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Understanding the 3D genome: emerging impacts on human disease

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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.

Keywords

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

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-

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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 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 organizationgained 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-functionrelationship 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 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 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 2,597 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 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 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 7,416 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 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 repositioning 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 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 1A (DCM1A)), 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.

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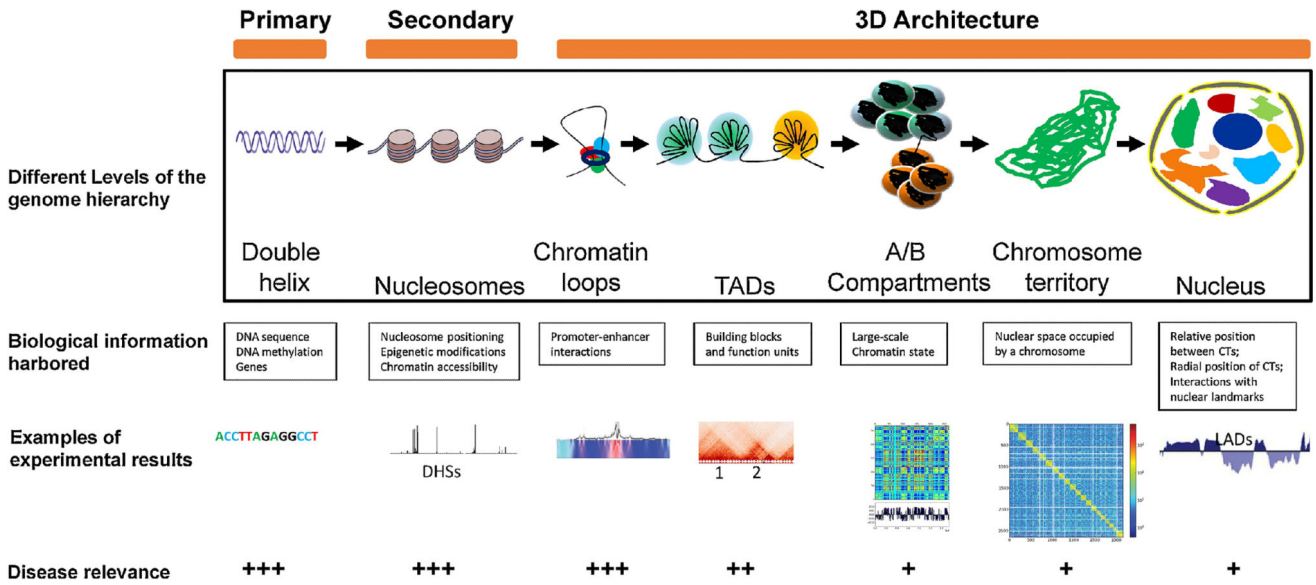

Fig 1. Hierarchical organization of the genome

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.

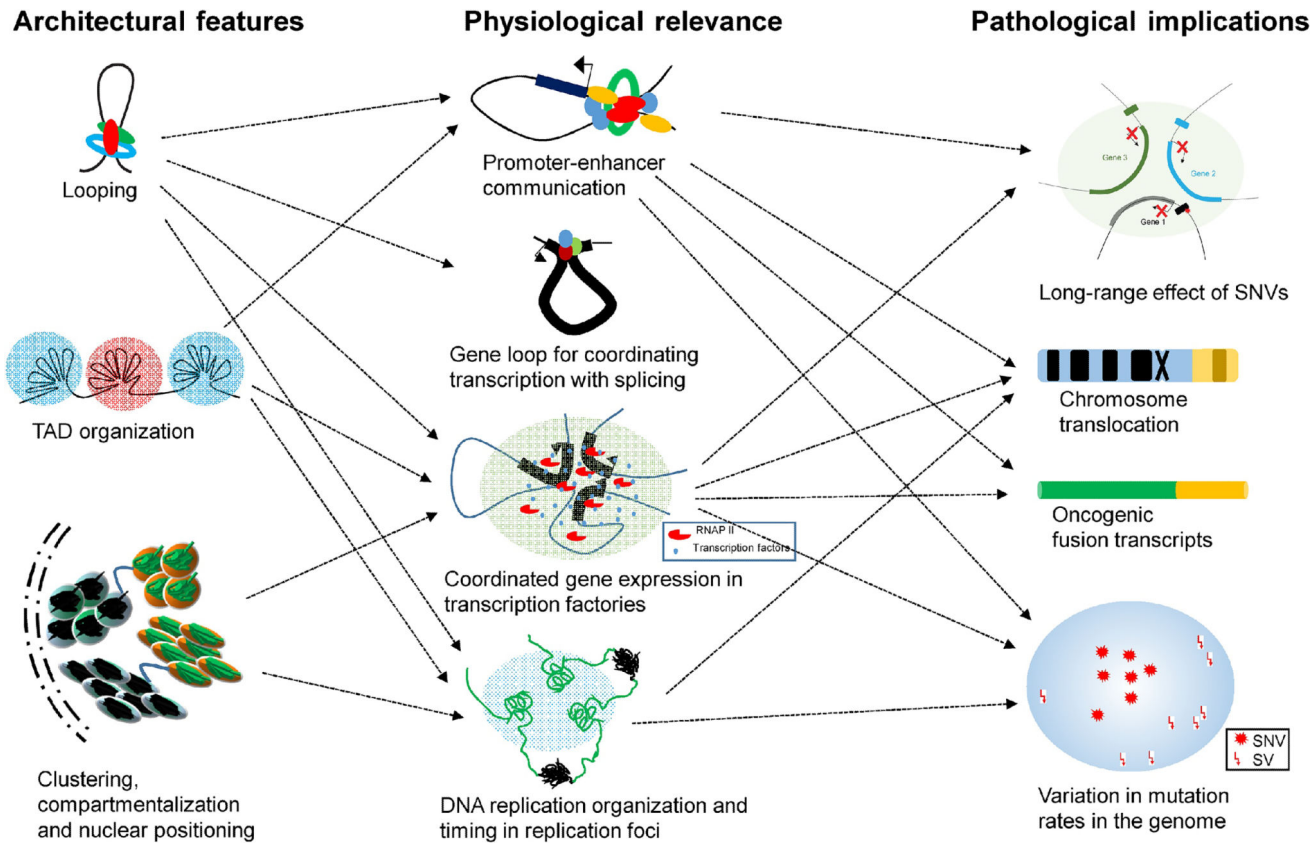

Fig 2. Functional relevance and pathological implications of the various architectural features of the 3D genome

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.

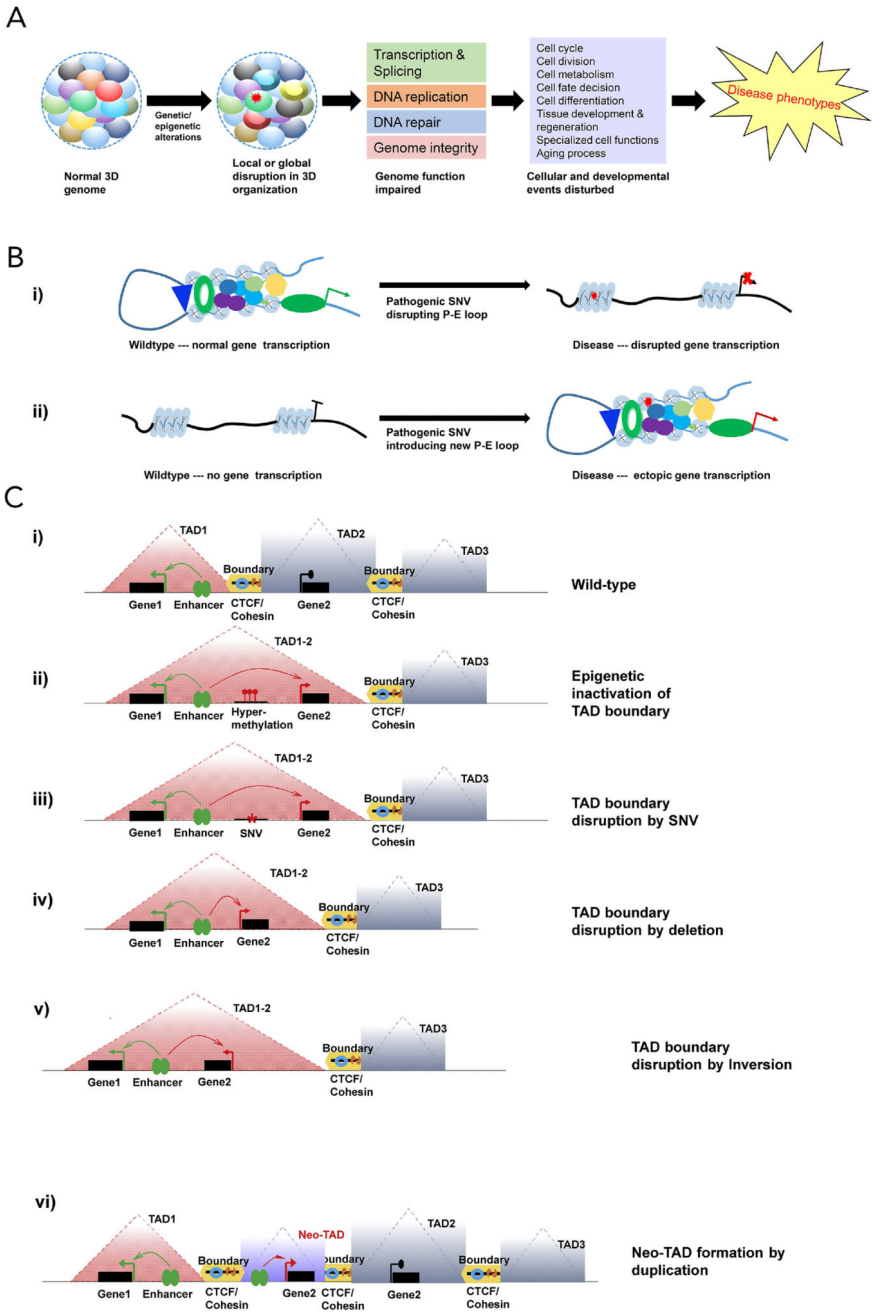

Fig 3. Disease mechanisms of 3D genome disruption

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.

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	612313	[179]
	5q14.3 microdeletion syndrome	*MEF2C*	Deletion	613443	[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*	Hypermethylation of CTCF binding site	-	[174]
	Colorectal cancer	-	SNVs in CTCF/cohesion binding site	-	[173]
	T cell acute lymphoblastic leukemia (T-ALL)	*TAL1, LMO2*	Deletion of CTCF/cohesion 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]

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
SMC1A	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 1A (DCM1A)	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