the failure to recombine in PAR1 (as observed for paternally derived 47, XXY). Studies of the X chromosome revealed a novel type of meiotic non-disjunction (not observed in autosome trisomies) due to recombination at or very close to the centromere and the presence of double recombinations within relatively short distances [109]. Such centromere-proximal crossovers are involved in sex chromosome trisomies [109,110] and are thought to disrupt cohesion in the peri/centromeric satellite-enriched regions and interfere with proper kinetochore function [111]. Although the phenomenon of pericentric repression of meiotic recombination (“the centromere effect”) is well established in several species [112–114], the precise mechanism of this repression is still unknown. Broadly, epigenetic changes in pericentromeric heterochromatin may compromise proper chromosome alignment, attachment to mitotic spindle fibers, and the ability to separate chromosomes during division [115,116]. Proper DNA methylation and histone modification have an impact on the correct chromosomal segregation [115], where chromosome-level hypomethylation (e.g. X chromosome), may result in a delay in centromere separation and lead to aneuploidy. Further, proper regulation of centromere proteins is required for accurate chromosome segregation during both mitosis and meiosis [117,118]. Notably, Yq has been observed to act as a hotspot for neocentromere formation [119] (centromere location that lacks alpha satellite DNA), and displayed reduced centromere efficiency, resulting in higher aneuploidy rates [120]. Previous analyses have indicated that heterogeneity of human centromeric DNA, including genetic features within

the array such as the spacing of CENP-B boxes on the X centromeric satellites (or the lack of CENP-B boxes on the Y centromere), influences chromosome segregation fidelity during cell division [121,122]. It is unclear how epigenetic positioning or span of centromere proteins along the length of the array influences “centromere strength” [123,124] or dictates patterns of chromosome segregation that could lead to SCAs in early development.

In addition to epigenetic regulation of centromere, structural rearrangement (e.g. inversions and translocations) and sequence variation due to expansion and contraction of satellite repeats contribute to our understanding of sex chromosome aneuploidies. X chromosome structural abnormalities, in particular X isochromosomes, are common in Turner syndrome [125]. For example, in Turner syndrome, the missing paternal sex chromosome might not be an X, but rather an unstable isodicentric Y [126,127]. Additionally, a case report of 47,X,i(Xq),Y in a 24-year-old infertile male with Klinefelter’s syndrome revealed an isochromosome X with a single small centromere [128]. The genomic organization of centromeric satellite arrays on the X and Y chromosomes is highly variable, with dramatic differences in array lengths and repeat organization [18,47,67]. It remains unknown whether variation in array repeat organization or rearrangements within the arrays which are difficult to detect cytogenetically, contribute to SCAs. We are now entering an age in genetics and genomics where we can explore the contributions of genomic and epigenetic features in chromosome stability (Fig. 2).

In addition to germline SCAs, somatic mosaicism most frequently affects sex chromosomes in blood and the brain [129]. With increased sequence data in population health initiatives, such as the UK Biobank, loss of Y are predicted to be numerous (whereas 20% of the UK Biobank male population (N = 205,011) has detectable LOY [130]). Although many factors influence the sex chromosome monosomies as we age, it is notable that X chromosome loss has been associated with the disjunction of the centromere in metaphase instead of anaphase, or premature centromere division [131], which preferentially affects the inactive chromosome and causes its elimination from the cell by micronucleus formation. Further, association studies using the UK Biobank identified heterozygous genetic variations flanking the centromere X (DXZ1) that increase the odds of chromosome X loss in hematopoietic cells [132], even after controlling for the preferred loss of the inactive chromosome. Interestingly, X chromosome aneuploidies and premature centromere division of the X chromosome are recognized features of aged cell populations in the brains of individuals with Alzheimer’s disease [133, 134]. Further, the loss of epigenetic maintenance of centromere protein and array size of the Y centromere is expected to contribute to aneuploidy and the loss of the Y chromosome over time [90,135,136]. Given the technology that is newly available to us, the next step to understanding the functional consequences of satellite DNA on sex chromosomes is clear: to build both genetic and epigenetic comparative satellite maps. These will help identify new genetic and epigenetic variation to associate with SCAs both in development and in somatic cells.

4. Sex chromosome variation and shifts in heterochromatin dosage

What are the consequences of a copy number variation of X and Y chromosomes in a human cell? Is there a cellular response to the gain or loss of heterochromatin in a

cell; that is, does the gain or loss of Xi facultative heterochromatin, and/or the gain or loss of Yq-heterochromatin influence normal cellular processes? The satellite DNAs and heterochromatin on the X and Y chromosomes are compartmentalized into specialized nuclear domains in normal cells [137]. Could a disruption of general maintenance of heterochromatin in cells, including variation in Barr body, peri/centric satellites and blocks of Yqh constitutive heterochromatin, result in broad epigenetic instability and have the potential to impact nuclear structural interactions [24]? The tolerance of Xi and Yqh gains and loss demonstrate that cells can and do function with such shifts in total heterochromatin, but are there subtle changes in genome-wide regulation? Further, how can one begin to test the influence of the heterochromatin dosage versus the dosage of genes (either on the Y or Xi chromosome that escape inactivation) in the case of SCAs?

For every extra X chromosome, all but one chromosome will become inactivated and form a highly compacted entity termed Barr body (Xi) that is also transcriptionally inactive with the exception of a handful of escaping genes. Previous studies have focused on the opportunity for dosage imbalance through genes that escape inactivation, however, we have yet to fully explore the unusual regulation required to maintain two or more inactive chromosomes in the cell. In cells with three X chromosomes, the two barr bodies do not occupy the same exact location at the nuclear periphery but rather they remain separate, suggesting that the Xi does not occupy a specific location at the lamina [138]. Further, specialized regulation of the Barr body is expected throughout the cell cycle, as observed with the Xi contact with the nucleolus during the mid-to-late S-phase [139]. The Barr body is enriched with histone variant macroH2A, heterochromatin protein-1 (HP1), histone H1 and the high mobility group protein HMG-I/Y [140]. Notably, HMG-I was identified due to its association with centromeric satellite DNAs (α-satellite) of the green monkey, where it may play a role in nucleosome phasing [141]. Further, gel mobility shift assays show that HMG-I forms specific complexes with satellite DNA in the mouse genome, and may play a role in the modulation of chromatin structure and accessibility by antagonizing histone H1 binding to AT-rich scaffold/matrix-associated regions (SARs/MARs) [142,143]. Unique features of the DXZ4 macrosatellite regulation on Xa versus Xi were already identified [144], yet it is unclear if other peri/centromeric satellites have differential epigenetic profiles (Xa versus Xi) that could contribute to segregation errors and loss of Xi. Understanding how the cellular processes adjust to variation in Barr body structures could also provide new insight into cancers, where loss is more frequent in poorly differentiated (more aggressive) breast cancers [145–147].

For the Y chromosome, studies from *Drosophila* and possibly other mammals suggest that the Y chromosome also has the ability to introduce genome-wide changes in gene expression [14,15]. In line with this, recent human data in leukocytes with LOY had dysregulated expression of autosomal genes [130,148]. The DNA methylation on the Y chromosomes is accelerated with increasing age [149,150]. The suppression of this chromosome could potentially be associated with a reduced risk of death [149]. This is in contrast with a rather detrimental effect of a loss of this satellite-rich chromosome. Moreover, a global DNA hypomethylation would present consequences for the whole chromatin 3D structure, including nucleus size and spatial organization [151]. Hypomethylation of several repeats, namely LINE-1, satellite 2, and the alpha satellite, was

associated with both the nuclear size and aneuploidy in ovarian cancers [184]. Repeats, including Alu, LINE-1, and satellite repeats, become more active and open in aging cells [152]. Simultaneous disruption of chromatin organization and hypomethylation of repetitive DNA are found in cancer cells, potentially leading to transcription errors, centromere weakening, and chromosome breaks [151], emphasizing the role of satellite DNA in essential processes in cell biology.

Satellite DNAs (peri/centromeric satellites on both X and Y, Yq-heterochromatin) and Barr body (Xi) are spatially compartmentalized domains that are defined by silenced chromatin and are found in close proximity to the nuclear lamina and/or nucleous. These sequences vary at the sequence level (when comparing sequences between distinct satellite arrays), yet have common features in terms of being associated with heterochromatin in the interphase nucleus. Although once thought to be transcriptionally inert and with unknown cellular function, improved genomic technologies provide a more information-rich environment, wherein satellite DNAs are regulated by different transcription factors (and can be distinguished by Xi vs. Xa); we are only now beginning to categorize the transcription factors and protein complexes, RNA transcription, and spatial interactions – presenting a large, unexplored epigenomic landscape. Future efforts to study these regions may benefit from natural systems defined by SCAs to study the influence of gains and losses of total heterochromatin. In addition, these natural systems can be complemented by now-available systems of direct manipulation of satellite sequences via techniques of genome editing, including modification of their epigenome [153], and DSB induction [154].

5. Satellite variation: challenges and promises of long read methods

New tools and methods to determine satellite variation on the X and Y chromosomes, especially during critical times of early development and senescence, will be vital to study the association of genetic and epigenetic features of satellite DNAs and SCAs. Genomic technologies (such as HiFi reads or ultra-long Nanopore reads), as well as methodological and algorithmic advances, have now enabled the assembly and characterization of satellite DNAs. Experimentally, repetitive DNA can be hard to manipulate for several reasons, including the potential to form secondary structures [155] that lead to increased mutation rates. The methods based on the restriction enzyme digestion rely on the presence of a specific target sequence in the satellite DNA. Moreover, BACs or plasmids with extreme GC content can be hard to manipulate and might drop out from experiments. It should be noted that all sequencing technologies have inherent and technological challenges and biases (Fig. 3A). Inherent challenges are dictated by biology — long repeat units, long repeat arrays, and high sequence identity between repeats. Indeed, the (nearly) identical sequences of satellites in general cause tangles in typical genome assembly graphs [156] that cannot be resolved without long-read technology. Technological challenges include GC content (GC-correction methods might be needed, especially for older Illumina data) or unusual sequence composition, including homopolymer runs. All these challenges are expected to be resolved in the near future. For Nanopore sequencing, advances in base-calling improved the quality of newly reported sequences, especially repetitive ones such as satellite arrays. Moreover, training models for the base-calling perform better if they are targeted, either for specific species or for a specific sequence composition (e.g. telomeric repeats [157]). Such

sequence composition includes methylation detection and the detection of homopolymers. Estimating the precise length of homopolymer runs is challenging for all sequencing technologies. For this reason, lengths estimated from the reads tend to be shorter than the reference [158], despite the efforts to reflect the dwell times spent in pores for repetitive sequences [159]. However, newer nanopores with two sensors instead of one (dual reader head) are expected to improve the accuracy of these challenging sequences. Another class of advancements was achieved by the employment of neural networks and deep learning [160,161]. Still, base-calling of satellite DNA might require slower, more accurate modes of sequence identification or a special training dataset. In PacBio HiFi reads, repetitive arrays are deciphered using consensus information after reading the same template multiple times. For satellite arrays, internal alignment of sequences and consensus formation remain challenging. It should be noted that each of the above-mentioned sequencing technologies will process satellite DNA differently. While it is expected that they will generally agree on which satellites are abundant (or not), individual estimates might differ (Fig. 3B). When sequencing reads are mapped to the reference genomes, two subsets of reads remain precarious: 1) those that either map to multiple locations in the genome or that cannot be anchored with high confidence [162] and 2) unmapped reads. The first can be reduced with longer reads and the proportion of second with more complete reference genomes. Many of the challenging orphaned reads are repetitive and originate from satellite-rich chromosomes such as Y [163]. Resolution of segmental duplication in diploid genomes also aids in resolving SNVs and indels in their proximity [164–166]. The combination of multiple sequencing technologies (with distinct advantages and disadvantages) remains the most prudent strategy.

For the studies of aneuploidy, obtaining a precise centromeric representation is critical. Previously, centromeres in older human reference releases were replaced by models idealizing individual units and the transitions between them [47]. While these models captured the sequence and the abundance of such satellite DNA in general, they did not necessarily reflected a sequence from an actual living individual. Today, tools such as CentromereArchitect aim to infer the full architecture of centromeres (both monomers and high-order repeats) [167]. Such tools require novel algorithmic advances. Indeed, computationally, new strategies (e.g. unique *k-mer* anchoring mapping approach used in initial assemblies by the T2T consortium) and software are needed to resolve heterochromatic portions of the genome (two examples include Winnowmap mapper that is specifically tailored to align repetitive reads [168] and TandemTools that are used for polishing of extra-long tandem repeats [41])). This is especially relevant for sex chromosomes, as Y/W chromosomes are typically populated by transposable elements and long satellite arrays. A prominent example is the Y chromosome in human, for which as much as ~30 Mb (depending on an individual) of the sequence was unknown since its first assembly in 2003 [79], with the exception of an indication of typical satellite classes. Yet, complete loss of this Yq heterochromatin is consistent with life, albeit first described in an infertile patient [169]. The new T2T Y chromosome assembly is expected to reveal not only how the Y chromosome is populated by human satellites (including HSAT II,III), but also their strand orientation, methylation pattern, and positioning of individual satellite arrays with respect to each other, representing a significant milestone since the

early reports describing the Y-chromosome specific repeated DNA formed by a tandem array of pentanucleotides GGAAT [170] (see https://github.com/marbl/CHM13). In another example, the newly assembled Y chromosome in *Drosophila miranda* added 41.5 Mb of pericentromeric and telomeric regions and over 100 Mb of highly repetitive sequence on this sex chromosome [171].

Lastly, another technology with the emerging utility for satellite biology is the chromosome conformation capture or the Hi-C technology. It provides a detailed look at the organization of chromosomes in the nucleus and their corresponding chromosomal territories and interactions. Sex chromosomes represent a special case in genome folding: X chromosome due to X chromosome inactivation, and Y due to the massive accumulation of satellites. Both active and inactive chromosomes occupy distinct chromosomal territories. In human, repetitive chromosomes tend to be located near the nuclear lamina, while gene-rich chromosomes remain in the nucleus [172]. Indeed, repetitive elements, including satellites, are believed to play role in 3D genomic folding and influence the formation of active and inactive compartments with a direct impact on gene expression [173]. The Y chromosome in human was found to participate in more inter-chromosomal interactions than expected based on its small size [174,175]. Moreover, most of the genome-wide contacts were formed between short chromosomes 19, 20, 21, and 22 [174], with chromosomes 21 and 22 fairly repetitive. This observation held even when the sequencing reads were required to map uniquely, perhaps suggesting the flexibility of the Y chromosome to participate in the genome-wide chromatin interactions [174]. In closing, an orthogonal use of the available technologies will provide a detailed look at the sequence composition, variation, chromosomal localization, and the interaction partners of the satellite DNA.

6. Summary and conclusions

The new complete sequences of sex chromosomes open up the possibility to study the centromeres of the human chromosomes with frequent aneuploidies. Moreover, in male individuals, the differentiation between X and Y provides a scenario where these chromosomes can be methodologically easier to distinguish than the rest of the diploid genome. Aside from aneuploidies in early embryonic development, many individuals experience the loss of X or Y chromosome throughout the course of their lives and aging, with demonstrable negative effects for the Y. While X and Y are special in some regards (reduced recombination in meiosis, potential epialleles on the X-chromosome, lack of CENP-B box on the Y) both biological and technical lessons learned from their comparative analysis across human populations extend to the rest of the genome and diploid chromosomes and are relevant for the aneuploidy in aging cells and autosomal aneuploidies during early embryonic development.

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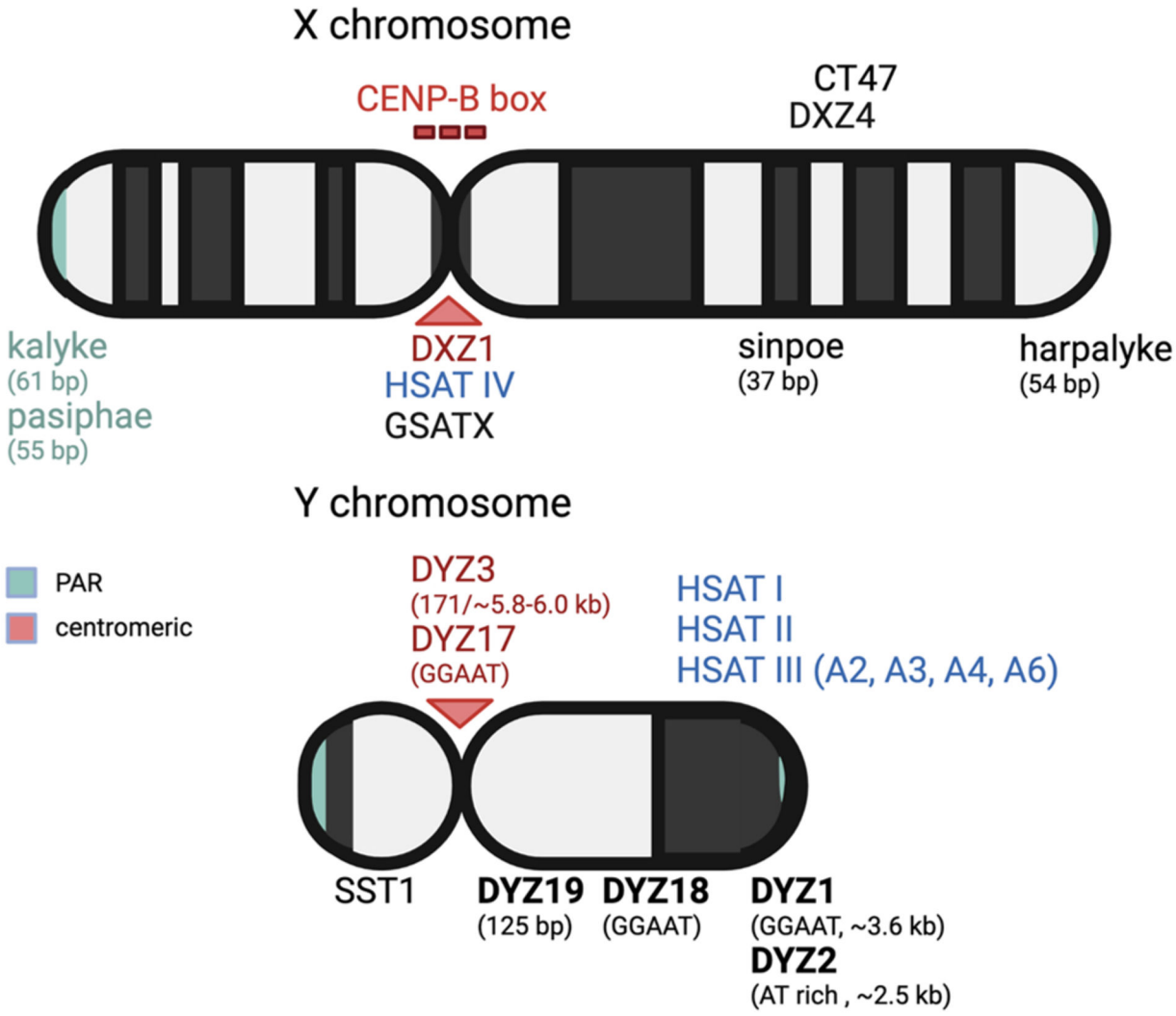

Fig. 1.

Repeats that involve satellite DNA on human sex chromosomes. Satellites on the human X and Y chromosomes are plotted along these chromosomes. The locations of many satellites discussed in Section 2 are depicted, most prominently DXZ and DYZ arrays, as well as HSAT. The human Y chromosome has the shortest centromere in the human genome and no CENP-B box. Figure created with BioRender.com.

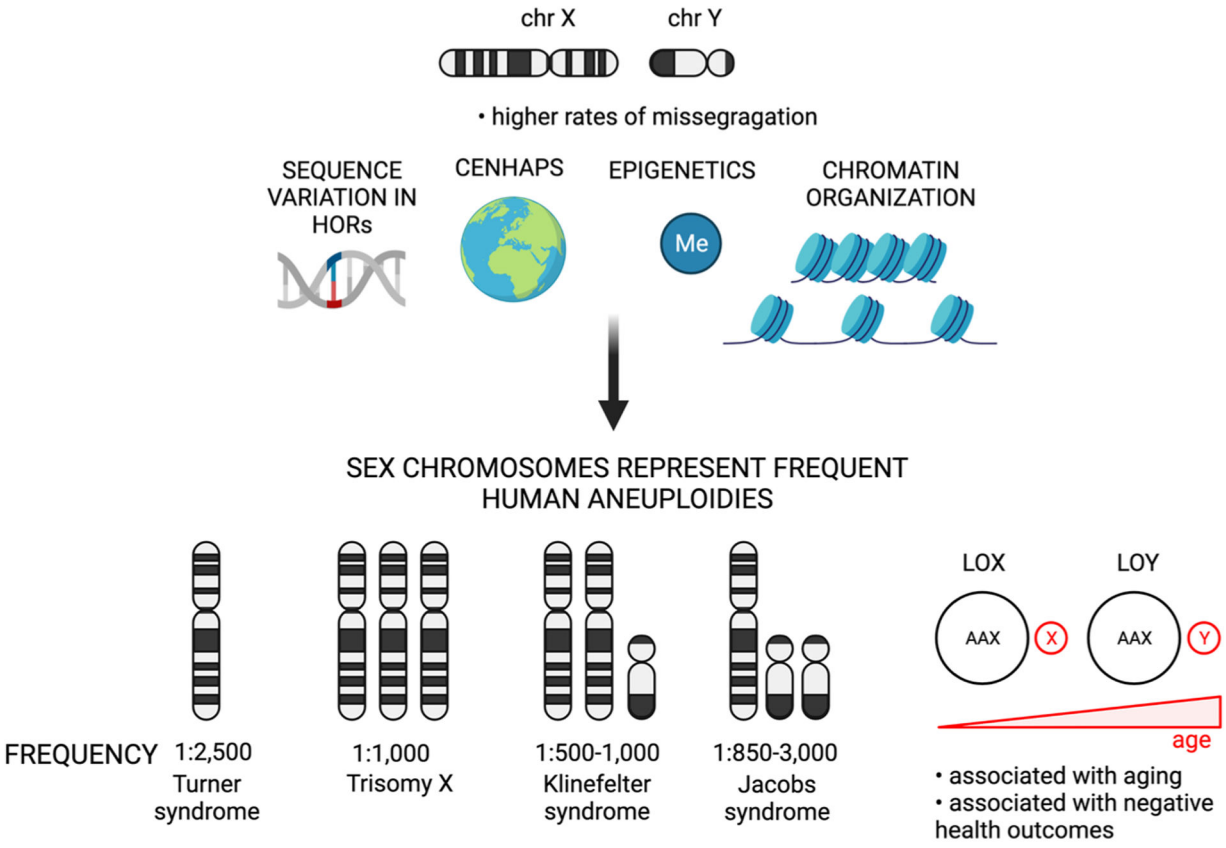

Fig. 2.

Factors influencing the variation in satellite arrays and the possible consequences of such variability. The specific underlying sequence, such as individual variants of HORs, cenhaps, epigenetics, and the chromatin organization are all possible contributors to the variation in satellites. This might in turn have consequences for human aneuploidies, and especially sex chromosome aneuploidies. These include those that arise in early development, such as Turner syndrome, Trisomy X, Klinefelter syndrome, or Jacobs syndrome, and those that arise later in life and are linked to aging, such as loss of X and Y chromosomes. Figure created with BioRender.com.

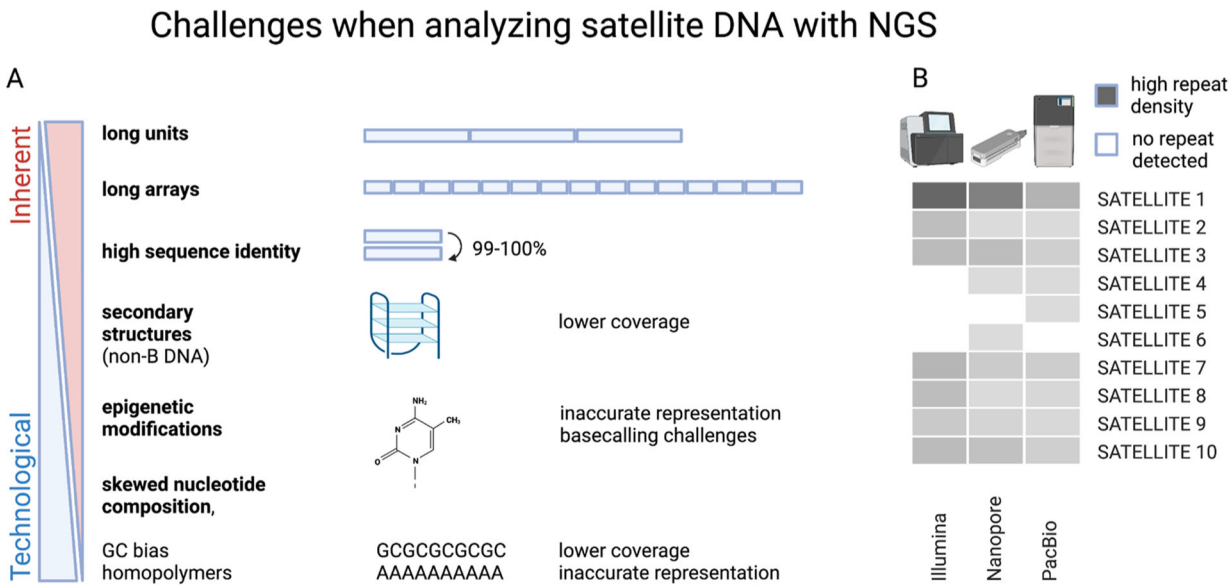

Fig. 3.

Challenges when analyzing satellite DNA with NGS. (A) The challenges are either inherent (e.g. long unit sizes of repeats or repeat arrays spanning hundreds of kbs) or technological (e.g. algorithms that inadequately assess homopolymer lengths). (B) Repeats and their abundance as estimated from the three technologies: Illumina, Nanopore, PacBio, for a single male individual (HG002). These differences depend on the technology used, thus revealing underlying biases. For example, estimates of AATGG were higher for Illumina, whereas some other repeats were predominantly captured by Nanopore or PacBio technology [183]. Repeats number 1–3, 7–9, and 17–20 were reprinted from the Supplementary Note 4 in [183]. Figure created with BioRender.com.

Table 1

Sex chromosome aneuploidies and their origin.

	Karyotype	Male meiosis I & II		Female Meiosis I & II		Heterochromatin dosage	Age dependency	Prevalence	Origin
Turner syndrome	X0	predominant[a]		yes[a]		−Xi	no[b]	1:2500[c]	Development[d]
Trisomy X	XXX	no	yes	predominant[e]	yes[e]	+Xi	possibly maternal[f]	1:1000[c]	
Klinefelter syndrome	XXY	yes	no	yes		+Yq	possibly maternal and paternal[g]	1:500–1000[c]	
Jacobs syndrome	XYY	no	yes	no		−Xi+2xYq	no[h]	1:850–3000[c]	
LOY	X	NA				−Yq	yes[i]	27.2%[i]	Somatic
LOX	X or Y					X(i)	yes[j]	1.37%[j]	

[a] [176]

[b] [176,177]

[c] https://www.uptodate.com/contents/sex-chromosome-abnormalities

[d] All the heterochromatin dosage models are derived from the XX karyotype

[e] the estimated split is 58–63% for meiosis I and 16–17.4% for meiosis II [178]

[f] [178]

[g] [179] and [185]

[h] [180]

[i] Strong stratification by age with the frequency of LOY in circulating blood cells of 21%, 32%, 44% and 51% in men aged 70–74, 75–79, 80–84 and 85 years or older [181]

[j] Strong age dependency with the LOX frequency of 0.07% at the age younger than 16 years to 7.3% in women over 65 years of age [182]