Seminars in Cell & Developmental Biology 90 (2019) 62–77

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Understanding the 3D genome: Emerging impacts on human disease

Anton Krumm[a,**], Zhijun Duan[b,c,*]

[a] Department of Microbiology, University of Washington, USA
[b] Institute for Stem Cell and Regenerative Medicine, University of Washington, USA
[c] Division of Hematology, Department of Medicine, University of Washington, USA

ARTICLE INFO

Article history:
Received 19 March 2018
Accepted 3 July 2018
Available online 12 July 2018

Keywords:
Chromatin
Chromosome
Hi-C
Three-dimensional (3D) genome architecture
3D genome organizer
Chromatin structural protein
Topologically
Associated domain (TAD)
Disease

ABSTRACT

Recent burst of new technologies that allow for quantitatively delineating chromatin structure has greatly expanded our understanding of how the genome is organized in the three-dimensional (3D) space of the nucleus. It is now clear that the hierarchical organization of the eukaryotic genome critically impacts nuclear activities such as transcription, replication, as well as cellular and developmental events such as cell cycle, cell fate decision and embryonic development. In this review, we discuss new insights into how the structural features of the 3D genome hierarchy are established and maintained, how this hierarchy undergoes dynamic rearrangement during normal development and how its perturbation will lead to human disease, highlighting the accumulating evidence that links the diverse 3D genome architecture components to a multitude of human diseases and the emerging mechanisms by which 3D genome derangement causes disease phenotypes.

© 2018 Elsevier Ltd. All rights reserved.

Contents

1. Introduction 62
2. Features of the 3D genome organization in the eukaryotic nucleus 63
   2.1. Hierarchical organization of eukaryotic genomes in the nucleus 63
   2.2. Dynamics of the 3D genome during cellular and developmental events 65
   2.3. Roles of genome organizers in the formation and maintenance of the 3D genome 65
   2.4. The functional relevance of the 3D genome 66
3. Biological relevance of the 3D genome organization for human disease 66
   3.1. Implications of the 3D genome hierarchy for human disease 66
   3.2. Emerging disease mechanisms of 3D genome disruption 67
4. Genome architectural proteins and human diseases 70
5. Conclusions and future prospects 71
Competing financial interests 72
Acknowledgements 72
References 72

1. Introduction

The genome, the major hereditary materials of the cell, resides in the nucleus, which serves as the cell's information processing center and controls the various activities of the cell, such as proliferation, homeostasis and division. Early biochemical and microscopy studies have revealed that the nucleus is not geometrically homogenous but rather highly compartmentalized, with the various nuclear activities organized into discrete, functionally-specialized sub-nuclear structures, called nuclear bodies. For example, the nucleolus, which assembles around the rDNA genes, is the largest nuclear body and the primary site of rRNA biogenesis

* Corresponding author at: Institute for Stem Cell and Regenerative Medicine, University of Washington, USA.
** Corresponding author.
E-mail addresses: akrumm@uw.edu (A. Krumm), zjduan@uw.edu (Z. Duan).

https://doi.org/10.1016/j.semcdb.2018.07.004
1084-9521/© 2018 Elsevier Ltd. All rights reserved.

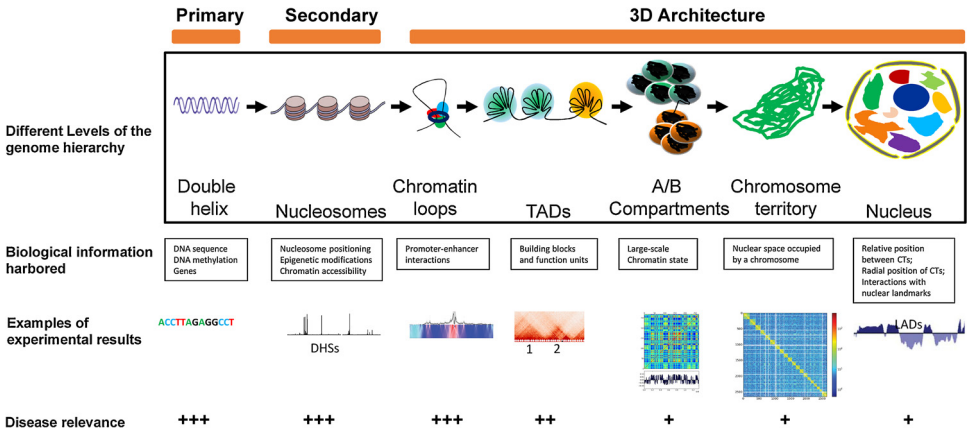

Fig. 1. Hierarchical organization of the genome.
Genomic DNA in the eukaryotic nucleus possesses multiple levels of organization. The primary structure of the genome here refers to the linear genomic DNA sequences, which harbors the information of DNA modification (e.g., DNA methylation) and genomic distribution of the various types of genes. The secondary structure refers to the nucleosome organization of chromatin. Nucleosomes are considered as the basic unit of chromatin and elicit about 7-fold linear compaction of genomic DNA. This level of structure provides a framework for further assembling the genomic DNA into the chromatin fiber and higher-order structures, as well as a diversity of regulatory mechanisms for genome functions, such as nucleosome positioning, histone modifications and chromatin accessibility. The 3D genome architecture, i.e., the higher-order organization of the genome in the 3D space of the nucleus, comprises multiple levels of topological features, including chromatin loops, sub-megabase-scale self-interacting domains (e.g., TADs), megabase-scale A/B compartments and chromosome territories. Chromatin looping is the fundamental mechanism for building the 3D architecture of chromatin. Promoter-enhancer loops provide a key mechanism for long-range gene regulation. Recent studies have suggested that TADs might be the basic structural and functional units of chromatin. Studies indicate that promoter-enhancer interactions occur much more frequently within TAD than between TADs. Each chromatin fiber is demarcated into transcriptionally active A or inactive B compartments that are defined by large-scale chromatin states. In mammalian cells, each interphase chromosome occupies a distinct nuclear space to form chromosome territories (CT). The radial position of a CT, the relative position between CTs, and the interactions between a CT and the nuclear landmarks are all of functional relevance. The visualization of the results of example assays for each level of structure is shown. The disease relevance of each level of structure is also indicated.

and assembly of ribosomes [1]. Other types of nuclear bodies include Cajal body, Clastosome, Nuclear speckle, Paraspeckle, Nuclear gems, PML body, Histone locus body, and Polycomb body (reviewed in [2,3]). Moreover, biochemical studies have demonstrated that the two most fundamental nuclear activities, transcription and replication, are also organized in discrete nuclear foci in mammalian nuclei, termed transcription and replication factories, respectively [4,5]. Meanwhile, the nuclear subcompartments near the nucleoli and nuclear envelope (except the nuclear pores) provide a transcriptionally silent microenvironment for heterochromatic regions to reside, which is critical for maintaining the genome integrity.

For the nearly two meters of genomic DNA to fit into the "tiny" nucleus with a diameter at the scale of several micrometers and to function properly, the genome in every human cell, like all the other eukaryotic genomes, is folded into string-like compact structures, chromatin fibers, whose other essential components are proteins and RNAs [6]. Thus, in addition to the primary (i.e., the DNA double helix) and secondary (i.e., the nucleosomes) structures, the genomic DNA in the nuclear space of eukaryotic cells also possesses a higher-order 3D organization (Fig. 1). While it is well established how DNA wraps into nucleosomes, both the underlying mechanisms instructing nucleosomes to fold into chromatin and further to adopt higher-order structures and the molecular details of this process have long remained elusive and debatable. It is only until the past few years, with the significant advance in microscopy-based DNA imaging technologies and the development of high throughput genomic tools for quantitatively measuring chromatin interactions, enormous new insights into chromatin folding and 3D organization have been obtained. For example, recent microscopy studies suggested that chromatin fibers are flexible and disordered chains assembled from both nucleosomes and nucleosome-depleted DNA [7,8], with a diameter ranging from 5 nm to 24 nm in human cells [8]. It is clear that, despite with some intrinsic stochastic properties, the 3D genome organization is nonrandom and of high functional relevance. It also appears that the spatial arrangement of the genome can be adapted to accomplishing cellular functions other than the genome function *per se*, such as cell migration, mechanotransduction and vision in nocturnal animals (reviewed in [9]).

In this review, we briefly introduce our current understanding of the chromatin folding and the spatial genome organization gained through recent technological developments. We then review emerging evidence linking the disruption of the different components and layers of the 3D genome organization to a range of human diseases, highlighting some of the important questions remaining to be addressed and the potential directions for new technology development in this fast advancing field.

2. Features of the 3D genome organization in the eukaryotic nucleus

Over the past decade, advances in both microscopic and DNA sequencing-based technologies, especially the development and application of the chromosome conformation capture (3C)-derived high throughput genomic methods for mapping chromatin interactions (Box 1), have yielded remarkable new insights into the chromatin folding principles, the organizational features and the structure-function relationship of the 3D genome [10–24].

2.1. Hierarchical organization of eukaryotic genomes in the nucleus

High-throughput 3C methods (e.g., Hi-C) have revealed that eukaryotic genomes are nonrandomly organized into a nested hierarchy in the nucleus [25–27]. This hierarchy consists of at least four distinct levels: whole chromosome territories (CTs) [28], large-scale active and repressive compartments (A/B compartments) [29], domains, e.g. topologically associated (TAD) [30,31], lamina associated (LAD) [32,33] or nucleolus associate (NAD) [34,35], and chromatin loops [36]. Early microscopy studies have revealed that individual chromosomes in mammalian cells occupy distinct

Box 1: Biochemical methods for mapping chromatin interactions.

Broadly, approaches for dissecting the 3D genome organization can be catalogued into two major groups, microscopy-based imaging technologies (summarized in [197]) and biochemical tools. Based on the biological origin of the chromatin contacts being surveyed, the latter can further be classified into three subgroups, including those for probing physical contacts between genomic loci and nuclear landmarks, those for detecting chromatin-RNA interactions, and those for mapping chromatin-chromatin interactions. Detecting physical contacts between chromatin and the nuclear landmarks such as the nuclear envelope and nucleolus can tell where specific genomic loci are localized within the nucleus. For example, chromatin immunoprecipitation (ChIP) and sedimentation fractionation have been used to map NADs, and DNA adenine methyltransferase identification (DamID) and ChiP has been widely used to map LADs. Increasing evidence suggests that RNAs, in particular noncoding RNAs (ncRNAs), play important roles in the 3D genome organization. Currently, there are at least five different methods for identifying chromatin-associated RNAs, including individual RNA-specific methods such as chromatin isolation by RNA purification (ChIRP) [106], capture hybridization analysis of RNA targets (CHART) [107] and RNA antisense purification (RAP) [108], and the recently developed methods for mapping all the chromatin-RNA interactions on the whole-genome scale, such as mapping RNA genome interactions (MARGI) [109] and GRID-seq [110].

The past decade has witnessed a burst of new technologies for probing chromatin-chromatin interactions (see the Table in this box). By measuring the relative spatial proximity between individual genomic loci, this group of methods are able to provide insight into the principles of chromatin folding, and into the relative positioning of individual chromosomes in relationship to one another. The vast majority of these methods belong to the chromosome conformation capture (3C) family, which measure spatial proximity between individual genomic loci by performing proximity ligation. However, it is noteworthy that there are now a few methods in this group that employ fundamentally different schemas other than proximity ligation. For example, RNA-TRAP (RNA tagging and recovery of associated proteins), designed to detect chromatin regions that are associated with a transcriptionally active gene of interest, combines RNA FISH and ChIP [200]. Genome architecture mapping (GAM) is a ligation- and hybridization-free method, which employs cryosectioning and microdissection to isolate thin, randomly oriented slices of individual nuclei, and then sequencing of these sections [201]. The more recently developed two methods, split-pool recognition of interactions by tag extension (SPRITE) [202] and multi-ChIA [203], also move away from proximity ligation. SPRITE enables genome-wide detection of higher-order DNA interactions by barcoding interacting molecules within an individual chromatin complex using a split-pool strategy [202], whereas multi-ChIA uses the microfluidics device of the 10x Genomics' Chromium instrument to barcode each chromatin complex in a Gel bead in Emulsion (GEM) droplet [203]. It is also noteworthy that the CRISPR/CAS9 genome editing system has now been applied to map locus-specific chromatin interactions in a new method, called CAPTURE (CRISPR affinity purification in situ of regulatory elements) [204].

Table Methods for mapping DNA-DNA interactions

Scale	Method	Underlying concept	Characteristics	Refs (PMID)
Locus-specific	3C	Proximity ligation	The founding method of the 3C family	[205]
	RNA-TRAP	Proximity biotinylation	Method that combines RNA FISH with ChIP to probe chromatin interactions associated with a transcriptionally active gene of interest	[200]
	CAPTURE	Proximity ligation & biotinylation	Method that enables biotinylated dCas9-mediated in situ capture of locus-specific chromatin interactions	[204]
	4C	Proximity ligation	Method for detecting chromatin interactions between a specific locus and the rest of the genome	[206,207]
	e4C	Proximity ligation	4C variant with improved sensitivity by replacing inverse PCR with primer extension	[208]
	Umi-4C	Proximity ligation	4C variant with improved sensitivity and specificity by using unique molecular identifiers (UMIs) to derive high-complexity quantitative chromatin contact profiles	[209]
	ACT	Proximity ligation	4C variant	[210]
	5C	Proximity ligation	Method for probing chromatin interactions between multiple selected loci	[211]
	Capture-3C	Proximity ligation	High-throughput version of 4C that combines 3C with the DNA capture technologies	[212]
	Capture Hi-C	Proximity ligation	High-throughput version of 4C that combines Hi-C with the DNA capture technologies	[213]
	Targeted DNase Hi-C	Proximity ligation	Method that combines DNase Hi-C with the DNA capture technologies	[123]
Protein-centered	ChIA-PET	Proximity ligation	Method that combines ChIP with proximity ligation to detect genome-wide chromatin interactions mediated by a specific protein	[214]
	HiChIP	Proximity ligation	A method that combines 3C with ChIP-seq to detect genome-wide chromatin interactions mediated by a specific protein	[215]
	PLAC-seq	Proximity ligation	Similar to HiChIP	[216]
Whole-genome	Hi-C	Proximity ligation	A method for mapping all the chromatin interactions in a cell population; proximity ligation is carried out in a large volume	[29]
	In situ Hi-C	Proximity ligation	In situ version of Hi-C that performs chromatin digestion and proximity ligation in intact nuclei	[36]
	TCC	Proximity ligation	Similar to Hi-C, except that proximity ligation is carried out on a solid phase	[217]
	DNase Hi-C	Proximity ligation	Hi-C variant that uses DNase I to fragment chromatin	[123]
	In situ DNase Hi-C	Proximity ligation	In situ version of DNase Hi-C that performs chromatin digestion and proximity ligation in intact nuclei	[46]
	Micro-C	Proximity ligation	Hi-C variant that uses micrococcal nuclease to digest chromatin	[218]
	C-walks	Proximity ligation	Hi-C variant that captures pairwise and multi-way chromosomal conformations	[219]
	BL-Hi-C	Proximity ligation	In situ Hi-C variant that uses HaeIII to digest chromatin	[220]
	GAM	Co-localization	Method for mapping 3D genome architecture by sequencing genomic DNA from a large collection of ultrathin nuclear sections	[201]
	SPRITE	Co-association	Method for mapping chromatin interactions by using combinatorial barcoding	[202]
	Multi-ChIA	Co-localization	Method using a microfluidics device enables mapping multiplex chromatin interactions with single-molecule precision; By coupling with chromatin immunoprecipitation, also allows for mapping chromatin interactions mediated by a protein of interest	[203]
Single-cell	sc Hi-C	Proximity ligation	Hi-C variant that enables mapping chromatin interactions within single cells	[44,198]
	snHi-C	Proximity ligation	3C variant that enables mapping chromatin interactions within single cells	[65]
	sciHi-C	Proximity ligation	Method for mapping chromatin interactions in large numbers of single cells by using combinatorial barcoding	[199]

nuclear space (CTs), with only a limited degree of intermingling between CTs [28,37], which was later recaptured by Hi-C studies [29]. Individual CTs show preferences for nuclear positioning in mammalian cells, which may correlate with genomic properties. In general, large and gene-poor chromosomes tend to be located near the nuclear periphery, whereas small and gene-rich chromosomes group together near the center of the nucleus [28,38]. Hi-C studies have also revealed that within individual CTs, chromosomes are partitioned into large compartments at the multi-Mb scale, containing either the active and open (A compartments) or inactive and closed chromatin (B compartments) [29]. The open A compartments consist of high GC-content regions, are gene rich, and are generally highly transcribed. In contrast, B compartments are gene-poor, and less transcriptionally active [29]. However, it remains to be established the extent to which A/B compartments are correlated with the classic, cytogenetically defined euchromatin/heterochromatin. A/B compartments are comprised of TADs, which are considered the basic units of chromosome and genome organization [14,25,26]. TADs are self-interacting domains and, seem to be conserved among cell types, tissues, and species; however, the extent of this conservation remains unclear [30,31]. Chromatin looping is an intrinsic property of chromatin fiber and the fundamental mechanism for building the 3D genome hierarchy [16].

2.2. Dynamics of the 3D genome during cellular and developmental events

Although the 3D genome organization is robust overall, it is characterized by dynamics and can undergo marked changes in the context of different biological conditions. Both the intrinsic randomness, which is attributed to the biophysical properties of chromatin fiber and other related macromolecules in the nucleus, and the constant influence of the DNA-based nuclear activities contribute to the dynamic nature of the 3D genome architecture [16]. The intrinsic randomness likely leads to the cell-to-cell variability of the 3D genome in individual cells. For example, recent super-resolution microscopy and single-cell Hi-C studies have noticed that the formation and the epigenetic states of TADs and chromatin loops within a TAD are highly heterogeneous between individual single cells [39–41]. The nuclear activity-based dynamics of the 3D genome is multifaceted. First, the 3D genome undergoes continuous changes during the cell cycle. It has long been observed in microscopy studies that chromosomes in proliferating mammalian cells are highly condensed in the mitotic phase to facilitate chromosome segregation, but decondensed in interphase to accommodate the diverse nuclear processes. Recent Hi-C studies have revealed that mitotic chromosomes fold into a homogenous linear instead of hierarchy structure that is locus- and cell type-independent, consistent with arrays of consecutive chromatin loops [42,43]. More recent single-cell Hi-C studies have further revealed that the different levels of the 3D genome organization, A/B compartments, TADs and long-range loops, are governed by distinct cell-cycle dynamics and all undergo continued changes throughout the cell cycle [44]. However, it is noteworthy that similar chromatin domains have been observed in both interphase and mitotic chromosomes by super-resolution live-cell imaging [45]. Second, the 3D chromatin structure can be allelic-specific. The 3D conformation of the inactive and active X chromosomes in both mouse and human female cells is strikingly different, with the inactive X chromosome exhibiting a unique bipartite structure [46–48]. Third, the 3D genome architecture can exhibit distinct features in different tissue/cell types. For example, tight packaging of the sperm genome leads to more long-range chromatin contacts compared to fibroblasts [49,50], whereas, the 3D genome in mature metaphase II oocytes is similar to that of mitotic cells, which lacks detectable TADs and A/B compartments [50,51]. It has also been revealed that, compared to proliferating cells, different stages of senescent cells show changes in the frequency of chromatin contacts [52,53]. Furthermore, comparison of chromatin contact maps in 21 primary human tissues and cell types has uncovered a class of highly tissue-specific genome organizational features termed FIREs, which are local interaction hotspots and correspond to active enhancers [54]. Fourth, global and local rearrangements of the 3D genome occur during cell differentiation, reprogramming, and tissue development. A/B compartment switching, changes in the number and size of TADs, switching of the epigenetic and transcriptional states of TADs, changes in the metaTADs organization, rearrangements of the repressive domains including LADs, NADs and polycomb domains, and rewiring of promoter-enhancer interactions have all been observed during both *in vitro* and *in vivo* cell differentiation [33,55–61], during human brain development [62], and during somatic cell reprograming [63,64]. Fifth, the 3D genome architecture undergoes striking reprogramming during early mammalian development. Two recent studies of mapping chromatin interactions in mouse gametes and early embryos have revealed several features of the reorganization of the 3D genome during early embryogenesis, including that (i) chromatin exists in a markedly relaxed state after fertilization, showing greatly diminished higher-order structure with very weak TADs and sparse distal interactions compared to those of later stage embryos; (ii) the maternal and paternal chromosomes are spatially separated from each other and display distinct compartmentalization in zygotes, which can be found as late as the 8-cell stage; (iii) establishment of chromatin higher-order architecture is a progressive and multi-level hierarchical process that lasts through preimplantation development; (iv) the establishment of the 3D genome architecture requires DNA replication but is at least partially independent of zygotic genome activation; and (v) chromatin higher-order structures are associated with DNA methylation state, histone modification state and chromatin accessibility [50,51]. Similar observations have also been obtained at the single-cell level [65,66]. However, it is noteworthy that, at the single-cell level, TADs and chromatin loops are present at similar strength in zygotic maternal and paternal nuclei, and A/B compartments are notably absent from maternal chromatin, suggesting that compartments and TADs are formed by different mechanisms [65,66]. And finally, the 3D genome can be reorganized in response to environmental stimuli [67,68]. It has been shown that hormone treatment can induce gene activity-related structural changes of TADs in human cells [67,68], whereas, heat shock-induced polycomb-mediated silencing led to widespread rearrangement of 3D genome organization in fly cells [67,68].

2.3. Roles of genome organizers in the formation and maintenance of the 3D genome

The establishment and maintenance of the 3D genome hierarchy requires participation of proteins and RNAs, in addition to DNA sequence elements, the so called *cis* determinants (e.g., protein binding sites, housekeeping genes, and macrosatellite repeats). Accumulating evidence has demonstrated the existence of genome organizers that participate in the formation, maintenance, or rearrangement of the 3D genome architecture. These organizers include chromatin architectural proteins such as the CCCTC-binding factor (CTCF) [57], the structural maintenance of chromosomes (SMC) protein complexes (e.g., cohesin and condensin [69–71]) and HP1α [72–74], nuclear matrix proteins (e.g., the lamina proteins [75]), DNA-binding transcription factors [76,77] (e.g., YY1 [78,79], SATB1 [80] and SATB2 [81]), chromatin remodeling complexes (e.g., the polycomb complex (PcG) proteins [82] and the NuRD components [41], coactivators (e.g., mediators [83]), and noncoding RNAs such as Xist [84], Firre [85,86], HOTTIP [87] and ThymoD [88].

Recent studies have underscored the critical role of CTCF and cohesin in the hierarchical chromatin folding, from chromatin looping to the establishment and maintenance of TADs and compartments [25,57,89–96]. According to the prominent loop extrusion model, CTCF and SMC proteins, cohesion or condensing, work together, i.e., cohesion or condensin acts as the extruding factor and CTCF as the boundary protein, to create unknotted chromatin loops, which in turn leads to the formation of TADs [97–99]. Indeed, condensin has recently been demonstrated as a mechanochemical motor [100] and the process of DNA loop extrusion by condensin has been visualized in real-time at the single-molecular level [101]. The DNA loop extrusion model is able to explain the diverse observations from Hi-C studies, such as the preferential orientation of CTCF motifs [97,102–104] and enrichments of CTCF and cohesin at TAD boundaries. It has further been suggested that CTCF, the cohesin release factor Wapl and transcription guide the positioning of cohesin in mammalian genomes [96], and that Wapl and the cohesin loading factor NIPBL together control the extension of chromatin loops and the formation of TADs [95]. However, the direct evidence that clarifies the role of CTCF and cohesin in the 3D genome formation only came from recent loss-of-function studies [92–94]. Acute CTCF depletion in mouse embryonic stem cells using the auxin-inducible degron system revealed that CTCF is absolutely required for CTCF-mediated chromatin looping and TAD formation and functions in a dose-dependent manner [94]. However, it appears that CTCF depletion did not affect the organization of A/B compartments, supporting that TADs and A/B compartments are formed by independent mechanisms [94]. Similar results, i.e., disruption of loops and TADs without destroying A/B compartments, were also observed when cohesin was removed [92,93], indicating that CTCF and cohesin act together to form loops and TADs but not A/B compartments. The two recent studies, one that removed cohesin from the genome in mouse liver cells by deleting the cohesin loading factor NIPBL [93] and the other that depleted the core cohesin component RAD21 in human colon-cancer cells [92], have also suggested that chromatin state defines cohesin-independent segregation of the genome into fine-scale compartments and that the cohesin-dependent formation of TADs has a role in guiding distant enhancers to their target genes.

In addition to CTCF and cohesin, the roles of other proteins in organizing the 3D genome are emerging. For example, HP1α is well established as an organizer of heterochromatin [105], and recent studies has further suggested that the formation of heterochromatin domain in both fly and mammalian cells might be driven by HP1α-mediated phase separation, i.e., upon DNA binding or phosphorylation, the HP1α protein nucleates into phase-separated droplets through oligomerization, which in turn induces compaction of DNA strands [72–74]. Another well-characterized example are the PcG proteins, which regulate key developmental genes and can guide the 3D genome organization at multiple levels by modifying histones, mediating chromatin looping, and organizing TADs [82]. More recently, the transcription factor YY1 has also emerged as a chromatin structural protein that promotes chromatin looping between promoters and enhancers, a prevalent feature of mammalian gene regulation [78,79].

Recent studies have identified many RNAs, mainly long noncoding RNAs (lncRNAs) that associate with chromatin in eukaryotic cells [106–110], indicating a structural role of lncRNAs in 3D genome organization. Among them, Xist and Firr are two of the well-characterized lncRNAs that play important roles in organizing the 3D chromatin architecture. Firre has been shown to mediate the colocalization of several genomic regions, located on different chromosomes [85,86]. The lncRNA Xist guides the formation of the 3D conformation of the inactive X chromosome during X chromosome inactivation [108,111–113]. Moreover, transcription of the lncRNA ThymoD can guide chromatin folding and compartmentalization to direct promoter-enhancer interactions specifying T cell fate [88]. However, despite these sporadic cases, future studies are required to determine whether and how nuclear lncRNAs play a general role in establishing and maintaining 3D genome architecture.

2.4. The functional relevance of the 3D genome

Existing evidence suggests that the formation of the hierarchical 3D genome is at least partially independent of transcription [50,114]. However, it is now clear that each level of the 3D genome hierarchy is of functional relevance and that the establishment of the 3D genome organization provides multiple additional regulatory layers to control gene expression (Fig. 2), which are complementary to the epigenetic mechanisms mediated by histone modification, DNA methylation or noncoding RNAs [5,18,115,116].

Chromatin condensation can regulate the accessibility of transcription factors to DNA, whereas spatial compartmentalization can constrain the availability of nuclear resources (e.g., transcription factors and co-factors). In mammalian cells, transcriptionally silent regions localize near the nuclear envelope and peri-nucleolar space, whereas active regions occupy the space in between [38,117,118]. LADs, lamina-associated domains, refer to the regions of the genome that interact with the nuclear lamina at the interior of the nuclear envelope [32,119,120]. LADs are transcriptionally repressed chromatin domains and generally enriched in repressive histone modifications [32,119,120]. Repositioning of active genes to LADs can result in their repression [111,121]. Similar to LADs, nucleolus-associated domains (NADs) are also gene poor, and typically characterized by repetitive DNA elements of the centromeric and pericentromeric regions [34,35].

Emerging evidence suggests that TADs are both structural and functional units that constrain, guide and facilitate enhancer-promoter interactions and coordinate gene regulation [14,26,122–124]. Thus, disruption of TAD boundaries can lead to aberrant gene regulation [97,103,125,126]. Also, it has been found that TADs represent replication time domains in mammalian cells [127,128]. At the fine-scale, chromatin looping can bring distant genomic regions into physical proximity, and chromatin looping-mediated physical contacts between gene promoters and other *cis*-regulatory elements (e.g., enhancers) are important for gene transcription and for coordinating transcription with RNA splicing [129–132]. The human genome contains many thousands of enhancers that, in any given human cell, are often located distantly from the genes they control [129–132]. Recent genome editing studies demonstrated a causal link between physical promoter-enhancer interactions and gene expression [133,134]. Furthermore, recent studies showed that YY1-mediated enhancer-promoter interactions are a general mechanism of mammalian gene regulation [78,79]. TAD formation enables physical co-localization and thereby coordinated gene expression (e.g., an enhancer regulates multiple genes or multiple enhancers regulate one gene within a TAD or a transcription factory), as well as insulation of un-desired enhancer-gene communications. Indeed, it appears that promoter-enhancer interactions occur much more frequently within a TAD than between TADs [122,123], and each TAD often contains several genes and multiple enhancers, allowing for coordinated gene regulation [14,26].

3. Biological relevance of the 3D genome organization for human disease

3.1. Implications of the 3D genome hierarchy for human disease

To this end, it appears that chromatin looping, organization into TADs and spatial compartmentalization are three fundamental

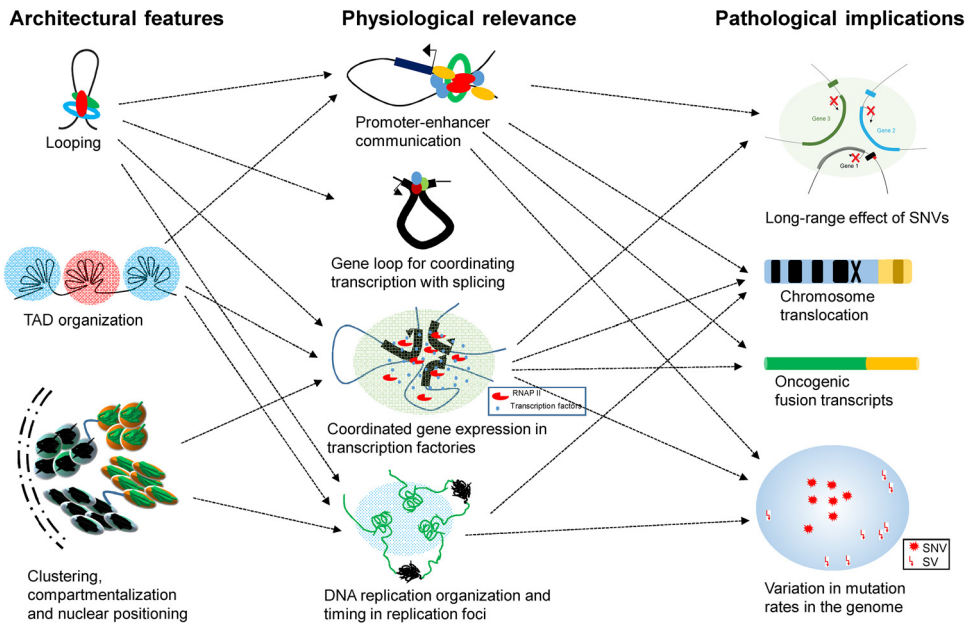

Fig. 2. Functional relevance and pathological implications of the various architectural features of the 3D genome.
Cartoons in the left panel show the different topological features for building the 3D genome, including chromatin looping, TAD organization, gene clustering, chromatin compartmentalization and nuclear positioning. These features provide the structural framework for the 3D organization of the various genomic activities. Genome functions related to the 3D organization such as physical interactions between promoters and enhancers during gene transcription, gene looping for coordinating transcription and splicing, coordinated gene expression in transcription factories and the organization and timing of DNA replication in replication foci/factories, are shown in the middle panel. Examples of their pathological consequences are shown in the right panel. More descriptions can be found in the main text. Note, in the cartoon illustrating the replication foci/factories in the bottom of the middle panel, early-replicating domains in the replication factory are indicated in green whereas the late-replicating domains outside are shown in black; In the cartoon showing the long-range effect of SNVs in the top of the right panel, a pathogenic SNV (single-nucleotide variation, the red star) in the enhancer of the gene 1 leads to the silencing of gene 1, and also causes the silencing the two coordinately regulated genes in the vicinity proximity (i.e., in the same transcription factory) via chromatin looping or gene clustering.

mechanisms for organizing the genome in 3D and thereby to modulate the DNA-templated nuclear processes, including transcription, splicing, DNA repair and replication. In accordance with their roles in physiological conditions these mechanisms can have potential pathogenic consequences (Fig. 2). For example, during recurrent chromosome translocation events, which frequently occur in certain cancer types such as hematologic malignancies and sarcomas, 3D genome-guided spatial proximity strongly influences translocation partner choice [135–140]. Also, coordinated gene transcription within TADs or transcription factories can lead to trans-splicing events that join exons from two different transcripts to produce chimeric mRNAs, a phenomenon underlying several oncogenic fusion transcripts [141,142]. Moreover, chromatin looping and TAD organization can provide a mechanism to magnify the long-range transcriptional and epigenetic effect of noncoding genetic variants (Fig. 2). As disease-risk single nucleotide variants (SNVs) often reside in distal *cis*-regulatory elements (e.g., enhancers and super-enhancers), they can affect human complex traits or disease phenotypes by inducing changes of the chromatin states at interacting regulatory elements and consequently target gene expression. This demonstrates that the 3D genome organization can guide how SNVs influence distal molecular phenotypes [143–145]. For example, in a recent HiChiP (a method for mapping chromatin interactions mediated by a protein of interest, see Box 1) study, it was found that 684 autoimmune disease–associated intergenic SNVs can influence 2597 target genes through chromatin interactions, with up to ten target genes for a single SNV [146]. Finally, nuclear compartmentalization also has pathogenic implications, highlighting the importance of nuclear positioning in gene regulation and DNA replication timing [147] (Fig. 2). Indeed, the nuclear position of genes or entire chromosomes often differs in disease cells [148–151]. Furthermore, recent studies demonstrated that 3D chromatin architecture is a major influence on both regional mutation rates of SNVs and the landscape of somatic copy-number alterations (SCNAs) in cancer, with SNVs enriched in regions of closed chromatin and insertions and deletions (indels) enriched in open chromatin regions [152–156] (Fig. 2).

3.2. *Emerging disease mechanisms of 3D genome disruption*

Recent studies highlighted a link between the disruption of the 3D genome and human diseases. In human diseases, 3D genome derangements are frequently caused by either deleterious mutations of the 3D genome organizers or the various genetic alterations of the genome, including SNVs, small insertion/deletions (indels), and chromosomal abnormalities (aneuploidy and structural variations (SVs), including insertions, deletions, duplications, translocations and inversions). Although, in most cases, it remains elusive whether a disease-associated 3D genome derangement is the cause or consequence of disease development, it is tempting to postulate that aberrant 3D genome architecture causes dysregulation of genome function (e.g., aberrant gene expression, dysregulation of DNA replication and repair), and thereby leads to disease phenotypes (Fig. 3A). For example, abnormal DNA replication caused by derangements in the 3D genome can affect cell cycle and cell division whereas incorrect DNA repair can affect genome integrity and maintenance and thus cause genome instability, both of which can trigger cancer development (Fig. 3A).

Recent studies indicated that there are at least two mechanisms by which disruption of 3D genome architecture causes altered expression of disease-relevant genes and thereby disease phenotypes (Fig. 3). In the first mechanism, disease-associated regulatory SNVs impair normal or create pathogenic promoter-enhancer interactions and thereby lead to aberrant gene expression and disease phenotypes (Fig. 3B). A large body of studies have demonstrated that this is an important and widely used mechanism

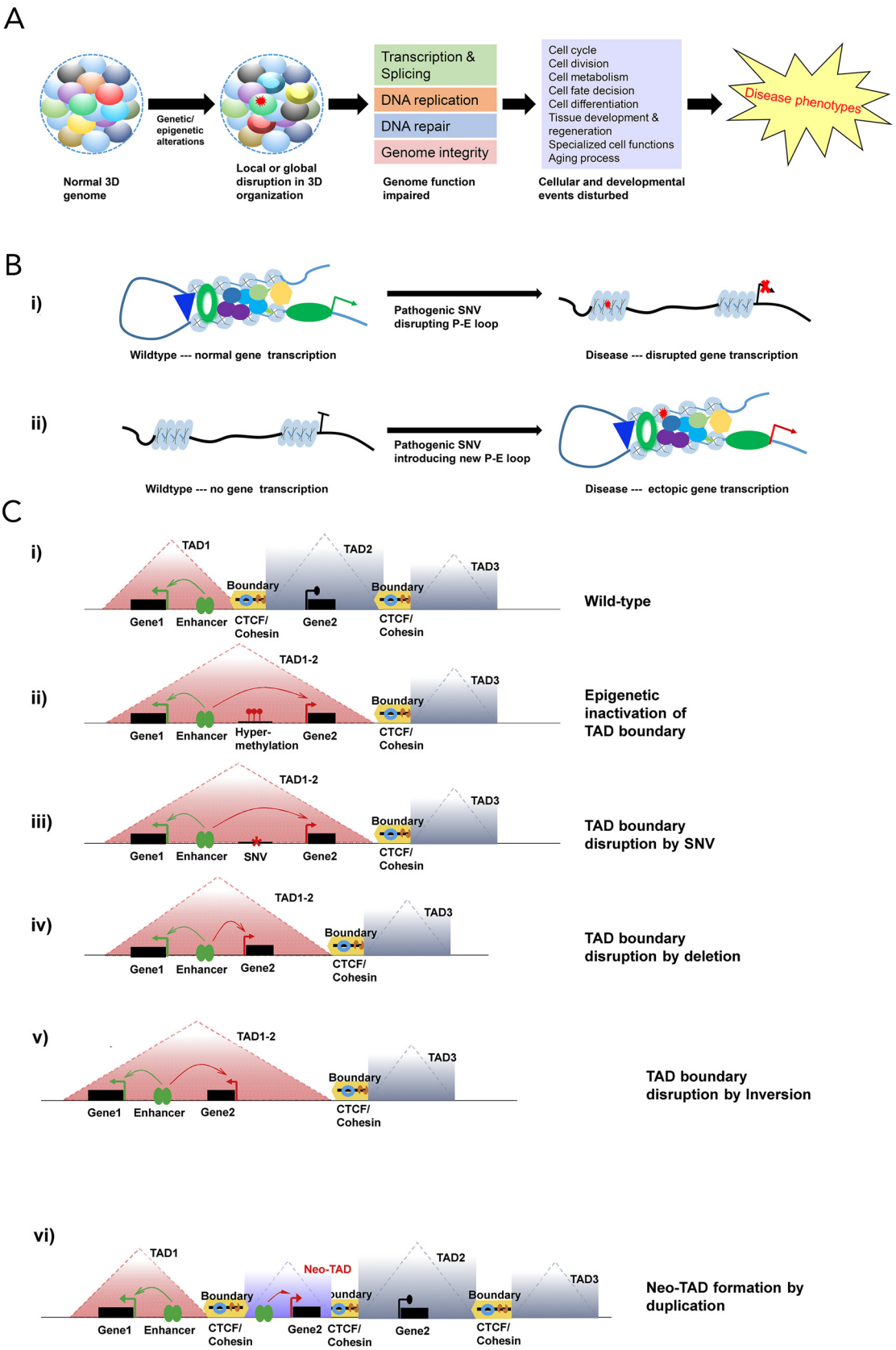

Fig. 3. Disease mechanisms of 3D genome disruption.
A) Schematic illustration of the molecular pathways by which genetic or epigenetic disruption of the 3D genome lead to disease phenotypes; B) cartoons showing that disease-causing noncoding SNVs can disrupt normal gene promoter-enhancer loops (i) or create aberrant promoter-enhancer loops (ii), and thereby leading to aberrant regulation of the disease-relevant genes; C) six examples of genetic or epigenetic mechanisms of TAD disruption that cause enhancer adoption/hijacking and consequently mis-expression of disease-driving genes.

for regulatory noncoding variants to play a role in many human diseases. For example, point mutations in the ZRS, a distal enhancer that tightly regulates the sonic hedgehog (*SHH*) expression in the developing limb, cause ectopic chromatin interactions between ZRS and the *SHH* promoter and thereby lead to *SHH* misexpressions in several congenital limb malformation disorders [157]. In another example, a recent study found that many coronary artery disease (CAD)-risk noncoding SNVs identified by genome-wide association studies (GWAS) exerted their disease effect either by disrupting or by strengthening enhancer–promoter interactions [146]. Similar analyses of chromatin interactions at disease-associated loci identified many novel candidate genes for a diversity of complex diseases, including inflammatory bowel disease [158], chronic kidney disease (CKD) [159], atherosclerotic disease [160], autoimmune disease [146,161], and prostate cancer [162,163]. Moreover, a recent study developed a computational approach that is based on chromatin interactions for predicting cancer-driving mutations in noncoding regions [164]. Together, these studies demonstrated that disease-linked regulatory SNVs modulate target gene expression by regulating chromatin interactions between genes and regulatory elements.

In the second disease mechanism, disruption of TADs leads to inappropriate communications between enhancers and genes that are normally insulated from each other by TAD organization and thereby allows distal enhancers to ectopically activate disease-relevant genes. This mechanism, called enhancer adoption or enhancer hijacking [165–168], underscores the importance of TAD organization for genomic integrity and disease. As discussed above, TADs are thought to function as regulatory units of gene expression by constraining promoter-enhancer interactions. Hence, it is not surprising that TAD disruption can cause rewiring of promoter-enhancer interactions and subsequent gene misregulation. Indeed, recent studies have identified a variety of pathogenic events that lead to enhancer adoption/hijacking via TAD disruption [169–171] (Fig. 3C). For example, since TADs are demarcated by boundary regions that are characterized by the binding of architectural proteins (e.g., CTCF and cohesin), genetic disruption or epigenetic inactivation of the architectural protein binding sites (i.e., CTCF binding sites) in a TAD boundary can lead to fusion of the two flanking TADs, affecting the encompassing genes [58,172–174]. Similarly, deletion of an entire TAD boundary will also lead to TAD fusion or disruption [172,175]. Moreover, complex genomic rearrangements such as inversions, deletions, duplications and translocations has the potential to cause TAD breakage and fusion or even formation of new TADs [166,167,172,176–178].

Several pioneering studies have identified TAD disruption-mediated enhancer adoption and gene misregulation as a novel mechanism for structure variation (SV)-caused congenital developmental diseases (Table 1). In the first such studies, the authors linked the phenotypes of 922 deletion cases recorded in the DECIPHER database to monogenic diseases that are associated with genes within or adjacent to the deletions using a bioinformatic approach. They found up to 11.8% of the deletions could result in TAD disruption and lead to enhancer adoption [166]. In a more recent study with 273 subjects harboring balanced chromosomal abnormalities (BCA) associated with a spectrum of human congenital anomalies, the authors found that 7.3% of the BCAs recurrently disrupted TADs encompassing known disease-relevant genes. They identified disruptions of the TAD organization that cause long-range regulatory perturbation of several disease-driving genes such as the *MEF2C* gene in the patients with 5q14.3 microdeletion syndrome [179] (Table 1). However, the first direct evidence demonstrating TAD disruption as a disease mechanism in human developmental disorders came from a recent mechanistic study of the pathogenicity of SVs in the limb malformations [172]. In this elegant study, the authors first identified the genomic rearrangements (deletions, inversions and duplications) associated with three types of human limb malformations, and found that these rearrangements altered the TAD organization in the *WNT6/IHH/EPHA4/PAX3* locus. The authors then re-engineered the same rearrangements in mice by using CRISPR/CAS9 genome editing, and found that these pathogenic structural changes led to ectopic long-range promoter-enhancer communications and thereby disease-causing gene misexpression both in the mutant mouse limb tissue and patient-derived fibroblasts. The authors further found that this rewiring of enhancer-promoter interactions happened only if the boundary elements (e.g., CTCF binding sites) were disrupted, highlighting the importance of the TAD integrity [172]. Furthermore, a recent study from the same research group revealed that genomic duplications cause disease phenotypes of Cook syndrome by leading to the formation of a new TAD (neo-TAD) in the *Sox9* locus, which in turn leads to ectopic interaction between the *Kcnj2* gene and the *Sox9* enhancers and thereby misexpression of *kcnj2* [176]. TAD disruption-caused enhancer adoption is also one of the mechanisms underlying the pathogenesis of lamin B1-caused autosomal dominant adult-onset demyelinating leukodystrophy (ADLD) [175]. Together, these studies demonstrate the functional relevance of TAD disruption in determining Mendelian phenotypes of developmental disorders.

Similar to enhancer adoption in developmental disorders, recent studies have suggested TAD disruption-mediated enhancer hijacking as an important mechanism of oncogene activation in cancers. For example, a recent study found that gain-of-function IDH mutations promote gliomagenesis by disrupting TAD organization and therefore causing ectopic chromatin interactions between the oncogene PDGFRA and a distal constitutive enhancer that induce PDGFRA deregulation [174]. The authors further demonstrated that the inactivation of the TAD boundary is caused by compromised CTCF binding to the boundary due to DNA hyper-methylation at the CTCF binding sites resulted from IDH mutation [174]. Several lines of evidence have suggested that TAD disruption-caused oncogene activation might be a prevalent mechanism for tumorigenesis. First, it has been demonstrated that CTCF and cohesin binding and CTCF site orientation play a critical role in TAD formation and maintenance, whereas recent studies have found that CTCF/cohesin-binding sites are frequently mutated across numerous cancer types [180], such as colorectal cancer [173] and leukaemia [181]. Second, recurrent mutations in many epigenetic regulators frequently occur as cancer-driving events across a wide range of cancer types [182]. The resulting gain- or loss-of function of these epigenetic regulators can cause epigenetic alterations that in turn may lead to epigenetic inactivation of TAD boundaries in a way similar to how IDH mutations lead to TAD disruption in gliomas [174]. Third, as a hallmark of cancer, oncogenic alterations such as SVs frequently occur in cancer genomes with the potential to disrupt TAD organization and normal promoter-enhancer interactions. Indeed, two recent Hi-C studies, which mapped the 3D genome organization in prostate cancer and multiple myeloma cell lines, respectively, found that copy number variation (CNV) breakpoints significantly overlap with TAD boundaries [183,184]. These studies also suggested that CNVs might help in the formation of cancer-specific TADs enriched in regulatory elements such as enhancers and promoters, and associated with aberrant gene expression [183,184]. Moreover, a recent study of pan-cancer analysis of somatic CNVs in 7416 cancer genomes across 26 tumor types found that TAD boundary disruption caused by recurrent deletions or tandem duplications led to the activation of the two oncogenes *IRS4* and *IGF2* through enhancer hijacking [178]. And fourth, oncogene activation by TAD disruption-mediated enhancer hijacking has been observed in numerous cancer types, including neuroblastoma [185,186], medulloblastoma [167], glioma [174], colorectal cancer [178], leukemia [177,181], sarcoma, uterine leiomyoma and

Table 1
Examples of TAD disruption-mediated enhancer adoption/hijacking in human diseases.

Disease type	Disease	Disease-relevant gene	Genetic /epigenetic alteration	OMIM ID	Refs.
Congenital developmental disorders	Type A1 Brachydactyly	*PAX3*	Deletion	112500	[172]
	F-syndrome	*WNT6*	Inversion, duplication	102510	[172]
	Cooks syndrome	*KCNJ2*	Duplication	106995	[176]
	Rett syndrome	*FOXG1*	Translocation	613454	[179]
	Glass syndrome	*SATB2*	Translocation	612,313	[179]
	5q14.3 microdeletion syndrome	*MEF2C*	Deletion	613,443	[179]
	Autosomal-dominant adultonset demyelinating leukodystrophy (ADLD)	*LMNB1*	Deletion	169500	[175]
	Mesomelic dysplasia	*ID4*	Deletion	605274	[170]
	Liebenberg syndrome	*PITX1*	Deletion, duplication	186550	[170]
Cancer	Glioma	*PDGFRA*	Hyper-methylation of CTCF binding site	–	[174]
	Colorectal cancer	–	SNVs in CTCF/cohesin binding site	–	[173]
	T cell acute lymphoblastic leukemia (T-ALL)	*TAL1, LMO2*	Deletion of CTCF/cohesin binding sites	–	[181]
	Neuroblastoma	*TERT*	Diverse SVs	–	[185,186]
	Lung cancer	*IRS4*	Deletion	–	[178]
	Colorectal cancer	*IGF2*	Tandem duplications	–	[178]
	Medulloblastoma	*GFI1, GFI1B*	Diverse SVs	–	[167]
	AML with inv(3)/t(3;3)	*EVI1*	Inversion	–	[177]

squamous cancers [178]. With more investigations into the 3D cancer genomes forthcoming, one can expect more such examples emerging. Compared to oncogene activation by TAD disruption, much less is known about the pathogenic repression of tumor suppressor genes in relation to the 3D cancer genome. It will be interesting to see whether tumor suppressors can be silenced through aberrant long-range chromatin interactions caused by TAD boundary disruption.

In conclusion, a growing number of studies demonstrated that genetic and epigenetic alterations can cause disease phenotypes by altering the two fundamental layers of the 3D genome hierarchy, chromatin loops and TADs. Additionally, other types of epigenetic alterations with the potential to affect other components of the 3D genome hierarchy, e.g., compartments and CTs, have also been observed in human diseases, as exemplified by pathogenic nuclear re-positioning of entire chromosomes or individual genes. For instance, movement of the X chromosome and the *Bdnf* gene, which encodes the major neurotrophin, in seizure foci of the human cortex is associated with epilepsy [187,188]. Moreover, as discussed above, such radial repositioning of chromosomes and gene loci also occurs across cancer types [148,149]. However, it must be pointed out that all the examples discussed here are correlative, and whether nuclear repositioning is causative for human disease remains to be examined.

4. Genome architectural proteins and human diseases

Chromatin architectural proteins act in concert with each other and other genome organizers including transcription factors and ncRNAs to play critical roles in the formation and maintenance of the 3D genome organization, and thus are pivotal in human development, tissue regeneration and disease. Indeed, an increasing number of genes encoding architectural proteins have been linked to a myriad of human diseases, including developmental disorders, neurodegenerative disorders, psychiatric disorders and accelerated aging disorders, as well as cancers (Table 2). For example, mutations and heterozygous deletions of the *CTCF* gene are implicated in autosomal dominant mental retardation 21 (MRD21) [189,190] and cancers [91]. Recurrent somatic mutations in the genes that encode the proteins constituting the cohesin complex have also been identified in many tumors such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [191]. In another example, mutations in the gene encoding SATB2, a chromatin organizer that tethers genomic regions to the nuclear matrix and is essential for craniofacial development, cause the Glass syndrome characterized by intellectual disability and various dysmorphic facial features (Table 1). Moreover, mutations in the gene *MED12* cause the FG syndrome and Fryns-Lujan syndrome (Table 2). However, among all of the structural protein-associated human diseases, it is the two groups of diseases, cohesinopathies and laminopathies that attract much interest.

Genetic mapping and DNA sequencing studies have revealed that mutations in the genes encoding the cohesin complex proteins and their regulators are responsible for cohesinopathies, a group of developmental and intellectual impairment diseases that include the Cornelia de Lange Syndrome (CdLS), Roberts syndrome (RBS), and Warsaw Breakage Syndrome (WABS) [192–194]. CdLS is mainly caused by mutations in the cohesin-loading factor NIPBL (>60%) as well as mutations in the cohesin subunits Smc1A, Smc3 and Rad21 (~5%). RBS, an autosomal recessive disorder, arises from mutations in the gene encoding cohesin acetyltransferase ESCO2, whereas WABS is caused by defective DDX11, a DNA helicase essential for chromatid cohesion. The cohesinopathies are characterized by a diversity of overlapping phenotypes including limb defects, craniofacial deformities, growth retardation, intellectual disability, cardiac malformations, and microcephaly, which is consistent with the multifaceted roles of cohesin proteins in mitotic chromosome condensation, sister chromatid cohesion, gene regulation, DNA repair, 3D genome organization, cell cycle, apoptosis, and tissue development. However, the precise molecular mechanisms underlying these syndromes remain to be elucidated.

Laminopathies are a wide spectrum of rare disorders arisen from mutations in genes encoding the intermediate filament nuclear lamins and lamin B receptor (LBR), which belong to the more generic nuclear envelopathies, diseases associated with defects of the nuclear envelope (reviewed in [195,196]). The nuclear lamina, composed of three types of filamentous protein (lamin A, B and C), are essential for the nuclear structure and the 3D genome organization by providing structural support to the nucleus and interacting with the genome. For example, about 40% of the human genome is organized into LADs, which range from 40 kb to 30 Mb. The nuclear lamin proteins therefore play diverse roles in many nuclear processes and cellular pathways, such as nuclear positioning, heterochromatin organization, gene transcription, nuclear

Table 2
Examples of chromatin architectural protein defects-caused human disorders.

Architectural protein	Disease	Inheritance format	OMIM ID
CTCF	autosomal dominant mental retardation 21 (MRD21)	Autosomal dominant	615502
MED12	FG syndrome	X-linked recessive	305450
MED12	Fryns-Lujan syndrome	X-linked recessive	309520
NIPBL	CdLS1	Autosomal dominant	122470
SMC1 A	CdLS2	X-linked dominant	300590
SMC3	CdLS3	Autosomal dominant	610759
RAD21	CdLS4	Autosomal dominant	606462
ESCO2	Roberts syndrome	Autosomal recessive	268300
DDX11	Warsaw Breakage Syndrome	Autosomal recessive	613398
Lamin A	Hutchinson–Gilford progeria syndrome (HGPS)	Autosomal dominant	176670
RECQL2	Werner syndrome	Autosomal recessive	277700
Lamin A/C	Emery–Dreifuss muscular dystrophy 2 (EDMD2)	Autosomal dominant	181350
Lamin A/C	Emery–Dreifuss muscular dystrophy 3 (EDMD3)	Autosomal recessive	616516
Lamin A/C	limb girdle muscular dystrophy type 1B (LGMD1B)	Autosomal dominant	159001
Lamin A/C	dilated cardiomyopathy type 1 A (DCM1 A)	Autosomal dominant	115200
Lamin A/C	Charcot-Marie-Tooth type 2B1 (CMT2B1)	Autosomal recessive	605588
Lamin A/C	Dunnigan-type familial partial lipodystrophy (FPLD)	Autosomal dominant	151660
LBR	Greenberg dysplasia	Autosomal recessive	215140
LBR	Pelger–Huet anomaly (PHA)	Autosomal dominant	169400

morphology, metabolism, mechanosensation, and cell locomotion. Hence, similar to cohesinopathies, laminopathies are also multisystem monogenic diseases, i.e., caused by a single genetic defect in a single gene but showing phenotypes in multiple tissues or organs. However, laminopathies exhibit a distinct feature, i.e., different mutations in the same gene often result in different disorders. For example, mutations in LMNA encoding the A/C-type lamins cause a large group of disorders ranging from premature ageing syndromes (Hutchinson–Gilford progeria syndrome (HGPS) and Werner syndrome) to myopathies (autosomal forms of Emery–Dreifuss muscular dystrophy (EDMD), limb girdle muscular dystrophy type 1B (LGMD1B) and dilated cardiomyopathy type 1 A (DCM1 A)), neuropathies (e.g., Charcot-Marie-Tooth type 2B1 (CMT2B1)) and Lipodystrophies (e.g., Dunnigan-type familial partial lipodystrophy (FPLD)) (Table 2). Also, different mutations in the gene encoding LBR cause at least two disorders, Greenberg dysplasia, a lethal and recessive chondrodystrophy, and the Pelger–Huet anomaly (PHA) (Table 2). PHA is an autosomal dominant disorder, characterized by hypolobulated neutrophil nuclei with coarse chromatin. Interestingly, the nuclear morphology changes in neutrophils resembling PHA that are acquired rather than congenital have also been described in a diversity of disease conditions, such as MDS, vitamin B12 and folate deficiency, and multiple myeloma, indicating that aberrant nuclear structure might be a common mechanism underlying these diseases.

Taken together, these congenital disorders caused by defective structural proteins showcase the critical roles of genome organizers in the various aspects of human development, tissue regeneration and aging processes. However, there is no clear understanding yet regarding how the 3D genome organization is disrupted as a result of the altered genome organizer in almost any of these diseases. Thus, whether or how disruption of the 3D genome causes the disease phenotypes remains to be elucidated. Future studies that comprehensively map the derangements in the 3D genome in these diseases and dissect the link between the derangements and disease phenotypes will likely uncover new disease mechanisms and identify novel therapeutic targets.

5. Conclusions and future prospects

The synthesis of a wide array of technologies ranging from the still rapidly developing DNA imaging technologies to the fast-growing high-throughput genomic tools for mapping chromatin interactions, the CRISPR/CAS genome engineering technology and the computational data analysis and modelling has greatly facilitated our understanding of the physical organization of the genome in the 3D nuclear space. It is becoming clear that the eukaryotic genome is organized as a nested hierarchy that comprises multiple levels of topological features including chromatin loops, TADs, A/B compartments and CTs. It appears that the hierarchical strata of the 3D genome provide multiple regulatory layers for gene regulation and other genome functions and undergo programmed spatiotemporal reorganization during animal development. Moreover, defects in the 3D genome at each layer of the organization accompanied by various genetic and epigenetic alterations have been observed in human disease. Although many aspects of the 3D genome architecture in human disease and their underlying mechanisms begin to emerge, future studies have to overcome several challenges to better understand the role of the spatial genome organization in disease.

Our understanding of the 3D genome and its regulatory roles in the various nuclear processes is still far from complete. There are many fundamental questions remaining with respect to how the genome is organized and functions. For example, how is TAD, suggested as the functional unit of gene regulation, related to the formation and nuclear localization of a transcription factory during transcription? In other words, does a transcription factory represent the physical existence of an active TAD or several active TADs? How is the specificity of a chromatin loop between a gene and its enhancer within a TAD achieved? How is a compartment (A or B) related to the nuclear positioning of its encompassing genomic loci? What factor(s) determines the A/B compartment state of a gene or a genomic locus in a given cell? To answer these important questions, new mapping technologies for spatial resolution of the 3D genome architecture are needed. Indeed, developing new mapping technologies is one of the main focuses of the 4D Nucleome Project [197]. Moreover, genome editing studies aimed at determining the functional consequences of perturbing the various structural features in a variety of biological contexts are also required. Such experiments will offer deeper mechanistic insights into the principles of the 3D genome organization and how perturbation of the different organizational features will affect nuclear activities, critical to understand the molecular mechanisms of how disruption of the 3D genome will cause disease.

Our understanding of how the spatiotemporal organization of the genome orchestrates normal tissue development is also very limited. Although the dynamic rearrangement of the 3D genome has recently been described during the early mouse embryonic development, during *in vitro* differentiation of mouse and human ESCs, and during somatic cell reprogramming, mechanistic insights

into how the spatiotemporal organization of the nucleus orchestrates normal tissue development remains elusive. For example, what are the driving forces that govern the 3D genome rearrangement during the various tissue-specific cell differentiation processes? Whether and how does the 3D genome impact the cell fate decision during these differentiation processes? Whether and how does the rearrangement of the 3D genome play a role in the precise spatiotemporal regulation of gene expression during tissue development? More specifically, for example, how does the 3D genome influence hematopoiesis, the process that produces all types of blood cells? It is well documented that the various blood precursors undergo dramatic nuclear morphological changes during blood cell maturation. For example, throughout terminal erythropoiesis, erythroblasts undergo gradual chromatin condensation with decreased cell and nucleus size, which ultimately leads to enucleation in red blood cells, whereas granulopoiesis is characterized by dramatic and specific changes in nuclear shape, with the nucleus segmented into lobes in mature neutrophils. It is unclear how the nuclear morphological change is linked to the 3D genome rearrangement and transcriptional re-wiring during blood differentiation. To address such questions, perturbation studies in the context of tissue development using the genome editing technologies will again be required. These experiments will not only shed light on the structure-function relationships of the genome in the context of normal tissue development, but also be critical to eventually understand the link between aberrant 3D genome architecture and human disease phenotypes. For example, aberrant nuclear morphologies are hallmarks for the diagnosis of many hematologic disorders, such as MDS. Thus, defining the functional relevance of the nuclear morphology-associated 3D genome rearrangement during normal and dysplastic hematopoiesis is of great importance both biologically and clinically.

There is a lack of reference maps of the 3D genome in human primary normal or diseased tissue cells. To this end, except a few studies [54,62], the vast majority of whole-genome chromatin interaction maps have been generated in cell lines. In particularly, mapping of 3D cancer genomes is by far exclusively limited to cancer cell lines [183,184]. Hence, a straightforward next step is to construct high-resolution reference maps of the 3D genome in human disease cells and their corresponding normal tissue cells. However, the cellular and genetic heterogeneity of primary disease samples, especially the heterogeneity within primary tumor samples, presents a daunting challenge to perform cell population-based high-throughput mapping studies. Thus, the recently developed single-cell Hi-C methods (Box 1) offer the promise of overcoming this technically challenge. Moreover, cell-to-cell variability of chromosome conformation in individual cells also requires surveying relatively large numbers of single cells before achieving statistically meaningful observations in single-cell assays. However, the current implements of the single-cell Hi-C methods have limitations either in throughput (i.e., the number of single cells being surveyed in a single experiment) or in resolution (i.e., the recovered distinct chromatin interactions per single cell). The scHi-C [44,198] and snHi-C [65] enable to detect up to two millions of chromatin contacts per cell but can only survey a limited number of cells per assay, whereas sciHi-C [199] enables to survey thousands of cells per assay but with relative low resolution. Thus, it is in great need to develop high-throughput and high-resolution single-cell Hi-C methods for dissecting the aberrant 3D genome architecture in the heterogeneous human primary disease samples.

Competing financial interests

The authors declare no competing interests.

Acknowledgements

This work was supported by the UW Bridge Fund (ZD), ASH Bridge Grant (ZD), and the NIH Common FundU54DK107979.

References

[1] T.D. Matheson, P.D. Kaufman, Grabbing the genome by the NADs, Chromosoma (2015).
[2] M. Dundr, T. Misteli, Biogenesis of nuclear bodies, Cold Spring Harbor Perspect. Biol. 2 (12) (2010), a000711.
[3] Y.S. Mao, B. Zhang, D.L. Spector, Biogenesis and function of nuclear bodies, Trends Genet. TIG 27 (8) (2011) 295–306.
[4] P.R. Cook, A model for all genomes: the role of transcription factories, J. Mol. Biol. 395 (1) (2010) 1–10.
[5] T. Misteli, E. Soutoglou, The emerging role of nuclear architecture in DNA repair and genome maintenance, nature reviews, Mol. Cell Biol. 10 (4) (2009) 243–254.
[6] G. Felsenfeld, M. Groudine, Controlling the double helix, Nature 421 (6921) (2003) 448–453.
[7] M.A. Ricci, C. Manzo, M.F. Garcia-Parajo, M. Lakadamyali, M.P. Cosma, Chromatin fibers are formed by heterogeneous groups of nucleosomes in vivo, Cell 160 (6) (2015) 1145–1158.
[8] H.D. Ou, S. Phan, T.J. Deerinck, A. Thor, M.H. Ellisman, C.C. O'Shea, ChromEMT: visualizing 3D chromatin structure and compaction in interphase and mitotic cells, Science 357 (6349) (2017).
[9] M. Bustin, T. Misteli, Nongenetic functions of the genome, Science 352 (6286) (2016), aad6933.
[10] W.A. Bickmore, The spatial organization of the human genome, Annu. Rev. Genom. Hum. Genet. 14 (2013) 67–84.
[11] G. Cavalli, T. Misteli, Functional implications of genome topology, Nat. Struct. Mol. Biol. 20 (3) (2013) 290–299.
[12] T. Cremer, M. Cremer, B. Hubner, H. Strickfaden, D. Smeets, J. Popken, M. Sterr, Y. Markaki, K. Rippe, C. Cremer, The 4D nucleome: evidence for a dynamic nuclear landscape based on co-aligned active and inactive nuclear compartments, FEBS Lett. 589 (20 Pt A) (2015) 2931–2943.
[13] E. de Wit, W. de Laat, A decade of 3C technologies: insights into nuclear organization, Gene Dev. 26 (1) (2012) 11–24.
[14] J. Dekker, E. Heard, Structural and functional diversity of topologically associating domains, FEBS Lett. 589 (20 Pt A) (2015) 2877–2884.
[15] A. Denker, W. de Laat, The second decade of 3C technologies: detailed insights into nuclear organization, Gene Dev. 30 (12) (2016) 1357–1382.
[16] Z. Duan, C.A. Blau, The genome in space and time: does form always follow function? How does the spatial and temporal organization of a eukaryotic genome reflect and influence its functions? Bioessays 34 (9) (2012) 800–810.
[17] J. Fraser, I. Williamson, W.A. Bickmore, J. Dostie, An overview of genome organization and how we got there: from FISH to Hi-C, Microbiol. Mol. Boil. Rev. MMBR 79 (3) (2015) 347–372.
[18] D.U. Gorkin, D. Leung, B. Ren, The 3D genome in transcriptional regulation and pluripotency, Cell Stem Cell 14 (6) (2014) 762–775.
[19] T. Misteli, Beyond the sequence: cellular organization of genome function, Cell 128 (4) (2007) 787–800.
[20] A. Pombo, N. Dillon, Three-dimensional genome architecture: players and mechanisms, nature reviews, Mol. Cell Biol. 16 (4) (2015) 245–257.
[21] I. Rajapakse, M. Groudine, On emerging nuclear order, J. Cell Biol. 192 (5) (2011) 711–721.
[22] V. Ramani, J. Shendure, Z. Duan, Understanding spatial genome organization: methods and insights, Genom. Proteomics Bioinf. 14 (1) (2016) 7–20.
[23] V.I. Risca, W.J. Greenleaf, Unraveling the 3D genome: genomics tools for multiscale exploration, Trends Genet. TIG (2015).
[24] H. Tjong, W. Li, R. Kalhor, C. Dai, S. Hao, K. Gong, Y. Zhou, H. Li, X.J. Zhou, M.A. Le Gros, C.A. Larabell, L. Chen, F. Alber, Population-based 3D genome structure analysis reveals driving forces in spatial genome organization, Proc. Natl. Acad. Sci. U.S. A. 113 (12) (2016) E1663–E1672.
[25] B.A. Bouwman, W. de Laat, Getting the genome in shape: the formation of loops, domains and compartments, Genome biology 16 (2015) 154.
[26] J.R. Dixon, D.U. Gorkin, B. Ren, Chromatin domains: the unit of chromosome organization, Mol. Cell 62 (5) (2016) 668–680.
[27] J.H. Gibcus, J. Dekker, The hierarchy of the 3D genome, Mol. Cell 49 (5) (2013) 773–782.
[28] T. Cremer, M. Cremer, Chromosome territories, Cold Spring Harbor Perspect. Biol. 2 (3) (2010), a003889.
[29] E. Lieberman-Aiden, N.L. van Berkum, L. Williams, M. Imakaev, T. Ragoczy, A. Telling, I. Amit, B.R. Lajoie, P.J. Sabo, M.O. Dorschner, R. Sandstrom, B. Bernstein, M.A. Bender, M. Groudine, A. Gnirke, J. Stamatoyannopoulos, L.A. Mirny, E.S. Lander, J. Dekker, Comprehensive mapping of long-range interactions reveals folding principles of the human genome, Science 326 (5950) (2009) 289–293.
[30] J.R. Dixon, S. Selvaraj, F. Yue, A. Kim, Y. Li, Y. Shen, M. Hu, J.S. Liu, B. Ren, Topological domains in mammalian genomes identified by analysis of chromatin interactions, Nature (2012).
[31] E.P. Nora, B.R. Lajoie, E.G. Schulz, L. Giorgetti, I. Okamoto, N. Servant, T. Piolot, N.L. van Berkum, J. Meisig, J. Sedat, J. Gribnau, E. Barillot, N. Bluthgen,

J. Dekker, E. Heard, Spatial partitioning of the regulatory landscape of the X-inactivation centre, Nature (2012).
[32] L. Guelen, L. Pagie, E. Brasset, W. Meuleman, M.B. Faza, W. Talhout, B.H. Eussen, A. de Klein, L. Wessels, W. de Laat, B. van Steensel, Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions, Nature 453 (7197) (2008) 948–951.
[33] D. Peric-Hupkes, W. Meuleman, L. Pagie, S.W. Bruggeman, I. Solovei, W. Brugman, S. Graf, P. Flicek, R.M. Kerkhoven, M. van Lohuizen, M. Reinders, L. Wessels, B. van Steensel, Molecular maps of the reorganization of genome-nuclear lamina interactions during differentiation, Mol. Cell 38 (4) (2010) 603–613.
[34] A. Nemeth, A. Conesa, J. Santoyo-Lopez, I. Medina, D. Montaner, B. Peterfia, I. Solovei, T. Cremer, J. Dopazo, G. Langst, Initial genomics of the human nucleolus, PLos Genet. 6 (3) (2010), e1000889.
[35] S. van Koningsbruggen, M. Gierlinski, P. Schofield, D. Martin, G.J. Barton, Y. Ariyurek, J.T. den Dunnen, A.I. Lamond, High-resolution whole-genome sequencing reveals that specific chromatin domains from most human chromosomes associate with nucleoli, Mol. Biol. Cell 21 (21) (2010) 3735–3748.
[36] S.S. Rao, M.H. Huntley, N.C. Durand, E.K. Stamenova, I.D. Bochkov, J.T. Robinson, A.L. Sanborn, I. Machol, A.D. Omer, E.S. Lander, E.L. Aiden, A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping, Cell 159 (7) (2014) 1665–1680.
[37] A. Gondor, R. Ohlsson, Chromosome crosstalk in three dimensions, Nature 461 (7261) (2009) 212–217.
[38] T. Takizawa, K.J. Meaburn, T. Misteli, The meaning of gene positioning, Cell 135 (1) (2008) 9–13.
[39] S. Wang, J.H. Su, B.J. Beliveau, B. Bintu, J.R. Moffitt, C.T. Wu, X. Zhuang, Spatial organization of chromatin domains and compartments in single chromosomes, Science 353 (6299) (2016) 598–602.
[40] A.N. Boettiger, B. Bintu, J.R. Moffitt, S. Wang, B.J. Beliveau, G. Fudenberg, M. Imakaev, L.A. Mirny, C.T. Wu, X. Zhuang, Super-resolution imaging reveals distinct chromatin folding for different epigenetic states, Nature 529 (7586) (2016) 418–422.
[41] T.J. Stevens, D. Lando, S. Basu, L.P. Atkinson, Y. Cao, S.F. Lee, M. Leeb, K.J. Wohlfahrt, W. Boucher, A. O'Shaughnessy-Kirwan, J. Cramard, A.J. Faure, M. Ralser, E. Blanco, L. Morey, M. Sanso, M.G.S. Palayret, B. Lehner, L. Di Croce, A. Wutz, B. Hendrich, D. Klenerman, E.D. Laue, 3D structures of individual mammalian genomes studied by single-cell Hi-C, Nature 544 (7648) (2017) 59–64.
[42] N. Naumova, M. Imakaev, G. Fudenberg, Y. Zhan, B.R. Lajoie, L.A. Mirny, J. Dekker, Organization of the mitotic chromosome, Science 342 (6161) (2013) 948–953.
[43] J.H. Gibcus, K. Samejima, A. Goloborodko, I. Samejima, N. Naumova, J. Nuebler, M.T. Kanemaki, L. Xie, J.R. Paulson, W.C. Earnshaw, L.A. Mirny, J. Dekker, A pathway for mitotic chromosome formation, Science (2018).
[44] T. Nagano, Y. Lubling, C. Varnai, C. Dudley, W. Leung, Y. Baran, N. Mendelson Cohen, S. Wingett, P. Fraser, A. Tanay, Cell-cycle dynamics of chromosomal organization at single-cell resolution, Nature 547 (7661) (2017) 61–67.
[45] T. Nozaki, R. Imai, M. Tanbo, R. Nagashima, S. Tamura, T. Tani, Y. Joti, M. Tomita, K. Hibino, M.T. Kanemaki, K.S. Wendt, Y. Okada, T. Nagai, K. Maeshima, Dynamic organization of chromatin domains revealed by super-Resolution live-cell imaging, Mol. Cell 67 (2) (2017) 282–293, e7.
[46] X. Deng, W. Ma, V. Ramani, A. Hill, F. Yang, F. Ay, J.B. Berletch, C.A. Blau, J. Shendure, Z. Duan, W.S. Noble, C.M. Disteche, Bipartite structure of the inactive mouse X chromosome, Genome Biol. 16 (2015) 152.
[47] L. Giorgetti, B.R. Lajoie, A.C. Carter, M. Attia, Y. Zhan, J. Xu, C.J. Chen, N. Kaplan, H.Y. Chang, E. Heard, J. Dekker, Structural organization of the inactive X chromosome in the mouse, Nature 535 (7613) (2016) 575–579.
[48] E.M. Darrow, M.H. Huntley, O. Dudchenko, E.K. Stamenova, N.C. Durand, Z. Sun, S.C. Huang, A.L. Sanborn, I. Machol, M. Shamim, A.P. Seberg, E.S. Lander, B.P. Chadwick, E.L. Aiden, Deletion of DXZ4 on the human inactive X chromosome alters higher-order genome architecture, Proceedings of the National Academy of Sciences of the United States of America 113 (31) (2016) E4504–E4512.
[49] N. Battulin, V.S. Fishman, A.M. Mazur, M. Pomaznoy, A.A. Khabarova, D.A. Afonnikov, E.B. Prokhortchouk, O.L. Serov, Comparison of the three-dimensional organization of sperm and fibroblast genomes using the Hi-C approach, Genome Biol. 16 (2015) 77.
[50] Y. Ke, Y. Xu, X. Chen, S. Feng, Z. Liu, Y. Sun, X. Yao, F. Li, W. Zhu, L. Gao, H. Chen, Z. Du, W. Xie, X. Xu, X. Huang, J. Liu, 3D chromatin structures of mature gametes and structural reprogramming during mammalian embryogenesis, Cell 170 (2) (2017) 367–381, e20.
[51] Z. Du, H. Zheng, B. Huang, R. Ma, J. Wu, X. Zhang, J. He, Y. Xiang, Q. Wang, Y. Li, J. Ma, X. Zhang, K. Zhang, Y. Wang, M.Q. Zhang, J. Gao, J.R. Dixon, X. Wang, J. Zeng, W. Xie, Allelic reprogramming of 3D chromatin architecture during early mammalian development, Nature 547 (7662) (2017) 232–235.
[52] T. Chandra, P.A. Ewels, S. Schoenfelder, M. Furlan-Magaril, S.W. Wingett, K. Kirschner, J.Y. Thuret, S. Andrews, P. Fraser, W. Reik, Global reorganization of the nuclear landscape in senescent cells, Cell Rep. 10 (4) (2015) 471–483.
[53] S.W. Criscione, M. De Cecco, B. Siranosian, Y. Zhang, J.A. Kreiling, J.M. Sedivy, N. Neretti, Reorganization of chromosome architecture in replicative cellular senescence, Sci. Adv. 2 (2) (2016), e1500882.
[54] A.D. Schmitt, M. Hu, I. Jung, Z. Xu, Y. Qiu, C.L. Tan, Y. Li, S. Lin, Y. Lin, C.L. Barr, B. Ren, A compendium of chromatin contact maps reveals spatially active regions in the human genome, Cell Rep. 17 (8) (2016) 2042–2059.
[55] J.R. Dixon, I. Jung, S. Selvaraj, Y. Shen, J.E. Antosiewicz-Bourget, A.Y. Lee, Z. Ye, A. Kim, N. Rajagopal, W. Xie, Y. Diao, J. Liang, H. Zhao, V.V. Lobanenkov, J.R. Ecker, J.A. Thomson, B. Ren, Chromatin architecture reorganization during stem cell differentiation, Nature 518 (7539) (2015) 331–336.
[56] J. Fraser, C. Ferrai, A.M. Chiariello, M. Schueler, T. Rito, G. Laudanno, M. Barbieri, B.L. Moore, D.C. Kraemer, S. Aitken, S.Q. Xie, K.J. Morris, M. Itoh, H. Kawaji, I. Jaeger, Y. Hayashizaki, P. Carninci, A.R. Forrest, F. Consortium, C.A. Semple, J. Dostie, A. Pombo, M. Nicodemi, Hierarchical folding and reorganization of chromosomes are linked to transcriptional changes in cellular differentiation, Mol. Syst. Biol. 11 (12) (2015) 852.
[57] J.E. Phillips-Cremins, M.E. Sauria, A. Sanyal, T.I. Gerasimova, B.R. Lajoie, J.S. Bell, C.T. Ong, T.A. Hookway, C. Guo, Y. Sun, M.J. Bland, W. Wagstaff, S. Dalton, T.C. McDevitt, R. Sen, J. Dekker, J. Taylor, V.G. Corces, Architectural protein subclasses shape 3D organization of genomes during lineage commitment, Cell 153 (6) (2013) 1281–1295.
[58] X. Ji, D.B. Dadon, B.E. Powell, Z.P. Fan, D. Borges-Rivera, S. Shachar, A.S. Weintraub, D. Hnisz, G. Pegoraro, T.I. Lee, T. Misteli, R. Jaenisch, R.A. Young, 3D chromosome regulatory landscape of human pluripotent cells, Cell Stem Cell 18 (2) (2016) 262–275.
[59] A.J. Rubin, B.C. Barajas, M. Furlan-Magaril, V. Lopez-Pajares, M.R. Mumbach, I. Howard, D.S. Kim, L.D. Boxer, J. Cairns, M. Spivakov, S.W. Wingett, M. Shi, Z. Zhao, W.J. Greenleaf, A. Kundaje, M. Snyder, H.Y. Chang, P. Fraser, P.A. Khavari, Lineage-specific dynamic and pre-established enhancer-promoter contacts cooperate in terminal differentiation, Nat. Genet. 49 (10) (2017) 1522–1528.
[60] B. Bonev, N. Mendelson Cohen, Q. Szabo, L. Fritsch, G.L. Papadopoulos, Y. Lubling, X. Xu, X. Lv, J.P. Hugnot, A. Tanay, G. Cavalli, Multiscale 3D genome rewiring during mouse neural development, Cell 171 (3) (2017) 557–572, e24.
[61] B.M. Javierre, O.S. Burren, S.P. Wilder, R. Kreuzhuber, S.M. Hill, S. Sewitz, J. Cairns, S.W. Wingett, C. Varnai, M.J. Thiecke, F. Burden, S. Farrow, A.J. Cutler, K. Rehnstrom, K. Downes, L. Grassi, M. Kostadima, P. Freire-Pritchett, F. Wang, B. Consortium, H.G. Stunnenberg, J.A. Todd, D.R. Zerbino, O. Stegle, W.H. Ouwehand, M. Frontini, C. Wallace, M. Spivakov, P. Fraser, Lineage-specific genome architecture Links enhancers and non-coding disease variants to target Gene promoters, Cell 167 (5) (2016) 1369–1384, e19.
[62] H. Won, L. de la Torre-Ubieta, J.L. Stein, N.N. Parikshak, J. Huang, C.K. Opland, M.J. Gandal, G.J. Sutton, F. Hormozdiari, D. Lu, C. Lee, E. Eskin, I. Voineagu, J. Ernst, D.H. Geschwind, Chromosome conformation elucidates regulatory relationships in developing human brain, Nature 538 (7626) (2016) 523–527.
[63] J.A. Beagan, T.G. Gilgenast, J. Kim, Z. Plona, H.K. Norton, G. Hu, S.C. Hsu, E.J. Shields, X. Lyu, E. Apostolou, K. Hochedlinger, V.G. Corces, J. Dekker, J.E. Phillips-Cremins, Local genome topology can exhibit an incompletely rewired 3D-folding State during somatic cell reprogramming, Cell Stem Cell 18 (5) (2016) 611–624.
[64] P.H. Krijger, B. Di Stefano, E. de Wit, F. Limone, C. van Oevelen, W. de Laat, T. Graf, Cell-of-origin-specific 3D genome structure acquired during somatic cell reprogramming, Cell Stem Cell 18 (5) (2016) 597–610.
[65] I.M. Flyamer, J. Gassler, M. Imakaev, H.B. Brandao, S.V. Ulianov, N. Abdennur, S.V. Razin, L.A. Mirny, K. Tachibana-Konwalski, Single-nucleus Hi-C reveals unique chromatin reorganization at oocyte-to-zygote transition, Nature 544 (7648) (2017) 110–114.
[66] J. Gassler, H.B. Brandao, M. Imakaev, I.M. Flyamer, S. Ladstatter, W.A. Bickmore, J.M. Peters, L.A. Mirny, K. Tachibana, A mechanism of cohesin-dependent loop extrusion organizes zygotic genome architecture, EMBO J. 36 (24) (2017) 3600–3618.
[67] F. Le Dily, D. Bau, A. Pohl, G.P. Vicent, F. Serra, D. Soronellas, G. Castellano, R.H. Wright, C. Ballare, G. Filion, M.A. Marti-Renom, M. Beato, Distinct structural transitions of chromatin topological domains correlate with coordinated hormone-induced gene regulation, Gene Dev. 28 (19) (2014) 2151–2162.
[68] L. Li, X. Lyu, C. Hou, N. Takenaka, H.Q. Nguyen, C.T. Ong, C. Cubenas-Potts, M. Hu, E.P. Lei, G. Bosco, Z.S. Qin, V.G. Corces, Widespread rearrangement of 3D chromatin organization underlies polycomb-mediated stress-induced silencing, Mol. Cell 58 (2) (2015) 216–231.
[69] V.S. Lioy, A. Cournac, M. Marbouty, S. Duigou, J. Mozziconacci, O. Espeli, F. Boccard, R. Koszul, Multiscale structuring of the E. coli chromosome by nucleoid-associated and condensin proteins, Cell (2018).
[70] Y. Murayama, C.P. Samora, Y. Kurokawa, H. Iwasaki, F. Uhlmann, Establishment of DNA-DNA interactions by the cohesin ring, Cell 172 (3) (2018) 465–477, e15.
[71] L.L.P. Hanssen, M.T. Kassouf, A.M. Oudelaar, D. Biggs, C. Preece, D.J. Downes, M. Gosden, J.A. Sharpe, J.A. Sloane-Stanley, J.R. Hughes, B. Davies, D.R. Higgs, Tissue-specific CTCF-cohesin-mediated chromatin architecture delimits enhancer interactions and function in vivo, Nat. Cell Biol. 19 (8) (2017) 952–961.
[72] A.R. Strom, A.V. Emelyanov, M. Mir, D.V. Fyodorov, X. Darzacq, G.H. Karpen, Phase separation drives heterochromatin domain formation, Nature 547 (7662) (2017) 241–245.
[73] A.G. Larson, D. Elnatan, M.M. Keenen, M.J. Trnka, J.B. Johnston, A.L. Burlingame, D.A. Agard, S. Redding, G.J. Narlikar, Liquid droplet formation by HP1alpha suggests a role for phase separation in heterochromatin, Nature 547 (7662) (2017) 236–240.

[74] S. Machida, Y. Takizawa, M. Ishimaru, Y. Sugita, S. Sekine, J.I. Nakayama, M. Wolf, H. Kurumizaka, Structural basis of heterochromatin formation by human HP1, Mol. Cell (2018).
[75] T. Dechat, K. Pfleghaar, K. Sengupta, T. Shimi, D.K. Shumaker, L. Solimando, R.D. Goldman, Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin, Gene Dev. 22 (7) (2008) 832–853.
[76] E. de Wit, B.A. Bouwman, Y. Zhu, P. Klous, E. Splinter, M.J. Verstegen, P.H. Krijger, N. Festuccia, E.P. Nora, M. Welling, E. Heard, N. Geijsen, R.A. Poot, I. Chambers, W. de Laat, The pluripotent genome in three dimensions is shaped around pluripotency factors, Nature 501 (7466) (2013) 227–231.
[77] R. Stadhouders, E. Vidal, F. Serra, B. Di Stefano, F. Le Dily, J. Quilez, A. Gomez, S. Collombet, C. Berenguer, Y. Cuartero, J. Hecht, G.J. Filion, M. Beato, M.A. Marti-Renom, T. Graf, Transcription factors orchestrate dynamic interplay between genome topology and gene regulation during cell reprogramming, Nat. Genet. (2018).
[78] J.A. Beagan, M.T. Duong, K.R. Titus, L. Zhou, Z. Cao, J. Ma, C.V. Lachanski, D.R. Gillis, J.E. Phillips-Cremins, YY1 and CTCF orchestrate a 3D chromatin looping switch during early neural lineage commitment, Genome Res. 27 (7) (2017) 1139–1152.
[79] A.S. Weintraub, C.H. Li, A.V. Zamudio, A.A. Sigova, N.M. Hannett, D.S. Day, B.J. Abraham, M.A. Cohen, B. Nabet, D.L. Buckley, Y.E. Guo, D. Hnisz, R. Jaenisch, J.E. Bradner, N.S. Gray, R.A. Young, YY1 Is a structural regulator of enhancer-promoter loops, Cell 171 (7) (2017) 1573–1588, e28.
[80] S. Cai, C.C. Lee, T. Kohwi-Shigematsu, SATB1 packages densely looped, transcriptionally active chromatin for coordinated expression of cytokine genes, Nat. Genet. 38 (11) (2006) 1278–1288.
[81] G. Dobreva, J. Dambacher, R. Grosschedl, SUMO modification of a novel MAR-binding protein, SATB2, modulates immunoglobulin mu gene expression, Gene Dev. 17 (24) (2003) 3048–3061.
[82] M. Entrevan, B. Schuettengruber, G. Cavalli, Regulation of genome architecture and function by polycomb proteins, Trends Cell Biol. 26 (7) (2016) 511–525.
[83] M.H. Kagey, J.J. Newman, S. Bilodeau, Y. Zhan, D.A. Orlando, N.L. van Berkum, C.C. Ebmeier, J. Goossens, P.B. Rahl, S.S. Levine, D.J. Taatjes, J. Dekker, R.A. Young, Mediator and cohesin connect gene expression and chromatin architecture, Nature 467 (7314) (2010) 430–435.
[84] J.T. Lee, Epigenetic regulation by long noncoding RNAs, Science 338 (6113) (2012) 1435–1439.
[85] E. Hacisuleyman, L.A. Goff, C. Trapnell, A. Williams, J. Henao-Mejia, L. Sun, P. McClanahan, D.G. Hendrickson, M. Sauvageau, D.R. Kelley, M. Morse, J. Engreitz, E.S. Lander, M. Guttman, H.F. Lodish, R. Flavell, A. Raj, J.L. Rinn, Topological organization of multichromosomal regions by the long intergenic noncoding RNA firre, Nat. Struct. Mol. Biol. 21 (2) (2014) 198–206.
[86] F. Yang, X. Deng, W. Ma, J.B. Berletch, N. Rabaia, G. Wei, J.M. Moore, G.N. Filippova, J. Xu, Y. Liu, W.S. Noble, J. Shendure, C.M. Disteche, The lncRNA firre anchors the inactive X chromosome to the nucleolus by binding CTCF and maintains H3K27me3 methylation, Genome Biol. 16 (2015) 52.
[87] K.C. Wang, Y.W. Yang, B. Liu, A. Sanyal, R. Corces-Zimmerman, Y. Chen, B.R. Lajoie, A. Protacio, R.A. Flynn, R.A. Gupta, J. Wysocka, M. Lei, J. Dekker, J.A. Helms, H.Y. Chang, A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression, Nature 472 (7341) (2011) 120–124.
[88] T. Isoda, A.J. Moore, Z. He, V. Chandra, M. Aida, M. Denholtz, J. Piet van Hamburg, K.M. Fisch, A.N. Chang, S.P. Fahl, D.L. Wiest, C. Murre, Non-coding transcription instructs chromatin folding and compartmentalization to dictate enhancer-promoter communication and T cell fate, Cell 171 (1) (2017) 103–119, e18.
[89] J.E. Phillips, V.G. Corces, CTCF: master weaver of the genome, Cell 137 (7) (2009) 1194–1211.
[90] B. Bonev, G. Cavalli, Organization and function of the 3D genome, nature reviews, Genetics 17 (11) (2016) 661–678.
[91] H.K. Norton, J.E. Phillips-Cremins, Crossed wires: 3D genome misfolding in human disease, J. Cell Biol. 216 (11) (2017) 3441–3452.
[92] S.S.P. Rao, S.C. Huang, B. Glenn St Hilaire, J.M. Engreitz, E.M. Perez, K.R. Kieffer-Kwon, A.L. Sanborn, S.E. Johnstone, G.D. Bascom, I.D. Bochkov, X. Huang, M.S. Shamim, J. Shin, D. Turner, Z. Ye, A.D. Omer, J.T. Robinson, T. Schlick, B.E. Bernstein, R. Casellas, E.S. Lander, E.L. Aiden, Cohesin loss eliminates all loop domains, Cell 171 (2) (2017) 305–320, e24.
[93] W. Schwarzer, N. Abdennur, A. Goloborodko, A. Pekowska, G. Fudenberg, Y. Loe-Mie, N.A. Fonseca, W. Huber, H.H.C.L. Mirny, F. Spitz, Two independent modes of chromatin organization revealed by cohesin removal, Nature 551 (7678) (2017) 51–56.
[94] E.P. Nora, A. Goloborodko, A.L. Valton, J.H. Gibcus, A. Uebersohn, N. Abdennur, J. Dekker, L.A. Mirny, B.G. Bruneau, Targeted degradation of CTCF decouples local insulation of chromosome domains from genomic compartmentalization, Cell 169 (5) (2017) 930–944, e22.
[95] J.H.I. Haarhuis, R.H. van der Weide, V.A. Blomen, J.O. Yanez-Cuna, M. Amendola, M.S. van Ruiten, P.H.L. Krijger, H. Teunissen, R.H. Medema, B. van Steensel, T.R. Brummelkamp, E. de Wit, B.D. Rowland, The cohesin release factor WAPL restricts chromatin loop extension, Cell 169 (4) (2017) 693–707, e14.
[96] G.A. Busslinger, R.R. Stocsits, P. van der Lelij, E. Axelsson, A. Tedeschi, N. Galjart, J.M. Peters, Cohesin is positioned in mammalian genomes by transcription, CTCF Wapl. Nat. 544 (7651) (2017) 503–507.
[97] A.L. Sanborn, S.S. Rao, S.C. Huang, N.C. Durand, M.H. Huntley, A.I. Jewett, I.D. Bochkov, D. Chinnappan, A. Cutkosky, J. Li, K.P. Geeting, A. Gnirke, A. Melnikov, D. McKenna, E.K. Stamenova, E.S. Lander, E.L. Aiden, Chromatin extrusion explains key features of loop and domain formation in wild-type and engineered genomes, Proc. Natl. Acad. Sci. U. S. A. 112 (47) (2015) E6456–E6465.
[98] E. Alipour, J.F. Marko, Self-organization of domain structures by DNA-loop-extruding enzymes, Nucleic Acids Res. 40 (22) (2012) 11202–11212.
[99] G. Fudenberg, M. Imakaev, C. Lu, A. Goloborodko, N. Abdennur, L.A. Mirny, Formation of chromosomal domains by loop extrusion, Cell Rep. 15 (9) (2016) 2038–2049.
[100] T. Terakawa, S. Bisht, J.M. Eeftens, C. Dekker, C.H. Haering, E.C. Greene, The condensin complex is a mechanochemical motor that translocates along DNA, Science 358 (6363) (2017) 672–676.
[101] M. Ganji, I.A. Shaltiel, S. Bisht, E. Kim, A. Kalichava, C.H. Haering, C. Dekker, Real-time imaging of DNA loop extrusion by condensin, Science (2018).
[102] E. de Wit, E.S. Vos, S.J. Holwerda, C. Valdes-Quezada, M.J. Verstegen, H. Teunissen, E. Splinter, P.J. Wijchers, P.H. Krijger, W. de Laat, CTCF binding polarity determines chromatin looping, Mol. Cell 60 (4) (2015) 676–684.
[103] Y. Guo, Q. Xu, D. Canzio, J. Shou, J. Li, D.U. Gorkin, I. Jung, H. Wu, Y. Zhai, Y. Tang, Y. Lu, Y. Wu, Z. Jia, W. Li, M.Q. Zhang, B. Ren, A.R. Krainer, T. Maniatis, Q. Wu, CRISPR inversion of CTCF sites alters genome topology and Enhancer/Promoter function, Cell 162 (4) (2015) 900–910.
[104] Z. Tang, O.J. Luo, X. Li, M. Zheng, J.J. Zhu, P. Szalaj, P. Trzaskoma, A. Magalska, J. Wlodarczyk, B. Ruszczycki, P. Michalski, E. Piecuch, P. Wang, D. Wang, S.Z. Tian, M. Penrad-Mobayed, L.M. Sachs, X. Ruan, C.L. Wei, E.T. Liu, G.M. Wilczynski, D. Plewczynski, G. Li, Y. Ruan, CTCF-mediated human 3D genome architecture reveals chromatin topology for transcription, Cell 163 (7) (2015) 1611–1627.
[105] D. Vermaak, H.S. Malik, Multiple roles for heterochromatin protein 1 genes in drosophila, Annu. Rev. Genet. 43 (2009) 467–492.
[106] C. Chu, K. Qu, F.L. Zhong, S.E. Artandi, H.Y. Chang, Genomic maps of long noncoding RNA occupancy reveal principles of RNA-chromatin interactions, Mol. Cell 44 (4) (2011) 667–678.
[107] M.D. Simon, C.I. Wang, P.V. Kharchenko, J.A. West, B.A. Chapman, A.A. Alekseyenko, M.L. Borowsky, M.I. Kuroda, R.E. Kingston, The genomic binding sites of a noncoding RNA, PNAS 108 (51) (2011) 20497–20502.
[108] J.M. Engreitz, A. Pandya-Jones, P. McDonel, A. Shishkin, K. Sirokman, C. Surka, S. Kadri, J. Xing, A. Goren, E.S. Lander, K. Plath, M. Guttman, The Xist lncRNA exploits three-dimensional genome architecture to spread across the X chromosome, Science 341 (6147) (2013), 1237973.
[109] B. Sridhar, M. Rivas-Astroza, T.C. Nguyen, W. Chen, Z. Yan, X. Cao, L. Hebert, S. Zhong, Systematic mapping of RNA-chromatin interactions in vivo, Curr. Biol. CB 27 (4) (2017) 602–609.
[110] X. Li, B. Zhou, L. Chen, L.T. Gou, H. Li, X.D. Fu, GRID-seq reveals the global RNA-chromatin interactome, Nat. Biotechnol. 35 (10) (2017) 940–950.
[111] C.K. Chen, M. Blanco, C. Jackson, E. Aznauryan, N. Ollikainen, C. Surka, A. Chow, A. Cerase, P. McDonel, M. Guttman, Xist recruits the X chromosome to the nuclear lamina to enable chromosome-wide silencing, Science (2016).
[112] E. Splinter, E. de Wit, E.P. Nora, P. Klous, H.J. van de Werken, Y. Zhu, L.J. Kaaij, W. van Ijcken, J. Gribnau, E. Heard, W. de Laat, The inactive X chromosome adopts a unique three-dimensional conformation that is dependent on Xist RNA, Gene Dev. 25 (13) (2011) 1371–1383.
[113] T. Jegu, E. Aeby, J.T. Lee, The X chromosome in space, Nat. Rev. Genet. 18 (6) (2017) 377–389.
[114] C.B. Hug, A.G. Grimaldi, K. Kruse, J.M. Vaquerizas, Chromatin architecture emerges during zygotic genome activation independent of transcription, Cell 169 (2) (2017) 216–228, e19.
[115] L. Chakalova, P. Fraser, Organization of transcription, Cold Spring Harbor Perspect. Biol. 2 (9) (2010), a000729.
[116] T. Sexton, E. Yaffe, E. Kenigsberg, F. Bantignies, B. Leblanc, M. Hoichman, H. Parrinello, A. Tanay, G. Cavalli, Three-dimensional folding and functional organization principles of the Drosophila genome, Cell 148 (3) (2012) 458–472.
[117] C. Zimmer, E. Fabre, Principles of chromosomal organization: lessons from yeast, J. Cell Biol. 192 (5) (2011) 723–733.
[118] P.J. Wijchers, P.H. Krijger, G. Geeven, Y. Zhu, A. Denker, M.J. Verstegen, C. Valdes-Quezada, C. Vermeulen, M. Janssen, H. Teunissen, L.C. Anink-Groenen, P.J. Verschure, W. de Laat, Cause and consequence of tethering a SubTAD to different nuclear compartments, Mol. Cell 61 (3) (2016) 461–473.
[119] J. Kind, L. Pagie, S.S. de Vries, L. Nahidiazar, S.S. Dey, M. Bienko, Y. Zhan, B. Lajoie, C.A. de Graaf, M. Amendola, G. Fudenberg, M. Imakaev, L.A. Mirny, K. Jalink, J. Dekker, A. van Oudenaarden, B. van Steensel, Genome-wide maps of nuclear lamina interactions in single human cells, Cell 163 (1) (2015) 134–147.
[120] J. Kind, L. Pagie, H. Ortabozkoyun, S. Boyle, S.S. de Vries, H. Janssen, M. Amendola, L.D. Nolen, W.A. Bickmore, B. van Steensel, Single-cell dynamics of genome-nuclear lamina interactions, Cell 153 (1) (2013) 178–192.
[121] M.I. Robson, J.I. de Las Heras, R. Czapiewski, P.Le Thanh, D.G. Booth, D.A. Kelly, S. Webb, A.R. Kerr, E.C. Schirmer, Tissue-specific gene repositioning by muscle nuclear membrane proteins enhances repression of critical developmental genes during myogenesis, Mol. Cell 62 (6) (2016) 834–847.
[122] F. Jin, Y. Li, J.R. Dixon, S. Selvaraj, Z. Ye, A.Y. Lee, C.A. Yen, A.D. Schmitt, C.A. Espinoza, B. Ren, A high-resolution map of the three-dimensional chromatin interactome in human cells, Nature 503 (7475) (2013) 290–294.

[123] W. Ma, F. Ay, C. Lee, G. Gulsoy, X. Deng, S. Cook, J. Hesson, C. Cavanaugh, C.B. Ware, A. Krumm, J. Shendure, C.A. Blau, C.M. Disteche, W.S. Noble, Z. Duan, Fine-scale chromatin interaction maps reveal the cis-regulatory landscape of human lincRNA genes, Nat. Methods 12 (1) (2015) 71–78.
[124] O. Symmons, L. Pan, S. Remeseiro, T. Aktas, F. Klein, W. Huber, F. Spitz, The Shh topological domain facilitates the action of remote enhancers by reducing the effects of genomic distances, Dev. Cell 39 (5) (2016) 529–543.
[125] W.A. Flavahan, Y. Drier, B.B. Liau, S.M. Gillespie, A.S. Venteicher, A.O. Stemmer-Rachamimov, M.L. Suva, B.E. Bernstein, Insulator dysfunction and oncogene activation in IDH mutant gliomas, Nature (2015).
[126] D.G. Lupianez, K. Kraft, V. Heinrich, P. Krawitz, F. Brancati, E. Klopocki, D. Horn, H. Kayserili, J.M. Opitz, R. Laxova, F. Santos-Simarro, B. Gilbert-Dussardier, L. Wittler, M. Borschiwer, S.A. Haas, M. Osterwalder, M. Franke, B. Timmermann, J. Hecht, M. Spielmann, A. Visel, S. Mundlos, Disruptions of topological chromatin domains cause pathogenic rewiring of gene-enhancer interactions, Cell 161 (5) (2015) 1012–1025.
[127] V. Dileep, F. Ay, J. Sima, D.L. Vera, W.S. Noble, D.M. Gilbert, Topologically associating domains and their long-range contacts are established during early G1 coincident with the establishment of the replication-timing program, Genome Res. 25 (8) (2015) 1104–1113.
[128] B.D. Pope, T. Ryba, V. Dileep, F. Yue, W. Wu, O. Denas, D.L. Vera, Y. Wang, R.S. Hansen, T.K. Canfield, R.E. Thurman, Y. Cheng, G. Gulsoy, J.H. Dennis, M.P. Snyder, J.A. Stamatoyannopoulos, J. Taylor, R.C. Hardison, T. Kahveci, B. Ren, D.M. Gilbert, Topologically associating domains are stable units of replication-timing regulation, Nature 515 (7527) (2014) 402–405.
[129] S. Kadauke, G.A. Blobel, Chromatin loops in gene regulation, Biochim. Biophys. Acta 1789 (1) (2009) 17–25.
[130] L.A. Pennacchio, W. Bickmore, A. Dean, M.A. Nobrega, G. Bejerano, Enhancers: five essential questions, nature reviews, Genetics 14 (4) (2013) 288–295.
[131] M. Bulger, M. Groudine, Functional and mechanistic diversity of distal transcription enhancers, Cell 144 (3) (2011) 327–339.
[132] J. Dekker, T. Misteli, Long-range chromatin interactions, Cold Spring Harbor Perspect. Biol. 7 (10) (2015).
[133] W. Deng, J. Lee, H. Wang, J. Miller, A. Reik, P.D. Gregory, A. Dean, G.A. Blobel, Controlling long-range genomic interactions at a native locus by targeted tethering of a looping factor, Cell 149 (6) (2012) 1233–1244.
[134] W. Deng, J.W. Rupon, I. Krivega, L. Breda, I. Motta, K.S. Jahn, A. Reik, P.D. Gregory, S. Rivella, A. Dean, G.A. Blobel, Reactivation of developmentally silenced globin genes by forced chromatin looping, Cell 158 (4) (2014) 849–860.
[135] J.M. Engreitz, V. Agarwala, L.A. Mirny, Three-dimensional genome architecture influences partner selection for chromosomal translocations in human disease, PloS One 7 (9) (2012), e44196.
[136] R.S. Mani, S.A. Tomlins, K. Callahan, A. Ghosh, M.K. Nyati, S. Varambally, N. Palanisamy, A.M. Chinnaiyan, Induced chromosomal proximity and gene fusions in prostate cancer, Science 326 (5957) (2009) 1230.
[137] M.N. Nikiforova, J.R. Stringer, R. Blough, M. Medvedovic, J.A. Fagin, Y.E. Nikiforov, Proximity of chromosomal loci that participate in radiation-induced rearrangements in human cells, Science 290 (5489) (2000) 138–141.
[138] J.J. Roix, P.G. McQueen, P.J. Munson, L.A. Parada, T. Misteli, Spatial proximity of translocation-prone gene loci in human lymphomas, Nat. Genet. 34 (3) (2003) 287–291.
[139] Y. Zhang, R.P. McCord, Y.J. Ho, B.R. Lajoie, D.G. Hildebrand, A.C. Simon, M.S. Becker, F.W. Alt, J. Dekker, Spatial organization of the mouse genome and its role in recurrent chromosomal translocations, Cell 148 (5) (2012) 908–921.
[140] O. Hakim, W. Resch, A. Yamane, I. Klein, K.R. Kieffer-Kwon, M. Jankovic, T. Oliveira, A. Bothmer, T.C. Voss, C. Ansarah-Sobrinho, E. Mathe, G. Liang, J. Cobell, H. Nakahashi, D.F. Robbiani, A. Nussenzweig, G.L. Hager, M.C. Nussenzweig, R. Casellas, DNA damage defines sites of recurrent chromosomal translocations in B lymphocytes, Nature 484 (7392) (2012) 69–74.
[141] H. Li, J. Wang, G. Mor, J. Sklar, A neoplastic gene fusion mimics trans-splicing of RNAs in normal human cells, Science 321 (5894) (2008) 1357–1361.
[142] D.S. Rickman, D. Pflueger, B. Moss, V.E. VanDoren, C.X. Chen, A. de la Taille, R. Kuefer, A.K. Tewari, S.R. Setlur, F. Demichelis, M.A. Rubin, SLC45A3-ELK4 is a novel and frequent erythroblast transformation-specific fusion transcript in prostate cancer, Cancer Res. 69 (7) (2009) 2734–2738.
[143] G. McVicker, B. van de Geijn, J.F. Degner, C.E. Cain, N.E. Banovich, A. Raj, N. Lewellen, M. Myrthil, Y. Gilad, J.K. Pritchard, Identification of genetic variants that affect histone modifications in human cells, Science 342 (6159) (2013) 747–749.
[144] S.M. Waszak, O. Delaneau, A.R. Gschwind, H. Kilpinen, S.K. Raghav, R.M. Witwicki, A. Orioli, M. Wiederkehr, N.I. Panousis, A. Yurovsky, L. Romano-Palumbo, A. Planchon, D. Bielser, I. Padioleau, G. Udin, S. Thurnheer, D. Hacker, N. Hernandez, A. Reymond, B. Deplancke, E.T. Dermitzakis, Population variation and genetic control of modular chromatin architecture in humans, Cell 162 (5) (2015) 1039–1050.
[145] F. Grubert, J.B. Zaugg, M. Kasowski, O. Ursu, D.V. Spacek, A.R. Martin, P. Greenside, R. Srivas, D.H. Phanstiel, A. Pekowska, N. Heidari, G. Euskirchen, W. Huber, J.K. Pritchard, C.D. Bustamante, L.M. Steinmetz, A. Kundaje, M. Snyder, Genetic control of chromatin States in humans involves local and distal chromosomal interactions, Cell 162 (5) (2015) 1051–1065.
[146] M.R. Mumbach, A.T. Satpathy, E.A. Boyle, C. Dai, B.G. Gowen, S.W. Cho, M.L. Nguyen, A.J. Rubin, J.M. Granja, K.R. Kazane, Y. Wei, T. Nguyen, P.G. Greenside, M.R. Corces, J. Tycko, D.R. Simeonov, N. Suliman, R. Li, J. Xu, R.A. Flynn, A. Kundaje, P.A. Khavari, A. Marson, J.E. Corn, T. Quertermous, W.J. Greenleaf, H.Y. Chang, Enhancer connectome in primary human cells identifies target genes of disease-associated DNA elements, Nat. Genet. 49 (11) (2017) 1602–1612.
[147] S. Shachar, T. Misteli, Causes and consequences of nuclear gene positioning, J. Cell Sci. 130 (9) (2017) 1501–1508.
[148] M. Cremer, K. Kupper, B. Wagler, L. Wizelman, J. von Hase, Y. Weiland, L. Kreja, J. Diebold, M.R. Speicher, T. Cremer, Inheritance of gene density-related higher order chromatin arrangements in normal and tumor cell nuclei, J. Cell Biol. 162 (5) (2003) 809–820.
[149] M. Leshner, M. Devine, G.W. Roloff, L.D. True, T. Misteli, K.J. Meaburn, Locus-specific gene repositioning in prostate cancer, Mol. Biol. Cell 27 (2) (2016) 236–246.
[150] K.J. Meaburn, P.R. Gudla, S. Khan, S.J. Lockett, T. Misteli, Disease-specific gene repositioning in breast cancer, J. Cell Biol. 187 (6) (2009) 801–812.
[151] K.J. Meaburn, T. Misteli, Locus-specific and activity-independent gene repositioning during early tumorigenesis, J. Cell Biol. 180 (1) (2008) 39–50.
[152] S. De, F. Michor, DNA replication timing and long-range DNA interactions predict mutational landscapes of cancer genomes, Nat. Biotechnol. 29 (12) (2011) 1103–1108.
[153] G. Fudenberg, G. Getz, M. Meyerson, L.A. Mirny, High order chromatin architecture shapes the landscape of chromosomal alterations in cancer, Nat. Biotechnol. 29 (12) (2011) 1109–1113.
[154] B. Schuster-Bockler, B. Lehner, Chromatin organization is a major influence on regional mutation rates in human cancer cells, Nature 488 (7412) (2012) 504–507.
[155] K.S. Smith, L.L. Liu, S. Ganesan, F. Michor, S. De, Nuclear topology modulates the mutational landscapes of cancer genomes, Nat. Struct. Mol. Biol. 24 (11) (2017) 1000–1006.
[156] K.D. Makova, R.C. Hardison, The effects of chromatin organization on variation in mutation rates in the genome, nature reviews, Genetics 16 (4) (2015) 213–223.
[157] M. Spielmann, S. Mundlos, Looking beyond the genes: the role of non-coding variants in human disease, Hum. Mol. Genet. 25 (R2) (2016) R157–R165.
[158] C.A. Meddens, M. Harakalova, N.A. van den Dungen, H. Foroughi Asl, H.J. Hijma, E.P. Cuppen, J.L. Bjorkegren, F.W. Asselbergs, E.E. Nieuwenhuis, M. Mokry, Systematic analysis of chromatin interactions at disease associated loci links novel candidate genes to inflammatory bowel disease, Genome Biol. 17 (1) (2016) 247.
[159] M.M. Brandt, C.A. Meddens, L. Louzao-Martinez, N.A.M. van den Dungen, N.R. Lansu, E.E.S. Nieuwenhuis, D.J. Duncker, M.C. Verhaar, J.A. Joles, M. Mokry, C. Cheng, Chromatin conformation links distal target genes to CKD loci, J. Am. Soc. Nephrol. JASN (2017).
[160] S. Haitjema, C.A. Meddens, S.W. van der Laan, D. Kofink, M. Harakalova, V. Tragante, H. Foroughi Asl, J. van Setten, M.M. Brandt, J.C. Bis, C. O'Donnell, C. Cheng, I.E. Hoefer, J. Waltenberger, E. Biessen, J.W. Jukema, P.A. Doevendans, E.E. Nieuwenhuis, J. Erdmann, J.L. Bjorkegren, G. Pasterkamp, F.W. Asselbergs, H.M. den Ruijter, M. Mokry, Additional candidate genes for human atherosclerotic disease identified through annotation based on chromatin organization, Circulation Cardiovasc. Genet. 10 (2) (2017).
[161] O.S. Burren, A. Rubio Garcia, B.M. Javierre, D.B. Rainbow, J. Cairns, N.J. Cooper, J.J. Lambourne, E. Schofield, X. Castro Dopico, R.C. Ferreira, R. Coulson, F. Burden, S.P. Rowlston, K. Downes, S.W. Wingett, M. Frontini, W.H. Ouwehand, P. Fraser, M. Spivakov, J.A. Todd, L.S. Wicker, A.J. Cutler, C. Wallace, Chromosome contacts in activated T cells identify autoimmune disease candidate genes, Genome Biol. 18 (1) (2017) 165.
[162] M. Du, L. Tillmans, J. Gao, P. Gao, T. Yuan, R.L. Dittmar, W. Song, Y. Yang, N. Sahr, T. Wang, G.H. Wei, S.N. Thibodeau, L. Wang, Chromatin interactions and candidate genes at ten prostate cancer risk loci, Sci. Rep. 6 (2016) 23202.
[163] M. Du, T. Yuan, K.F. Schilter, R.L. Dittmar, A. Mackinnon, X. Huang, M. Tschannen, E. Worthey, H. Jacob, S. Xia, J. Gao, L. Tillmans, Y. Lu, P. Liu, S.N. Thibodeau, L. Wang, Prostate cancer risk locus at 8q24 as a regulatory hub by physical interactions with multiple genomic loci across the genome, Hum. Mol. Genet. 24 (1) (2015) 154–166.
[164] K. Kim, K. Jang, W. Yang, E.Y. Choi, S.M. Park, M. Bae, Y.J. Kim, J.K. Choi, Chromatin structure-based prediction of recurrent noncoding mutations in cancer, Nat. Genet. 48 (11) (2016) 1321–1326.
[165] L.A. Lettice, S. Daniels, E. Sweeney, S. Venkataraman, P.S. Devenney, P. Gautier, H. Morrison, J. Fantes, R.E. Hill, D.R. FitzPatrick, Enhancer-adoption as a mechanism of human developmental disease, Hum. Mutat. 32 (12) (2011) 1492–1499.
[166] J. Ibn-Salem, S. Kohler, M.I. Love, H.R. Chung, N. Huang, M.E. Hurles, M. Haendel, N.L. Washington, D. Smedley, C.J. Mungall, S.E. Lewis, C.E. Ott, S. Bauer, P.N. Schofield, S. Mundlos, M. Spielmann, P.N. Robinson, Deletions of chromosomal regulatory boundaries are associated with congenital disease, Genome Biol. 15 (9) (2014) 423.
[167] P.A. Northcott, C. Lee, T. Zichner, A.M. Stutz, S. Erkek, D. Kawauchi, D.J. Shih, V. Hovestadt, M. Zapatka, D. Sturm, D.T. Jones, M. Kool, M. Remke, F.M. Cavalli, S. Zuyderduyn, G.D. Bader, S. VandenBerg, L.A. Esparza, M. Ryzhova, W. Wang, A. Wittmann, S. Stark, L. Sieber, H. Seker-Cin, L. Linke, F. Kratochwil, N. Jager, I. Buchhalter, C.D. Imbusch, G. Zipprich, B. Raeder, S. Schmidt, N. Diessl, S. Wolf, S. Wiemann, B. Brors, C. Lawerenz, J. Eils, H.J. Warnatz, T. Risch, M.L. Yaspo, U.D. Weber, C.C. Bartholomae, C. von Kalle, E. Turanyi, P. Hauser, E. Sanden, A. Darabi, P. Siesjo, J. Sterba, K. Zitterbart, D. Sumerauer, P. van Sluis, R. Versteeg, R. Volckmann, J. Koster, M.U.

Schuhmann, M. Ebinger, H.L. Grimes, G.W. Robinson, A. Gajjar, M. Mynarek, K. von Hoff, S. Rutkowski, T. Pietsch, W. Scheurlen, J. Felsberg, G. Reifenberger, A.E. Kulozik, A. von Deimling, O. Witt, R. Eils, R.J. Gilbertson, A. Korshunov, M.D. Taylor, P. Lichter, J.O. Korbel, R.J. Wechsler-Reya, S.M. Pfister, Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma, Nature 511 (7510) (2014) 428–434.
[168] M. Yu, B. Ren, The Three-dimensional organization of mammalian genomes, Annu. Rev. Cell Dev. Biol. 33 (2017) 265–289.
[169] A.L. Valton, J. Dekker, TAD disruption as oncogenic driver, Curr. Opin. Genet. Dev. 36 (2016) 34–40.
[170] D.G. Lupianez, M. Spielmann, S. Mundlos, Breaking TADs: how alterations of chromatin domains result in disease, Trends in genetics : TIG 32 (4) (2016) 225–237.
[171] V.B. Kaiser, C.A. Semple, When TADs go bad: chromatin structure and nuclear organisation in human disease, 6, F1000 Research, 2017.
[172] D.G. Lupianez, K. Kraft, V. Heinrich, P. Krawitz, F. Brancati, E. Klopocki, D. Horn, H. Kayserili, J.M. Opitz, R. Laxova, F. Santos-Simarro, B. Gilbert-Dussardier, L. Wittler, M. Borschiwer, S.A. Haas, M. Osterwalder, M. Franke, B. Timmermann, J. Hecht, M. Spielmann, A. Visel, S. Mundlos, Disruptions of topological chromatin domains cause pathogenic rewiring of gene-enhancer interactions, Cell 161 (5) (2015) 1012–1025.
[173] R. Katainen, K. Dave, E. Pitkanen, K. Palin, T. Kivioja, N. Valimaki, A.E. Gylfe, H. Ristolainen, U.A. Hanninen, T. Cajuso, J. Kondelin, T. Tanskanen, J.P. Mecklin, H. Jarvinen, L. Renkonen-Sinisalo, A. Lepisto, E. Kaasinen, O. Kilpivaara, S. Tuupanen, M. Enge, J. Taipale, L.A. Aaltonen, CTCF/cohesin-binding sites are frequently mutated in cancer, Nat. Genet. 47 (7) (2015) 818–821.
[174] W.A. Flavahan, Y. Drier, B.B. Liau, S.M. Gillespie, A.S. Venteicher, A.O. Stemmer-Rachamimov, M.L. Suva, B.E. Bernstein, Insulator dysfunction and oncogene activation in IDH mutant gliomas, Nature 529 (7584) (2016) 110–114.
[175] E. Giorgio, D. Robyr, M. Spielmann, E. Ferrero, E. Di Gregorio, D. Imperiale, G. Vaula, G. Stamoulis, F. Santoni, C. Atzori, L. Gasparini, D. Ferrera, C. Canale, M. Guipponi, L.A. Pennacchio, S.E. Antonarakis, A. Brussino, A. Brusco, A large genomic deletion leads to enhancer adoption by the lamin B1 gene: a second path to autosomal dominant adult-onset demyelinating leukodystrophy (ADLD), Hum. Mol. Genet. 24 (11) (2015) 3143–3154.
[176] M. Franke, D.M. Ibrahim, G. Andrey, W. Schwarzer, V. Heinrich, R. Schopflin, K. Kraft, R. Kempfer, I. Jerkovic, W.L. Chan, M. Spielmann, B. Timmermann, L. Wittler, I. Kurth, P. Cambiaso, O. Zuffardi, G. Houge, L. Lambie, F. Brancati, A. Pombo, M. Vingron, F. Spitz, S. Mundlos, Formation of new chromatin domains determines pathogenicity of genomic duplications, Nature 538 (7624) (2016) 265–269.
[177] S. Groschel, M.A. Sanders, R. Hoogenboezem, E. de Wit, B.A.M. Bouwman, C. Erpelinck, V.H.J. van der Velden, M. Havermans, R. Avellino, K. van Lom, E.J. Rombouts, M. van Duin, K. Dohner, H.B. Beverloo, J.E. Bradner, H. Dohner, B. Lowenberg, P.J.M. Valk, E.M.J. Bindels, W. de Laat, R. Delwel, A single oncogenic enhancer rearrangement causes concomitant EVI1 and GATA2 deregulation in leukemia, Cell 157 (2) (2014) 369–381.
[178] J. Weischenfeldt, T. Dubash, A.P. Drainas, B.R. Mardin, Y. Chen, A.M. Stutz, S.M. Waszak, G. Bosco, A.R. Halvorsen, B. Raeder, T. Efthymiopoulos, S. Erkek, C. Siegl, H. Brenner, O.T. Brustugun, S.M. Dieter, P.A. Northcott, I. Petersen, S.M. Pfister, M. Schneider, S.K. Solberg, E. Thunissen, W. Weichert, T. Zichner, R. Thomas, M. Peifer, A. Helland, C.R. Ball, M. Jechlinger, R. Sotillo, H. Glimm, J.O. Korbel, Pan-cancer analysis of somatic copy-number alterations implicates IRS4 and IGF2 in enhancer hijacking, Nat. Genet. 49 (1) (2017) 65–74.
[179] C. Redin, H. Brand, R.L. Collins, T. Kammin, E. Mitchell, J.C. Hodge, C. Hanscom, V. Pillalamarri, C.M. Seabra, M.A. Abbott, O.A. Abdul-Rahman, E. Aberg, R. Adley, S.L. Alcaraz-Estrada, F.S. Alkuraya, Y. An, M.A. Anderson, C. Antolik, K. Anyane-Yeboa, J.F. Atkin, T. Bartell, J.A. Bernstein, E. Beyer, I. Blumenthal, E.M. Bongers, E.H. Brilstra, C.W. Brown, H.T. Bruggenwirth, B. Callewaert, C. Chiang, K. Corning, H. Cox, E. Cuppen, B.B. Currall, T. Cushing, D. David, M.A. Deardorff, A. Dheedene, M. D'Hooghe, B.B. de Vries, D.L. Earl, H.L. Ferguson, H. Fisher, D.R. FitzPatrick, P. Gerrol, D. Giachino, J.T. Glessner, T. Gliem, M. Grady, B.H. Graham, C. Griffis, K.W. Gripp, A.L. Gropman, A. Hanson-Kahn, D.J. Harris, M.A. Hayden, R. Hill, R. Hochstenbach, J.D. Hoffman, R.J. Hopkin, M.W. Hubshman, A.M. Innes, M. Irons, M. Irving, J.C. Jacobsen, S. Janssens, T. Jewett, J.P. Johnson, M.C. Jongmans, S.G. Kahler, D.A. Koolen, J. Korzelius, P.M. Kroisel, Y. Lacassie, W. Lawless, E. Lemyre, K. Leppig, A.V. Levin, H. Li, H. Li, E.C. Liao, C. Lim, E.J. Lose, D. Lucente, M.J. Macera, P. Manavalan, G. Mandrile, C.L. Marcelis, L. Margolin, T. Mason, D. Masser-Frye, M.W. McClellan, C.J. Mendoza, B. Menten, S. Middelkamp, L.R. Mikami, E. Moe, S. Mohammed, T. Mononen, M.E. Mortenson, G. Moya, A.W. Nieuwint, Z. Ordulu, S. Parkash, S.P. Pauker, S. Pereira, D. Perrin, K. Phelan, R.E. Aguilar, P.J. Poddighe, G. Pregno, S. Raskin, L. Reis, W. Rhead, D. Rita, I. Renkens, F. Roelens, J. Ruliera, P. Rump, S.L. Schilit, R. Shaheen, R. Sparkes, E. Spiegel, B. Stevens, M.R. Stone, J. Tagoe, J.V. Thakuria, B.W. van Bon, J. van de Kamp, I. van Der Burgt, T. van Essen, C.M. van Ravenswaaij-Arts, M.J. van Roosmalen, S. Vergult, C.M. Volker-Touw, D.P. Warburton, M.J. Waterman, S. Wiley, A. Wilson, M.C. Yerena-de Vega, R.T. Zori, B. Levy, H.G. Brunner, N. de Leeuw, W.P. Kloosterman, E.C. Thorland, C.C. Morton, J.F. Gusella, M.E. Talkowski, The genomic landscape of balanced cytogenetic abnormalities associated with human congenital anomalies, Nat. Genet. 49 (1) (2017) 36–45.
[180] V.B. Kaiser, M.S. Taylor, C.A. Semple, Mutational biases drive elevated rates of substitution at regulatory sites across cancer types, PLos Genet. 12 (8) (2016), e1006207.
[181] D. Hnisz, A.S. Weintraub, D.S. Day, A.L. Valton, R.O. Bak, C.H. Li, J. Goldmann, B.R. Lajoie, Z.P. Fan, A.A. Sigova, J. Reddy, D. Borges-Rivera, T.I. Lee, R. Jaenisch, M.H. Porteus, J. Dekker, R.A. Young, Activation of proto-oncogenes by disruption of chromosome neighborhoods, Science 351 (6280) (2016) 1454–1458.
[182] M.A. Dawson, The cancer epigenome: concepts, challenges, and therapeutic opportunities, Science 355 (6330) (2017) 1147–1152.
[183] P.C. Taberlay, J. Achinger-Kawecka, A.T. Lun, F.A. Buske, K. Sabir, C.M. Gould, E. Zotenko, S.A. Bert, K.A. Giles, D.C. Bauer, G.K. Smyth, C. Stirzaker, S.I. O'Donoghue, S.J. Clark, Three-dimensional disorganization of the cancer genome occurs coincident with long-range genetic and epigenetic alterations, Genome Res. 26 (6) (2016) 719–731.
[184] P. Wu, T. Li, R. Li, L. Jia, P. Zhu, Y. Liu, Q. Chen, D. Tang, Y. Yu, C. Li, 3D genome of multiple myeloma reveals spatial genome disorganization associated with copy number variations, Nat. Commun. 8 (1) (2017) 1937.
[185] M. Peifer, F. Hertwig, F. Roels, D. Dreidax, M. Gartlgruber, R. Menon, A. Kramer, J.L. Roncaioli, F. Sand, J.M. Heuckmann, F. Ikram, R. Schmidt, S. Ackermann, A. Engesser, Y. Kahlert, W. Vogel, J. Altmuller, P. Nurnberg, J. Thierry-Mieg, D. Thierry-Mieg, A. Mariappan, S. Heynck, E. Mariotti, K.O. Henrich, C. Gloeckner, G. Bosco, I. Leuschner, M.R. Schweiger, L. Savelyeva, S.C. Watkins, C. Shao, E. Bell, T. Hofer, V. Achter, U. Lang, J. Theissen, R. Volland, M. Saadati, A. Eggert, B. de Wilde, F. Berthold, Z. Peng, C. Zhao, L. Shi, M. Ortmann, R. Buttner, S. Perner, B. Hero, A. Schramm, J.H. Schulte, C. Herrmann, R.J. O'Sullivan, F. Westermann, R.K. Thomas, M. Fischer, Telomerase activation by genomic rearrangements in high-risk neuroblastoma, Nature 526 (7575) (2015) 700–704.
[186] L.J. Valentijn, J. Koster, D.A. Zwijnenburg, N.E. Hasselt, P. van Sluis, R. Volckmann, M.M. van Noesel, R.E. George, G.A. Tytgat, J.J. Molenaar, R. Versteeg, TERT rearrangements are frequent in neuroblastoma and identify aggressive tumors, Nat. Genet. 47 (12) (2015) 1411–1414.
[187] J. Borden, L. Manuelidis, Movement of the X chromosome in epilepsy, Science 242 (4886) (1988) 1687–1691.
[188] A. Walczak, A.A. Szczepankiewicz, B. Ruszczycki, A. Magalska, K. Zamlynska, J. Dzwonek, E. Wilczek, K. Zybura-Broda, M. Rylski, M. Malinowska, M. Dabrowski, T. Szczepinska, K. Pawlowski, M. Pyskaty, J. Wlodarczyk, I. Szczerbal, M. Switonski, M. Cremer, G.M. Wilczynski, Novel higher-order epigenetic regulation of the bdnf gene upon seizures, J. Neurosci. 33 (6) (2013) 2507–2511.
[189] A. Gregor, M. Oti, E.N. Kouwenhoven, J. Hoyer, H. Sticht, A.B. Ekici, S. Kjaergaard, A. Rauch, H.G. Stunnenberg, S. Uebe, G. Vasileiou, A. Reis, H. Zhou, C. Zweier, De novo mutations in the genome organizer CTCF cause intellectual disability, Am. J. Hum. Genet. 93 (1) (2013) 124–131.
[190] F. Bastaki, P. Nair, M. Mohamed, E.M. Malik, M. Helmi, M.T. Al-Ali, A.R. Hamzeh, Identification of a novel CTCF mutation responsible for syndromic intellectual disability - a case report, BMC Med. Genet. 18 (1) (2017) 68.
[191] J.A. Kennedy, B.L. Ebert, Clinical implications of genetic mutations in myelodysplastic syndrome, J. Clin. Oncol. 35 (9) (2017) 968–974.
[192] J. Liu, I.D. Krantz, Cohesin and human disease, Annu. Rev. Genomics Hum. Genet. 9 (2008) 303–320.
[193] M. Zakari, K. Yuen, J.L. Gerton, Etiology and pathogenesis of the cohesinopathies, wiley interdisciplinary reviews, Dev. Biol. 4 (5) (2015) 489–504.
[194] R. Banerji, R.V. Skibbens, M.K. Iovine, How many roads lead to cohesinopathies? Dev. Dyn. 246 (11) (2017) 881–888.
[195] B.C. Capell, F.S. Collins, Human laminopathies: nuclei gone genetically awry, Nat. Rev. Genet. 7 (12) (2006) 940–952.
[196] H.J. Worman, G. Bonne, Laminopathies": a wide spectrum of human diseases, Exp. Cell. Res. 313 (10) (2007) 2121–2133.
[197] J. Dekker, A.S. Belmont, M. Guttman, V.O. Leshyk, J.T. Lis, S. Lomvardas, L.A. Mirny, C.C. O'Shea, P.J. Park, B. Ren, J.C.R. Politz, J. Shendure, S. Zhong, D.N. Network, The 4D nucleome project, Nature 549 (7671) (2017) 219–226.
[198] T. Nagano, Y. Lubling, T.J. Stevens, S. Schoenfelder, E. Yaffe, W. Dean, E.D. Laue, A. Tanay, P. Fraser, Single-cell Hi-C reveals cell-to-cell variability in chromosome structure, Nature 502 (7469) (2013) 59–64.
[199] V. Ramani, X. Deng, R. Qiu, K.L. Gunderson, F.J. Steemers, C.M. Disteche, W.S. Noble, Z. Duan, J. Shendure, Massively multiplex single-cell Hi-C, Nat. Methods 14 (3) (2017) 263–266.
[200] D. Carter, L. Chakalova, C.S. Osborne, Y.F. Dai, P. Fraser, Long-range chromatin regulatory interactions in vivo, Nat. Genet. 32 (4) (2002) 623–626.
[201] R.A. Beagrie, A. Scialdone, M. Schueler, D.C. Kraemer, M. Chotalia, S.Q. Xie, M. Barbieri, I. de Santiago, L.M. Lavitas, M.R. Branco, J. Fraser, J. Dostie, L. Game, N. Dillon, P.A. Edwards, M. Nicodemi, A. Pombo, Complex multi-enhancer contacts captured by genome architecture mapping, Nature 543 (7646) (2017) 519–524.
[202] S. Quinodoz, N. Ollikainen, B. Tabak, A. Palla, J. Schmidt, E. Detmar, M. Lai, A. Shishkin, P. Bhat, V. Trinh, E. Aznauryan, P. Russell, C. Cheng, M. Jovanovic, A. Chow, P. McDonel, M. Garber, M. Guttman, Higher-order inter-chromosomal hubs shape 3-dimensional genome organization in the nucleus, BioRxiv (2017).
[203] M. Zheng, S.Z. Tian, R. Maurya, B. Lee, M. Kim, D. Capurso, E. Piecuch, L. Gong, J.J. Zhu, C.H. Wong, C.Y. Ngan, P. Wang, X. Ruan, C.-L. Wei, Y. Ruan, Multiplex

Chromatin Interaction Analysis with Single-Molecule Precision, bioRxiv, 2018.
[204] X. Liu, Y. Zhang, Y. Chen, M. Li, F. Zhou, K. Li, H. Cao, M. Ni, Y. Liu, Z. Gu, K.E. Dickerson, S. Xie, G.C. Hon, Z. Xuan, M.Q. Zhang, Z. Shao, J. Xu, In situ capture of chromatin interactions by biotinylated dCas9, Cell 170 (5) (2017) 1028–1043, e19.
[205] J. Dekker, K. Rippe, M. Dekker, N. Kleckner, Capturing chromosome conformation, Science 295 (5558) (2002) 1306–1311.
[206] Z. Zhao, G. Tavoosidana, M. Sjolinder, A. Gondor, P. Mariano, S. Wang, C. Kanduri, M. Lezcano, K.S. Sandhu, U. Singh, V. Pant, V. Tiwari, S. Kurukuti, R. Ohlsson, Circular chromosome conformation capture (4C) uncovers extensive networks of epigenetically regulated intra- and interchromosomal interactions, Nat. Genet. 38 (11) (2006) 1341–1347.
[207] M. Simonis, P. Klous, E. Splinter, Y. Moshkin, R. Willemsen, E. de Wit, B. van Steensel, W. de Laat, Nuclear organization of active and inactive chromatin domains uncovered by chromosome conformation capture-on-chip (4C), Nat. Genet. 38 (11) (2006) 1348–1354.
[208] S. Schoenfelder, T. Sexton, L. Chakalova, N.F. Cope, A. Horton, S. Andrews, S. Kurukuti, J.A. Mitchell, D. Umlauf, D.S. Dimitrova, C.H. Eskiw, Y. Luo, C.L. Wei, Y. Ruan, J.J. Bieker, P. Fraser, Preferential associations between co-regulated genes reveal a transcriptional interactome in erythroid cells, Nat. Genet. 42 (1) (2010) 53–61.
[209] O. Schwartzman, Z. Mukamel, N. Oded-Elkayam, P. Olivares-Chauvet, Y. Lubling, G. Landan, S. Izraeli, A. Tanay, UMI-4C for quantitative and targeted chromosomal contact profiling, Nat. Methods 13 (8) (2016) 685–691.
[210] J.Q. Ling, T. Li, J.F. Hu, T.H. Vu, H.L. Chen, X.W. Qiu, A.M. Cherry, A.R. Hoffman, CTCF mediates interchromosomal colocalization between Igf2/H19 and Wsb1/Nf1, Science 312 (5771) (2006) 269–272.
[211] J. Dostie, T.A. Richmond, R.A. Arnaout, R.R. Selzer, W.L. Lee, T.A. Honan, E.D. Rubio, A. Krumm, J. Lamb, C. Nusbaum, R.D. Green, J. Dekker, Chromosome conformation capture carbon copy (5C): a massively parallel solution for mapping interactions between genomic elements, Genome Res. 16 (10) (2006) 1299–1309.
[212] J.R. Hughes, N. Roberts, S. McGowan, D. Hay, E. Giannoulatou, M. Lynch, M. De Gobbi, S. Taylor, R. Gibbons, D.R. Higgs, Analysis of hundreds of cis-regulatory landscapes at high resolution in a single, high-throughput experiment, Nat. Genet. 46 (2) (2014) 205–212.
[213] B. Mifsud, F. Tavares-Cadete, A.N. Young, R. Sugar, S. Schoenfelder, L. Ferreira, S.W. Wingett, S. Andrews, W. Grey, P.A. Ewels, B. Herman, S. Happe, A. Higgs, E. LeProust, G.A. Follows, P. Fraser, N.M. Luscombe, C.S. Osborne, Mapping long-range promoter contacts in human cells with high-resolution capture Hi-C, Nat. Genet. 47 (6) (2015) 598–606.
[214] M.J. Fullwood, M.H. Liu, Y.F. Pan, J. Liu, H. Xu, Y.B. Mohamed, Y.L. Orlov, S. Velkov, A. Ho, P.H. Mei, E.G. Chew, P.Y. Huang, W.J. Welboren, Y. Han, H.S. Ooi, P.N. Ariyaratne, V.B. Vega, Y. Luo, P.Y. Tan, P.Y. Choy, K.D. Wansa, B. Zhao, K.S. Lim, S.C. Leow, J.S. Yow, R. Joseph, H. Li, K.V. Desai, J.S. Thomsen, Y.K. Lee, R.K. Karuturi, T. Herve, G. Bourque, H.G. Stunnenberg, X. Ruan, V. Cacheux-Rataboul, W.K. Sung, E.T. Liu, C.L. Wei, E. Cheung, Y. Ruan, An oestrogen-receptor-alpha-bound human chromatin interactome, Nature 462 (7269) (2009) 58–64.
[215] M.R. Mumbach, A.J. Rubin, R.A. Flynn, C. Dai, P.A. Khavari, W.J. Greenleaf, H.Y. Chang, HiChIP: efficient and sensitive analysis of protein-directed genome architecture, Nat. Methods 13 (11) (2016) 919–922.
[216] R. Fang, M. Yu, G. Li, S. Chee, T. Liu, A.D. Schmitt, B. Ren, Mapping of long-range chromatin interactions by proximity ligation-assisted ChIP-seq, Cell Res. 26 (12) (2016) 1345–1348.
[217] R. Kalhor, H. Tjong, N. Jayathilaka, F. Alber, L. Chen, Genome architectures revealed by tethered chromosome conformation capture and population-based modeling, Nat. Biotechnol. 30 (1) (2012) 90–98.
[218] T.H. Hsieh, A. Weiner, B. Lajoie, J. Dekker, N. Friedman, O.J. Rando, Mapping nucleosome resolution chromosome folding in yeast by micro-C, Cell 162 (1) (2015) 108–109.
[219] P. Olivares-Chauvet, Z. Mukamel, A. Lifshitz, O. Schwartzman, N.O. Elkayam, Y. Lubling, G. Deikus, R.P. Sebra, A. Tanay, Capturing pairwise and multi-way chromosomal conformations using chromosomal walks, Nature 540 (7632) (2016) 296–300.
[220] Z. Liang, G. Li, Z. Wang, M.N. Djekidel, Y. Li, M.P. Qian, M.Q. Zhang, Y. Chen, BL-Hi-C is an efficient and sensitive approach for capturing structural and regulatory chromatin interactions, Nat. Commun. 8 (1) (2017) 1622.