INSULATED DOMAIN ORGANIZATION AND REGULATION OF METAZOAN GENOMES

KEERTHIVASAN R. C.

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Department of Biological Sciences

Indian Institute of Science Education and Research Mohali

Knowledge city, Sector 81, SAS Nagar, Manauli PO, Mohali 140306, Punjab, India.

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This thesis is dedicated to the 3D genome

Declaration

The work presented in this thesis has been carried out by me under the guidance of Dr. Kuljeet Sandhu at the Indian Institute of Science Education and Research Mohali. This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgment of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Keerthivasan R. C.

In my capacity as the supervisor of the candidate's thesis work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. Kuljeet Singh Sandhu

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Synopsis

Genomes are non-randomly organized inside the nucleus. The discovery of highly compact transcriptionally inactive heterochromatin and loosely packed transcriptionally active euchromatin in the inter-phase nucleus highlighted the association of the higher-order chromatin conformation with the transcriptional states of genes (Heitz 1928). Further studies reveal the presence of chromosomal territories that minimizes the intermingling of chromosomes and maintains the defined positions of chromosomes inside the nucleus in an evolutionarily conserved manner (T. Cremer et al. 1993; Eils et al. 1996). For several decades, microscopy-based techniques like DNA FISH, chromosome painting, immunofluorescence, and electron microscopy have been the preferred methods to study the 3D organization of chromatin (Fawcett 1966; Gall and Pardue 1969; Rudkin and Stollar 1977; Betzig et al. 2006; Markaki et al. 2012). The recently developed proximity-ligation based methods, such as 3C, 4C, 5C, and Hi-C, in combination with next-generation sequencing technologies, have made it possible to investigate the genome-wide higher-order chromatin conformations across different cellular and developmental models (Dekker et al. 2002; Z. Zhao et al. 2006; Dostie et al. 2006; Lieberman-Aiden et al. 2009; Rao et al. 2014).

A key finding through Hi-C studies is the Topologically Associating Domains (TADs), which are self-interacting and insulated domains of approximately 100-200kb in metazoan genomes. The boundaries of TADs are marked with CTCF, cohesin, ZNF143, and Top2b (Sexton et al. 2012; Nora et al. 2012; Dixon et al. 2012; Rao et al. 2014; Tang et al. 2015; Uusküla-Reimand et al. 2016). In particular, the role of CTCF and Cohesins is being interrogated by several studies (Dixon et al. 2012; Nora et al. 2017; Rao et al. 2017; Schwarzer et al. 2017; Davidson et al. 2019). The ‘loop extrusion’ model suggests that the rings formed by Cohesins extrude DNA until it encounters CTCF binding sites oriented in a convergent manner (Fudenberg et al. 2016; Ganji et al. 2018; Davidson et al. 2019). TADs are the ancient features of metazoan genomes, are stable across different cell-types, and serve as a basic topological unit of epigenetic reprogramming through insulating transcriptional states during development (Dixon et al. 2012; 2015; Harmston et al. 2017; Szabo et al. 2018). Several studies have shown that the enhancers interact with their target promoters predominantly inside TADs (Lupiáñez et al. 2015; Narendra et al. 2015; Symmons et al. 2016; Andrey and Mundlos 2017). While the field of 3D genome organization has made significant and rapid progress in the last decade, some of the critical questions regarding TADs and chromatin loops remain unaddressed and ignored. In this thesis, we have attempted to address the following two questions:

1) Do insulated chromatin domains regulate the genome in an allele-specific manner?

Motivation

H19 and Igf2 genes are developmentally important and reciprocally imprinted genes located adjacently in mammalian genomes. H19 is expressed from the maternal chromosome, while the Igf2 gene is expressed from the paternal chromosome (DeChiara, Efstratiadis, and Robertson 1990; DeChiara, Robertson, and Efstratiadis 1991; M. S. Bartolomei, Zemel, and Tilghman 1991; Y. Zhang and Tycko 1992; Rachmilewitz et al. 1992; Jinno et al. 1995). The parentally fixed mono-allelic expression of these genes is regulated by allele-specific higher-order chromatin structures formed by CTCF and Cohesins (Murrell, Heeson, and Reik 2004; Kurukuti et al. 2006; Nativio et al. 2009). Maternal H19 and Igf2 genes are insulated from each other in two distinct active and inactive chromatin domains (Murrell, Heeson, and Reik 2004; Kurukuti et al. 2006). It remains unknown whether or not such allele-specific conformations are present genome-wide and are implicated in allele-specific regulation of

mono-allelically expressed (MAE) genes. With the availability of genome-wide datasets of mitotically stable random MAE genes (A. Gimelbrant et al. 2007; Zwemer et al. 2012; Nag et al. 2013; Gendrel et al. 2014; Nag et al. 2015) and the allele-specific Hi-C datasets (Rao et al. 2014; Rivera-Mulia et al. 2018), it is now possible to test the hypothesis whether the CTCF mediated genome architecture implicates in allele-specific regulation of genes.

Results

Since mono- and bi-allelically expressed genes differ epigenetically and functionally (Nag et al. 2013; 2015), we first tested if the chromosomal locations of MAE genes are linearly segregated from that of BAE genes in genomes. Through multiple different analyses, we observe that the domains of MAE genes are non-randomly segregated from the domains of BAE genes in the linear genome. The border of MAE and BAE clusters are marked by CTCF binding sites, which warrants the role of higher-order chromatin structure in the insulation of MAE and BAE genes. Indeed, MAE genes are preferably located inside the insulator chromatin loops, while BAE genes are mostly associated with enhancer-linking loops. Through comparison across cell-types and species, we find that the gain or loss of insulator loops is correlated with gain or loss of mono-allelic expression of genes, highlighting that the CTCF mediated insulation of MAE clusters might serve as pre-requisite for mono-allelic expression. To test the causal association between CTCF mediated insulation and the mono-allelic expression, we analyze Hi-C, and RNA-seq data of control and CTCF depleted mouse embryonic stem cells. We observe that the CTCF depletion significantly perturbs the insulation and the expression of MAE genes as compared to BAE genes. Through allele-specific analysis, we further establish that the inactive allele is more compact and insulated than active allele, and is de-repressed upon CTCF depletion. These analyses establish the wide-spread allele-specific role of CTCF in the mammalian genomes. We hypothesize that the CTCF functions as a typical insulator around inactive allele but regulates the active allele through its enhancer-looping function.

2) How are distinct transcriptional states of TADs concurrently regulated genome-wide during development?

Motivation

The prevailing model of transcriptional regulation suggests that the genes are activated when their promoters establish proximity to the cognate enhancers, popularly known as the enhancer-looping model (Ong and Corces 2014; Rao et al. 2014; Bonev and Cavalli 2016; Bonev et al. 2017). Insulated TAD boundaries forbid non-specific enhancer-promoters interactions across domains (Lupiáñez et al. 2015; Narendra et al. 2015; Symmons et al. 2016). However, a recent study suggests that a gene is activated through the decondensation of chromatin domains, and hence the spatial proximity decreased between a promoter and its enhancers (Benabdallah et al. 2019). This is further supported by another study that suggests a highly condensed form of inactive TADs and decondensed form of active TADs using super-resolution microscopy (Szabo et al. 2018). We, therefore, have attempted to map condensed and decondensed chromatin domains genome-wide, and investigate their role in regulating transcriptional dynamics during development.

Results

One of the ways, the condensed and decondensed chromatin states can be identified is by subjecting the chromatin to nuclease digestion inside the nucleus. The scope of popular methods, like DNase-seq, FAIRE-seq, ATAC-seq (Giresi et al. 2007; Song and Crawford 2010; Buenrostro et al. 2015), is limited to the nucleosome-free accessible DNA and therefore suited to identify narrow sites of transcription factor binding. A few authors have observed the quantitative differences in inter-nucleosomal packing

through restriction digestion of chromatin (P. B. Chen et al. 2014). Interestingly, restriction endonuclease is routinely used to digest chromatin in some of the molecular techniques, like Hi-C, presuming that *in-situ* restriction digestion of chromatin is likely to be uniform owing to the use of SDS, heat and prolonged treatment with restriction endonuclease. We hypothesize that the restriction digestion in these assays can serve as a real test for the intrinsic resistance or lack thereof of chromatin to the restriction digestion. If true, it would also suggest that the techniques involving restriction digestion might have a potential bias in the final readouts.

We first establish that the *in-situ* restriction digestion of chromatin is not uniform when compared to in-solution restriction digestion of naked DNA. This is verified by correcting the read counts of restriction endonuclease digested chromatin and naked DNA (RED-seq data) against the density of restriction sites, GC content, and mappability. These observations motivated us to extend our analyses to publicly available 44 Hi-C datasets. The known condensed regions in the genome, such as Lamina-Associated Domains (LADs), inactive X-chromosome in mammals, and polytene bands in Drosophila, exhibit strikingly low one-dimensional Hi-C read counts when compared to decondensed domains. We systematically rule out that the observed bias in read counts for the condensed and the decondensed domain is a consequence of known systematic biases, formaldehyde-cross-linking, and ligation steps of Hi-C. The bias due to differential restriction digestion is not appropriately handled by existing normalization methods and needs an additional corrective step. We repurpose the observed bias and identify novel condensed domains, other than LADs, that are associated with polycomb repressed chromatin. Using the model of mouse embryonic stem cell differentiation to neuronal progenitor cells, we demonstrate that the 1D read count of Hi-C data can reliably capture the developmental dynamics of chromatin condensation and decondensation.

List of publications

The thesis is based on the following articles

1. **K. R. Chandradoss**#, B. Chawla#, S. Dhuppar, R. Nayak, R. Ramachandran, S. Kurukuti, A. Majumder and K. Sandhu. CTCF mediated genome architecture regulates the dosage of mitotically stable mono-allelic expression of autosomal genes. bioRxiv, November 2017; www.biorxiv.org/content/10.1101/178749v2; (Submitted to Cell reports)

2. **K. R. Chandradoss**#, P. Guthikonda#, S. Kethavath, M. Dass, H. Singh, R. Nayak, S. Kurukuti*, K. Sandhu*. Biased visibility in Hi-C datasets marks dynami cally regulated condensed and decondensed chromatin states genome-wide. **BMC Genomics** (2020) 21:175; https://doi.org/10.1186/s12864-020-6580-6

Other work

1. M. Bagadia#, **K. R. Chandradoss**#, Y. Jain, H. Singh, M. Lal, and K. Sandhu*. Evolutionary Loss of Genomic Proximity to Conserved Noncoding Elements Impacted the Gene Expression Dynamics During Mammalian Brain Development. **GENETICS** April 1, 2019 vol. 211 no. 4 1239-1254; https://doi.org/10.1534/genetics.119.301973

2. Y. Jain#, **K. R. Chandradoss**#, A. Tahir#, M. Bagadia, J. Bhattacharya, and K. Sandhu*. Convergent evolution of a genomic rearrangement may elucidate cancer resistance in hystrico- and sciuromorpha rodents. (Manuscript in preparation)

3. A. Singh, P. Choudhuri, **K. R. Chandradoss**, M. Lal, S. Mishra, and K. Sandhu*. Does genome surveillance explain the global discrepancy between binding and effect of chromatin factors? **FEBS Letters**, published online on Jan 12, 2020. https://doi.org/10.1002/1873-3468.13729

Co-first author; * Corresponding author

Contents

Section - 1
Domain-level organization

The organization of chromatin into heterochromatin and euchromatin in the interphase nucleus posed the age-old question of how the three-dimensional (3D) organization of the two-meter long genetic material regulates gene expression. Like proteins, the one-dimensional (1D) genome during the interphase is highly organized in a non-random and hierarchical manner with secondary-tertiary structures and thus, leading to the organization in three-dimensions. Early microscopic studies revealed the presence of chromosome banding patterns (i.e., alternative domains of tightly packed transcriptionally inactive heterochromatin and loosely packed transcriptionally active euchromatin) in polytene chromosomes (Painter 1933; Muller and Prokofyeva 1935; D'angelo 1946; Alanen 1986). Then, a study involving Chromatin Immuno Precipitation (ChIP) identified long genomic domains that are associated with Polycomb repressive complexes (Orlando and Paro 1993). Independently, several other studies identified large domains of early and late replication (Sparvoli, Levi, and Rossi 1994; Ferreira et al. 1997; H. Ma et al. 1998; Jackson and Pombo 1998). Modern-day techniques, such as DNA adenine methyltransferase identification (DamID), ChIP-chip, and ChIP-seq further confirmed the existence of chromatin domains genome-wide (Orlando and Paro 1993; B. van Steensel, Delrow, and Henikoff 2001; Pickersgill et al. 2006; W. E. Johnson et al. 2006; D. S. Johnson et al. 2007; Guelen et al. 2008). Therefore, the linear organization of the genome is strongly linked with the domain-level regulation of essential genomic functions like transcription and replication (Bickmore and van Steensel 2013; Sexton and Cavalli 2015; Dekker and Heard 2015; Dixon, Gorkin, and Ren 2016).

The linear genome of eukaryotes is non-randomly organized and divided into domains called isochores of differential GC content, such as GC rich gene-clusters and intergenic/gene-poor regions (Lawrence 1999; Hurst, Pál, and Lercher 2004; Kosak and Groudine 2004; Costantini et al. 2006). Such domain organization is conserved across evolution and originated from genes that are co-expressed, involved in the same metabolic pathway, interacting at protein level, and to some extent, to minimize their transcriptional noise (Cohen et al. 2000; Spellman and Rubin 2002; J. M. Lee and Sonnhammer 2003; Teichmann and Veitia 2004; Singh, Bagadia, and Sandhu 2016). Concurrent deposition and maintenance of similar epigenetic states in maintaining the transcriptional activity of genes inside the domains is hypothesized as the primary constraint and supported by the identification of large domains that are maintained by complexes, such as hometic *bithorax* locus by polycomb repressive complex in *Drosophila* (Orlando and Paro 1993; de Wit et al. 2008; Filion et al. 2010). Further, the organization at the domain level also has a huge role in embryonic development, and diseases (Kleinjan and van Heyningen 2005; Kleinjan and Lettice 2008; van Heyningen and Bickmore 2013). Therefore, the linear genome is divided into domains that are insulated from each other and regulated by epigenetic modifiers.

In parallel to the developments of domain architecture in the linear genome, several microscopic studies revealed the non-random folding of the genome in 3D space. One of the keys observations of the late 20th century is the discovery of the territorial organization of chromosomes as 'chromosome territories' (CT) (T. Cremer et al. 1993; T. Cremer and Cremer 2001; Thomas Cremer and Cremer 2010). Further, the development of high-throughput techniques revealed the segregation of chromosomes into distinct self-associating domains, currently referred to as Topologically Associating Domains (TADs) (Nora et al. 2012; Sexton et al. 2012; Dixon et al. 2012). These domains are stable across cell-types and evolution, and they are considered as the basic structural and functional units of three-dimensional (3D) genome (Dixon et al. 2012; Rao et al. 2014; Harmston et al. 2017; Szabo et al. 2018). Therefore, the organization of genome and its role in gene regulation requires a complete understanding of the 3D chromatin architecture at domain-level.

1.1 Techniques to study 3D genome

The non-random organization of the genome has been studied since the early 20th century. For decades, microscopy methods dominated the field of 3D genome organization. While the electron microscope revealed the presence of heterochromatin and euchromatin, the revolutionary Fluorescent *in situ* hybridization (FISH) visualized the spatial organization at the level of gene-to-gene interactions (Heitz 1928; Gall and Pardue 1969; Alanen 1986; T. Cremer et al. 1993; Speicher, Gwyn Ballard, and Ward 1996). The development of proximity-ligation based Chromosome Conformation Capture (3C) and the derived techniques overcame the limitation of low throughput output of microscopy-based techniques, though at the cost of lost quantitative details like distances among loci, the cell-to-cell variation thereof, the dynamic events like looping out of loci, territorial localization, simultaneous or mutually exclusives interactions among loci etc. Nevertheless, the 3C based techniques completed by 3D FISH imaging has been instrumental in deciphering the genome conformations in great detail. The genome-wide chromatin interaction maps obtained through Hi-C identified the presence of compartments, Topologically Associating Domains (TADs), and chromatin loops (Dostie et al. 2006; Lieberman-Aiden et al. 2009; Dixon et al. 2012; Nora et al. 2012; Hou et al. 2012; Sexton et al. 2012). Ligation free techniques such as Genome Architecture Mapping (GAM), Split-Pool Recognition of Interactions by Tag Extension (SPRITE), and Chromatin-Interaction Analysis via DROPlet-based and barcode-linked sequencing (ChIA-DROP) have uncovered a new level of complexity in chromatin interactions, such as those involving more than two regions at a time and inter-chromosomal interaction hubs with sub-nucleolar compartments (Beagrie et al. 2017; Quinodoz et al. 2018; M. Zheng et al. 2019). Therefore, we can classify the techniques to study higher-order genome architecture into three broad categories, such as follows.

1) Microscopy

For centuries, different kinds of microscopic techniques have been used to study the genome organization. While simple light and electron microscopes identified heterochromatin (Heitz 1928; Alanen 1986), metaphase chromosomes (Earnshaw and Laemmli 1983) and their radial loops (Marsden and Laemmli 1979), and chromosome bands (Saitoh and Laemmli 1994), DNA-FISH became the popular technique to study gene-to-gene interactions (Gall and Pardue 1969; Langer-Safer, Levine, and Ward 1982). It uses fluorescently tagged DNA oligonucleotides as probes and visualizes the hybridized tags to single-stranded genomic DNA using microscopes. It is being used widely to measure physical 3D distance among chromosomal regions (Garimberti and Tosi 2010; Oluwadare, Highsmith, and Cheng 2019; Kempfer and Pombo 2019). A chromatin contact between two regions is usually defined loosely based on a distance cutoff from a scale that depends on the resolution of the microscope (Barbieri et al. 2017; Maass et al. 2018; Barutcu et al. 2018; Finn et al. 2019; Kempfer and Pombo 2019).

Apart from measuring spatial distance between two genomic loci, FISH can be applied to study the different aspects of genome organization. Rapid image processing and visualization of 2D-FISH is used to determine the relative spatial localization of a loci to its chromosomal territory (i.e., looping-in/out mechanisms) (Kosak and Groudine 2004; Kadauke and Blobel 2009; Thomas Cremer et al. 2006), chromatin condensation at submegabase level (Chambeyron and Bickmore 2004), inter-chromosomal contacts (Branco and Pombo 2006), and genomic rearrangements or abnormalities (Knoll et al. 1989; Branco and Pombo 2006), etc. More accurate 3D reconstruction of spatial arrangements by 3D-FISH is used to visualize fine enhancer – promoter interactions (Beagrie et al. 2017). Further, FISH can be

combined with live-cell imaging to visualize the transcriptional activation/repression of loci/chromosomes during development (Robinett et al. 1996; Belmont and Straight 1998; Lucas et al. 2014; Germier et al. 2018).

Along with more modern techniques and super-resolution microscopic instruments, it is now possible to target loci up to 5kb (Simonis et al. 2006; Ferrai et al. 2010; Shelagh Boyle et al. 2011; Beliveau et al. 2012; Beliveau, Apostolopoulos, and Wu 2014; Beliveau et al. 2015; Barbieri et al. 2017; Beagrie et al. 2017). Recent advances have also overcome the more significant limitation (i.e., low-throughput) of the early microscopy techniques (Hanhui Ma, Reyes-Gutierrez, and Pederson 2013; Hanhui Ma et al. 2016; S. Wang et al. 2016). Further, real-time imaging of chromatin loop extrusion by condensin and cohesin in cell-free systems has also shown the power of microscopes in studying the higher-order genome architecture (Ganji et al. 2018; Davidson et al. 2019).

2) Proximity-ligation based techniques

Chromosome Conformation Capture (3C) was first developed to detect the frequency of interaction between any two genomic loci by quantitative PCR (Dekker et al. 2002). Since then, several variants have emerged, and yet, they start with a 3C template (Figure 1.1.1) (Simonis et al. 2006; Z. Zhao et al. 2006; Dostie et al. 2006; Lieberman-Aiden et al. 2009; Belton et al. 2012; Rao et al. 2014; Hsieh et al. 2015; Ramani et al. 2016). Briefly, chromatin is fixed inside the nucleus along with proteins by treating formaldehyde as a fixing agent. Then, the cross-linked chromatin is fragmented by a restriction endonuclease (in some cases, DNase and Mnase are also used). A step involving ligation (either in solution or *in situ*) joins chromatin to create junctions, which are in spatial proximity, and finally, cross-linking is reversed to get the so-called 3C template. The 3C template contains fragments that have pairs from two different regions from the same chromosome (intra-chromosomal pair) or entirely from two different chromosomes (inter-chromosomal pair) (de Wit and de Laat 2012; Denker and Laat 2016).

(a) 4C: one-to-all interactions: Chromosome Conformation Capture on Chip (4C) identifies all the interacting regions to any region of interest (i.e., bait, anchor, or viewpoint). The main advantage of 4C over 3C is that it does not require any prior knowledge about the interacting partners. The protocol proceeds with the preparation of a 3C template, and there is a second round of digestion and ligation. This results in smaller circles that contain bait and interacting partners (Figure 1.1.1). Then, an inverse PCR step amplifies all the interacting partners that are identified either by tiling array or sequencing (Simonis et al. 2006; Z. Zhao et al. 2006; Splinter et al. 2011). A potential disadvantage is an intrinsic bias due to the PCR amplification. Fragments are amplified differentially due to their differences in the size and GC content. This bias is partially removed but not entirely in 4C-seq that uses 4bp cutter instead of 6bp cutter in traditional 3C techniques. The use of 4bp cutter allows the formation of multiple concatemers that minimizes the intrinsic bias and increases the complexity of the library (Werken et al. 2012; Denker and Laat 2016).

(b) 5C: many-to-many interactions: Being an intermediate between 4C and Hi-C, Chromosome Conformation Capture Carbon Copy (5C) relies on multiplexed ligation-mediated amplification (LMA) and investigates the interactions among a set of regions. Primers are designed and hybridized to a 3C template. If there is an interaction between two regions of interest, primers are ligated and a carbon copy of the junction is made (Figure 1.1.1). Then, carbon copies are amplified using universal primers

and sequenced to generate a contact map (Dostie et al. 2006; Nora et al. 2012; Denker and Laat 2016). The main disadvantage of 5C is the designing of primers that requires extensive prior knowledge about the regions of interest. To overcome this, Hi-C was invented.

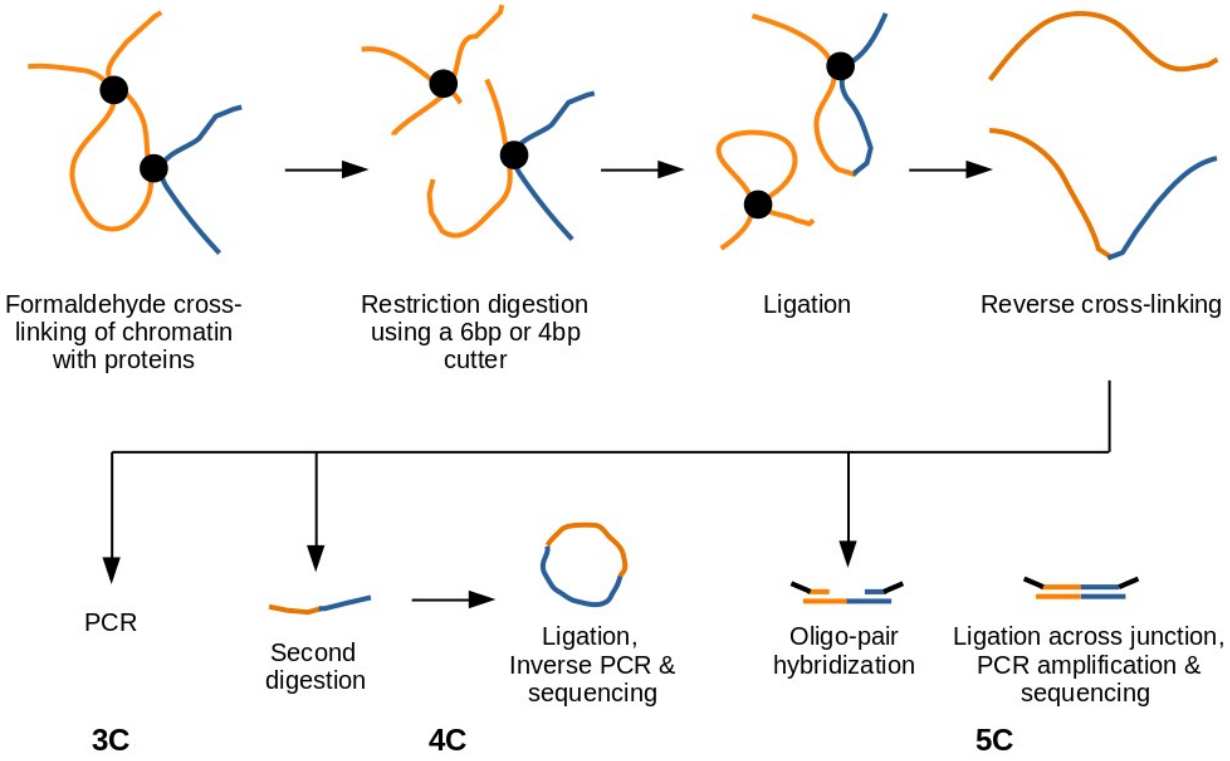

Figure 1.1.1 Basic steps involved in 3C techniques.

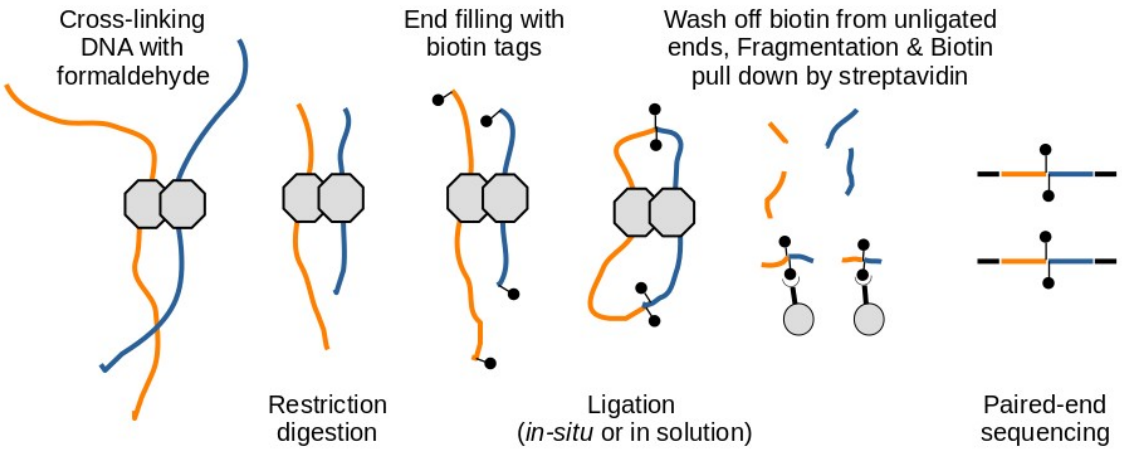

Figure 1.1.2 Experimental steps in Hi-C to capture all-to-all chromatin interactions based on proximity-ligation of chromatin after cross-linking and restriction digestion.

(c) Hi-C: all-to-all interactions: With the development of massive parallel sequencing techniques, High-throughput Chromosome Conformation Capture (Hi-C) is the first 3C method to study chromatin interaction genome-wide. In contrast to above techniques, Hi-C does not require primer designing and

it has some modification in generating 3C template (Figure 1.1.2). It starts with cross-linking using formaldehyde and digestion with restriction endonuclease. Before ligation (both in solution and *in situ*), ends are tagged with biotin to identify Hi-C junctions after ligation. Biotin is washed off from unligated ends, fragmented, and pulled down by streptavidin to enrich for Hi-C junctions. Finally, they are sequenced by paired-end sequencing.

A contact map is generated to visualize genome-wide interactions (Lieberman-Aiden et al. 2009; Belton et al. 2012; Rao et al. 2014). Several variants have emerged and they are Tethered Conformation Capture (TCC) (Kalhor et al. 2012), capture Hi-C (Mifsud et al. 2015), Micro-C (use of micro-coccal nuclease instead of restriction endonuclease) (Hsieh et al. 2015), DNase HiC (use of DNase instead of restriction endonuclease) (Ramani et al. 2016), Liquid chromatin Hi-C (Belaghzal et al. 2019), and Methyl-HiC (G. Li et al. 2019). Several tools are available for Hi-C processing, such as HiCUP (Wingett et al. 2015), HiC-Pro (Wingett et al. 2015), hiclib (Imakaev et al. 2012), TADbit (Serra et al. 2017), etc. While Hi-C is high throughput in coverage, it does not decipher the quantitative and visual insights that *in-situ* techniques like FISH can endow, as discussed in the 'Microscopy' section. Hi-C also suffers from several systematic biases, like differential ligation efficiency of restriction fragments of different lengths, PCR bias due difference in GC content of ligated ends, and the read mappability to the genome (Yaffe and Tanay 2011). These biases, as well as other unknown, are generally corrected using matrix-balancing methods (Imakaev et al. 2012). We have elaborated more on these biases in section-3 and have also uncovered yet another bias, the restriction digestion bias, in the Hi-C read counts.

(d) ChIA-PET: many-to-many interactions mediated by a protein of interest: Chromatin Interaction Analysis by Paired-End Tagged sequencing (ChIA-PET) is the combination of 3C technique Hi-C with Chromatin Immuno-Precipitation (ChIP). After cross-linking and digestion of chromatin, the complexes mediated by a protein of interest (such as CTCF, cohesin subunits, and RNAPII) is enriched by ChIP using a special antibody. Then, the rest of Hi-C protocol is performed with a few added changes (Fullwood et al. 2009; Handoko et al. 2011; Tang et al. 2015). While the main advantage is that we can find interactions mediated by a protein of interest (that can go unnoticed in Hi-C), the main disadvantage is that chromatin fragments that are linearly closer are ligated to give a false interaction irrespective them being in a loop. Certain control steps such as the degree of protein enrichment (by ChIP), minimum number of PETs to call as a loop and interactions within 1mb are used to ensure the quality of ChIA-PET interactions (Fullwood et al. 2009; Denker and Laat 2016).

3) Ligation-free techniques

Although 3C techniques unveiled several aspects of higher-order genome architecture, it heavily relied upon the ligation of chromatin fragments in complexes. Since a chromatin fragment can either ligate up to two others fragments at a time or fragments which are already ligated with others, not all interactions in a complex cluster could be captured in 3C techniques (O'Sullivan et al. 2013). Recent techniques that do not involve ligation have paved the way to understand the complex interactions among enhancers and promoters (Kempfer and Pombo 2019).

(a) Genome Architecture Mapping (GAM): Thin nuclear sections are made from a population of fixed cells in random orientations using ultra-thin cryo-sectioning (Figure 1.1.3) and the nuclear slices

are separated using laser microdissection. These steps are advantageous over other techniques as they do not involve DNA extraction and cell sorting, and thereby preserving the complex nuclear structures with minimal disturbance. Then, genome amplification of DNA present in the slices and barcoding are performed before pooling DNA from all slices. After sequencing, reads are separated based on the barcoding and significant chromatin interactions between two regions are inferred from the frequency of co-segregation in nuclear slices by applying a mathematical model 'statistical inference of co-segregation' (SLICE). The main advantage is that two or more spatially interacting genomic regions that are engaging in a complex interaction are more frequently found in the same nuclear sections (Beagrie et al. 2017; Kempfer and Pombo 2019).

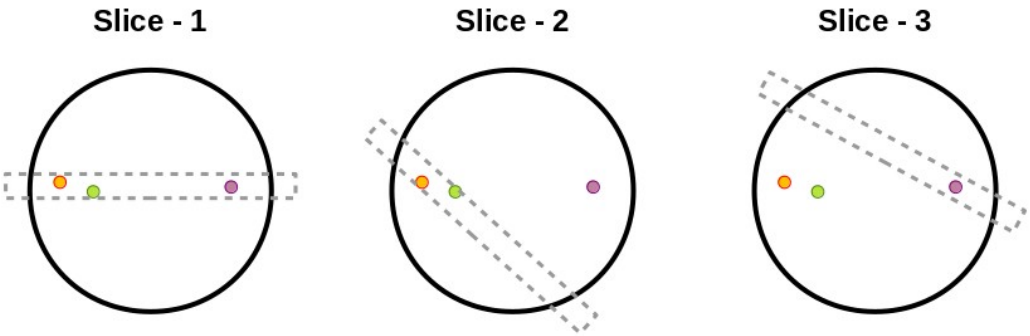

Figure 1.1.3 Nuclear sectioning in Genome Architecture Mapping (GAM).

(b) Split-Pool Recognition of Interactions by Tag Extension (SPRITE): The initial steps are similar to those in 3C. It starts with nuclear fixation and digestion into chromatin complexes. Then, the complexes are split across wells in a 96-well plate and tagged uniquely. The tagged complexes are then pooled and again split in an another 96-well plate and tagged uniquely again. By repeating this splitting and pooling of complexes, and sequencing, chromatin interactions in a complex are identified based on their final unique concatenation of barcodes (Quinodoz et al. 2018; Kempfer and Pombo 2019).

(c) Chromatin-Interaction Analysis via DROPlet-based and barcode-linked sequencing (ChIA-DROP): The cross-linked and fragmented chromatin complexes are separated and tagged uniquely through droplet formation in a microfluidics device. Then, the complexes are pooled and sequenced. Chromatin fragments in a complex are separated based on their unique barcode (M. Zheng et al. 2019).

Therefore, the above-mentioned techniques summarizes the different approaches to study the higher-order genome architecture and every technique has its own advantages and disadvantages. Although 3C techniques are widely used these days and ligation-free techniques are still under development, the chromatin contacts that are identified by these modern techniques are often verified by FISH. Since FISH and 3C are technically and conceptually different, comparing their results is often non-trivial. However, a number of measures (for example: similar fixation steps in 3C and FISH) can be taken for better comparison by DNA FISH (Giorgetti and Heard 2016).

1.2 Hierarchical organization of three-dimensional genomes

The genome was first visualized under the microscope as highly condensed structures as metaphase chromosomes during cell division independently by several scientists. Then, Emil Heitz observed the presence of darkly stained heterochromatin near the nuclear periphery and lightly stained euchromatin towards the nuclear interior (Figure 1.2.1) (Heitz 1928). This organization led to the discovery of the three-dimensional organization of the genome inside the interphase nuclei. The heterochromatin shields the transcriptionally active and open chromatin from several mutagens (Hsu 1975). Exception to this is the inverted nuclei with heterochromatin at the nuclear interior and euchromatin at the nuclear periphery (Figure 1.2.1), which predominantly exists in the rods of nocturnal animals to facilitate their vision more efficiently in the dark (Solovei et al. 2009; Eskiw and Fraser 2009).

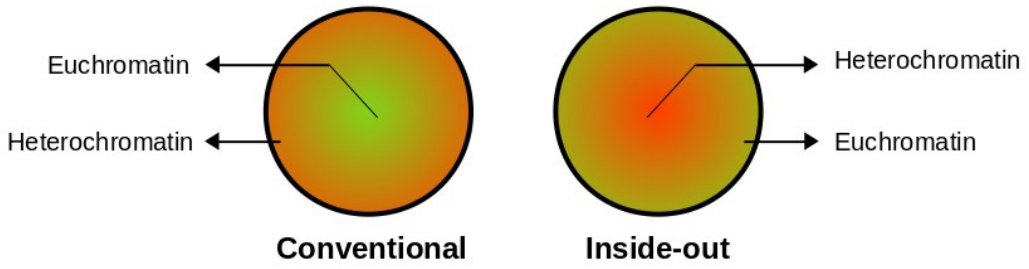

Figure 1.2.1 Euchromatin and heterochromatin in conventional and inside-out configuration.

Chromosome territories

During interphase, chromosomes exist in highly decondensed form and occupy territories with intermingling surfaces (Figure 1.2.2) (Stack, Brown, and Dewey 1977; Zorn et al. 1979; Lichter et al. 1988; Pinkel et al. 1988; T. Cremer et al. 1993; Speicher, Gwyn Ballard, and Ward 1996; T. Cremer and Cremer 2001; Branco and Pombo 2006). Such territorial organization of chromosome was first proposed by Carl Rabl and the term ‘chromosome territory’ was coined by Theodor Boveri (Thomas Cremer and Cremer 2010). Modern 3C techniques also confirmed the presence of chromosome territories by relatively higher intra-chromosomal interaction frequencies when compared to inter-chromosomal interaction frequencies (Lieberman-Aiden et al. 2009; Rao et al. 2014). Further, gene rich and poor chromosomes differ in their radial arrangement. While gene rich and early replicating human chr19 is located towards the nuclear center, gene-poor and late-replicating human chr18 is located towards nuclear periphery (Croft et al. 1999; S. Boyle et al. 2001). Such radial positioning of chromosomes with respect to their gene density is conserved across primates (Tanabe et al. 2002).

Lamina Associated Domains (LADs)

Initial studies of chromatin interactions with nuclear lamina in human fibroblasts revealed about 1300 domains of varying sizes (100kb – 10mb with a median 0.5mb) and covering up to 40% of the genome (Guelen et al. 2008). LADs are generally GC poor, low gene dense regions and formed as early as zygote stage (Bas van Steensel and Belmont 2017; Borsos et al. 2019). They are of two types (Figure 1.2.3) (Peric-Hupkes et al. 2010; Meuleman et al. 2013). (i) Constitutive LADs: These are LADs in most of the cell-types. They are highly compact and have strong association with H3K9me3 and H3K9me2. (ii) Facultative LADs: These are cell type specific LADs.

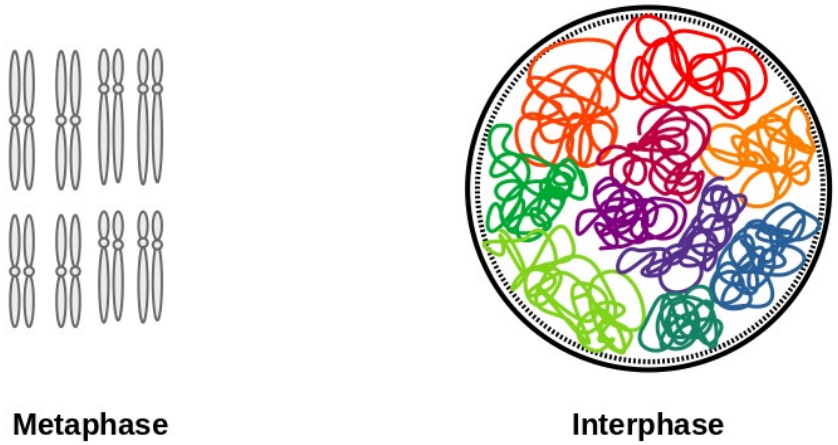

Figure 1.2.2 Nuclear chromosomal arrangement during metaphase and interphase.

Such domain-like architectures are also present in worms and flies. Nuclear lamina is highly repressive in nature and genes that are located inside these domains are transcriptionally inactive (Pickersgill et al. 2006; Guelen et al. 2008; Peric-Hupkes et al. 2010; van Bemmel et al. 2010). Artificial relocation of genes from the nuclear center to nuclear lamina, in general, leads to the silencing of those genes with some exceptions (Finlan et al. 2008; Reddy et al. 2008; Kumaran and Spector 2008; Dialynas et al. 2010).

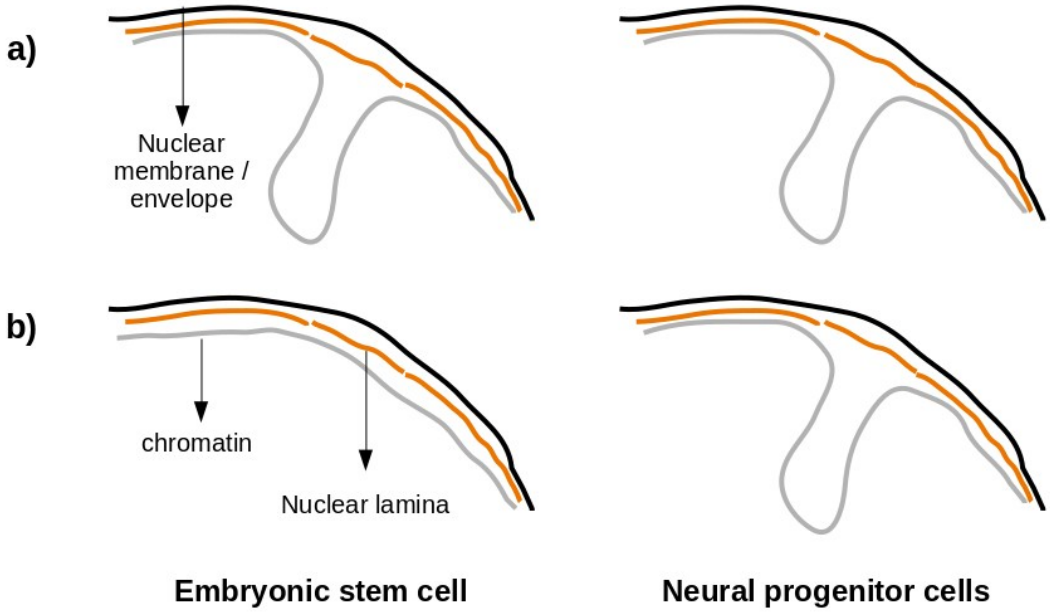

Figure 1.2.3 Types of LADs such as (a) constitutive and (b) facultative.

Compartments

Genome-wide chromatin interaction maps revealed the presence of long-range interactions among chromatin domains of similar epigenetic properties by a plaid pattern and the spatial segregation of chromatin into two major compartments, such as A (active and de-condensed) and B (inactive and compact/condensed) (Figure 1.2.4) (Lieberman-Aiden et al. 2009). Higher resolution Hi-C contact maps further divided these compartments into six sub-compartments such as A1, A2, B1, B2, B3, and B4 (Table 1.2.1) (Rao et al. 2014; S. Wang et al. 2016; Wijchers et al. 2016).

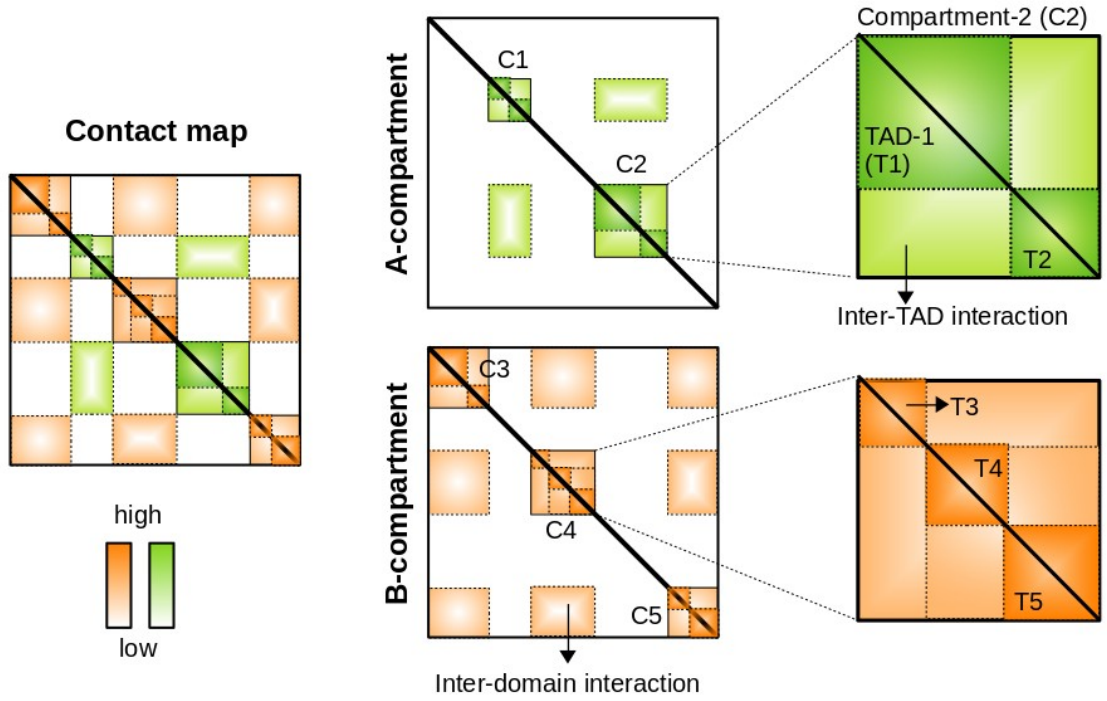

Figure 1.2.4 Hierarchical organization of compartments and TADs in 3D genome.

Table 1.2.1 Sub-compartments

	A1	**A2**	**B1**	**B2**	**B3**
Compartment type	A	A	B	B	B
Gene density	High	High	Low	Low	Low
Gene expression	Highly expressed	Highly expressed	Lowly or not expressed	Lowly or not expressed	Lowly or not expressed
GC content	High	Lower than A1	Low	Low	Low
Replication timing	Early and finishes at the beginning of S phase	Early and continues replicating into the middle of S	Peaks at the middle of S phase	Late	Late

		phase			
Activating histone marks	H3K4me3, H3K4me2, H3K79me2, H3K27ac, and H3K4me1	H3K4me3, H3K4me2, H3K79me2, H3K27ac, and H3K4me1			
H3K9me3		More associated than A1			
H3K27me3			Highly associated	Lesser than B1	Lesser than B1
H3K36me3	Highly associated	Highly associated	Negatively associated	Negatively associated	Negatively associated
Nuclear lamina				Highly associated	Highly associated but lesser than B2
NAD	Depleted	Depleted		Highly associated	Depleted
Remarks			Facultative hetero-chromatin	62% of pericentromeric hetero-chromatin	

The sub-compartment B4 is exclusively present in the human chr19. It is only 0.3% of the genome, but contains KRAB-ZNF genes (130 out of the 278 superfamily genes) and highly associated with both activating H3K36me3 and heterochromatin H3K9me3 and H3K20me3 (Rao et al. 2014).

Compartments are very stable, formed by micro-phase separation, and independent of TAD formation (discussed below). All the cell-types have shown the presence of compartments except oocyte MII and pachytene spermatocytes (they have redefined compartments) (Nora et al. 2017; Schwarzer et al. 2017; Rao et al. 2017; Du et al. 2017; Erdel and Rippe 2018; Alavattam et al. 2019; Y. Wang et al. 2019; Falk et al. 2019). During differentiation, compartments switch their status from A to B in order to repress pluripotent genes and B to A in order to activate cell-type specific genes (Lieberman-Aiden et al. 2009; Dixon et al. 2015). A very recent study showed that interactions with nuclear lamina could prime regions for their formation into B compartments (Borsos et al. 2019).

TADs, sub-TADs, and chromatin loops

Topologically Associating Domains (TADs) are self-associating domains (i.e., regions inside a domain tend to interact more with themselves and less with the regions from neighboring domains) with demarcated boundaries (Sexton et al. 2012; Nora et al. 2012; Dixon et al. 2012). They are stable across cell-types, conserved across evolution, and correlate with several linear genomic features, such as replication, active, and inactive domains (Dixon et al. 2012; Sexton et al. 2012; Rao et al. 2014;

Harmston et al. 2017). They are called the basic structural and functional unit of high-order genome architecture (Szabo et al. 2018). They guide enhancer – promoter interactions (Sexton et al. 2012; Dixon et al. 2012; Shen et al. 2012; Rao et al. 2014; Lupiáñez et al. 2015; Narendra et al. 2015; Symmons et al. 2016; Szabo et al. 2018). TAD boundaries are demarcated by a number of factors, such as CTCF, cohesin, tRNA, SINE, ZNF143, Top2b, and house-keeping genes (active transcription) (Figure 1.2.5) (Dixon et al. 2012; Hou et al. 2012; Rao et al. 2014; Bailey et al. 2015; Uusküla-Reimand et al. 2016). Loss of TAD boundaries leads to the fusion of two adjacent domains, rewiring of enhancer – promoter interactions, the spread of active epigenetic mark, and abnormal phenotypes (Figure 1.2.6) (Lupiáñez et al. 2015; Narendra et al. 2015; Franke et al. 2016; Anderson et al. 2019).

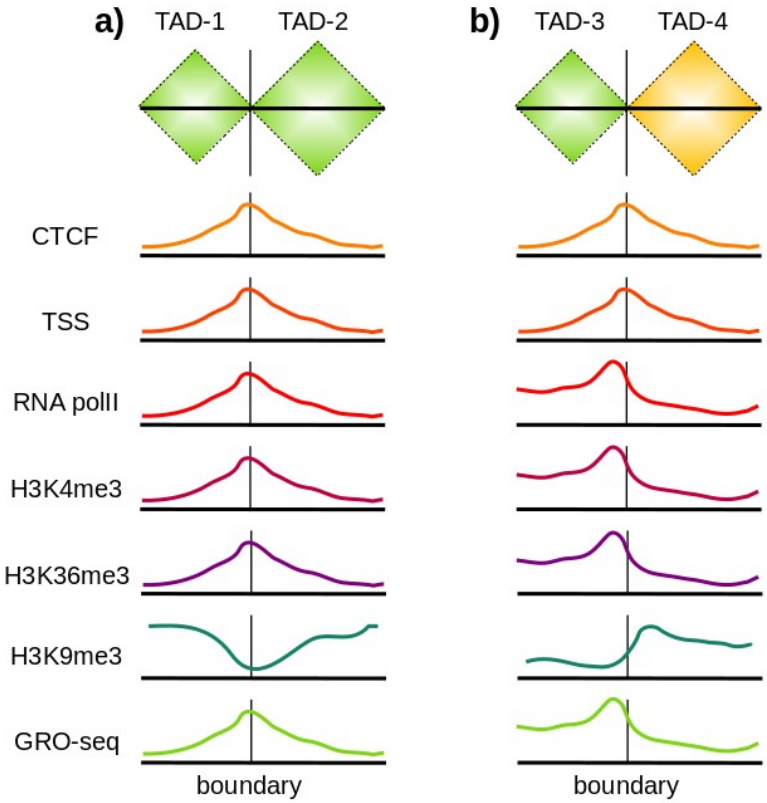

Figure 1.2.5 Enrichment of CTCF, TSS density, RNA polII, GRO-seq and histone modifications around two different types of TAD boundaries, such as active-active and active-inactive.

Although they are stable across cell-types, they are reestablished after every cell division (Figure 1.2.7) (Naumova et al. 2013; Gibcus et al. 2018; H. Zhang et al. 2019). Metaphase of mitosis shows no higher-order structures, such as TADs and compartments (Naumova et al. 2013; Gibcus et al. 2018). TADs start to appear slowly from the 'bottom-up'. Smaller sub-TADs are formed after metaphase, and then, they converge to form multi-domain TAD structures until late G1 (Figure 1.2.7) (H. Zhang et al. 2019). Further, there is an allele-specific dynamics of TADs formation. During oogenesis, cells get arrested in meiosis II, and they have no TADs and compartments (Du et al. 2017) (Figure 1.2.8). However, during spermatogenesis, pachytene spermatocytes have refined compartments with no TADs, and fully developed sperms have well-established TADs and compartments (Alavattam et al. 2019; Y.

Wang et al. 2019). After fertilization, TADs appear slowly in the maternal genome, and they undergo reprogramming in the paternal genome (Figure 1.2.8) (Du et al. 2017).

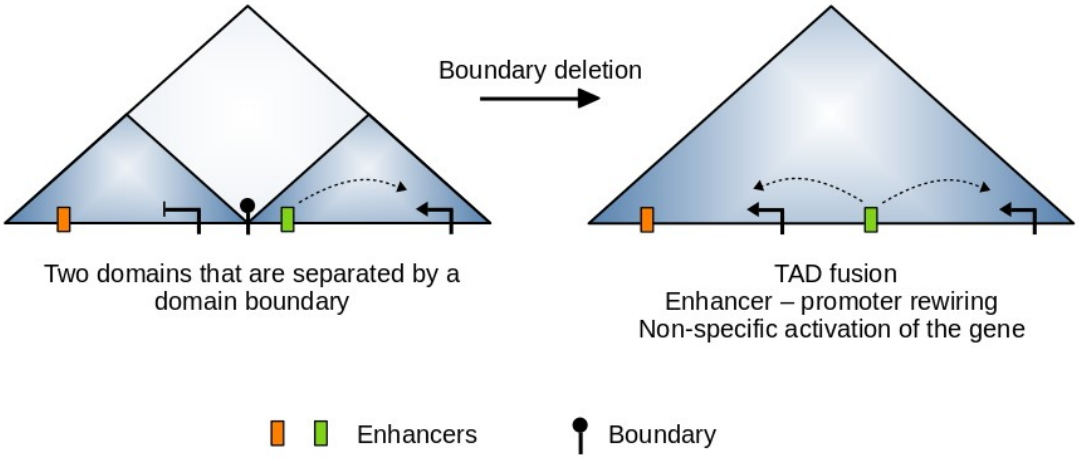

Figure 1.2.6 Loss of TAD boundary and enhancer – promoter rewiring.

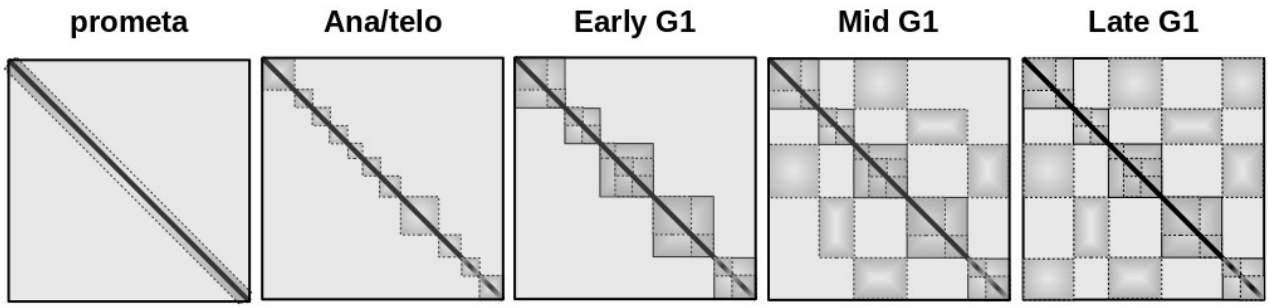

Figure 1.2.7 Dynamics of TADs during cell cycle.

The famous ‘loop extrusion’ model is widely accepted as the mode of domain formation. Computational simulations and real-time *in-vitro* experiments show the extrusion of chromatin via molecular motors, such as condensin and cohesin (Alipour and Marko 2012; Sanborn et al. 2015; Fudenberg et al. 2016; Goloborodko, Marko, and Mirny 2016; Stigler et al. 2016; Nora et al. 2017; Terakawa et al. 2017; Ganji et al. 2018; Davidson et al. 2019). While condensin is predominantly present during mitosis and helps in the formation of mitotic chromosomes by arrays of consecutive loops, cohesin exerts the potential for being the ‘loop extruding factor’ during interphase and thus, help in the formation of TADs (Nora et al. 2017; Rao et al. 2017; Schwarzer et al. 2017; Gibcus et al. 2018).

Independent loss of cohesin and CTCF leads to the loss of loops and TADs. Compartments are preserved and even reinforced (in case of cohesin removal) (Figure 1.2.9) (Haarhuis et al. 2017; Schwarzer et al. 2017; Rao et al. 2017; Nora et al. 2017). Moreover, several studies showed the co-localization of cohesin with CTCF with an offset towards to the 3’ ends of convergent motifs and loss of CTCF leads to the loss of TAD boundaries genome-wide (Parelho et al. 2008; Rubio et al. 2008; Stedman et al. 2008; Wendt et al. 2008; Tang et al. 2015; Nora et al. 2017). Therefore, cohesin

complexes extrude the chromatin via their loops until they find two CTCF motifs in convergent orientation.

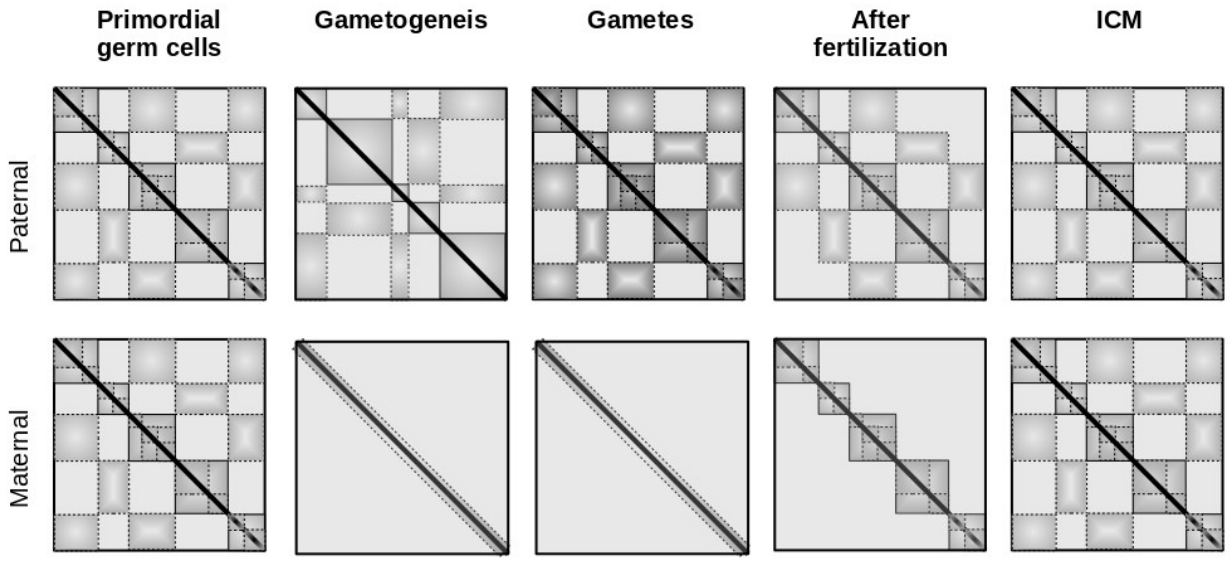

Figure 1.2.8 Allelic reprogramming of TADs before and after fertilization.

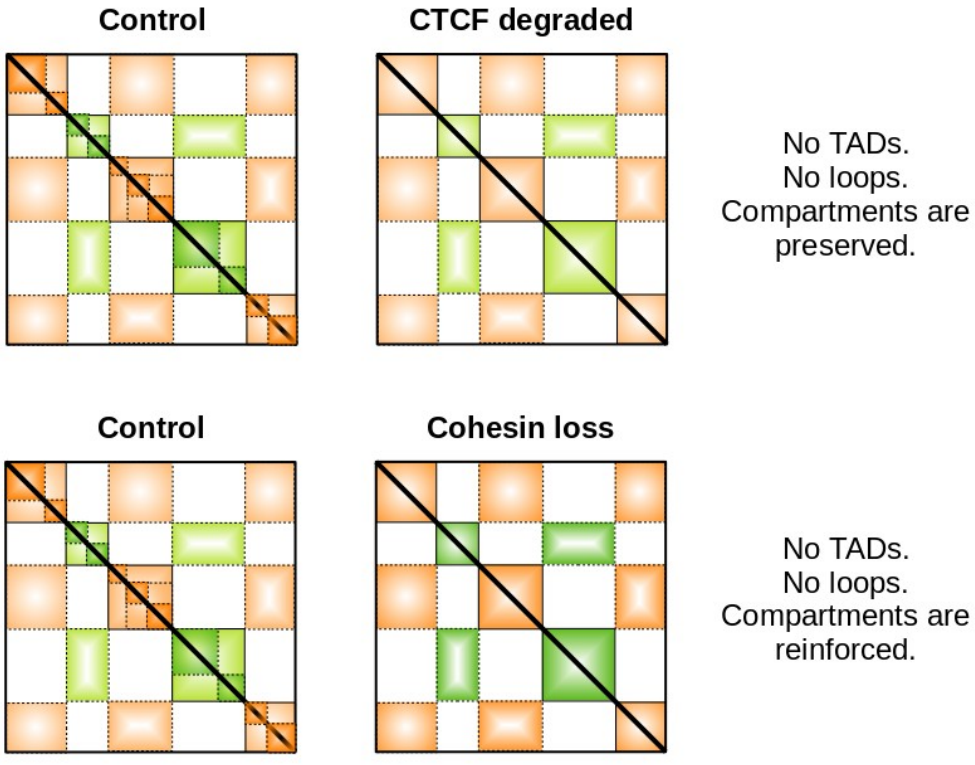

Figure 1.2.9 Genome organization before and after CTCF/cohesin loss

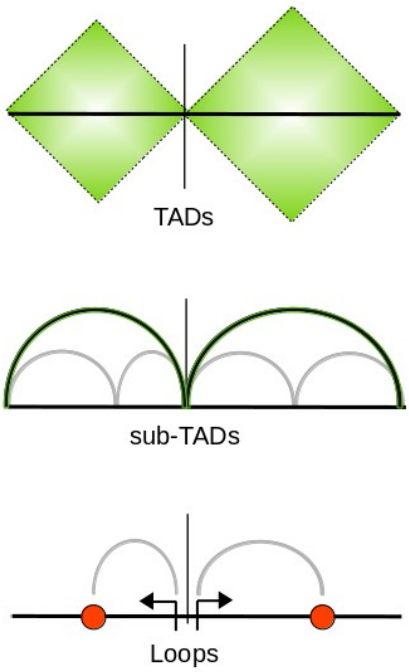

Figure 1.2.10 Hierarchical organization of TADs.

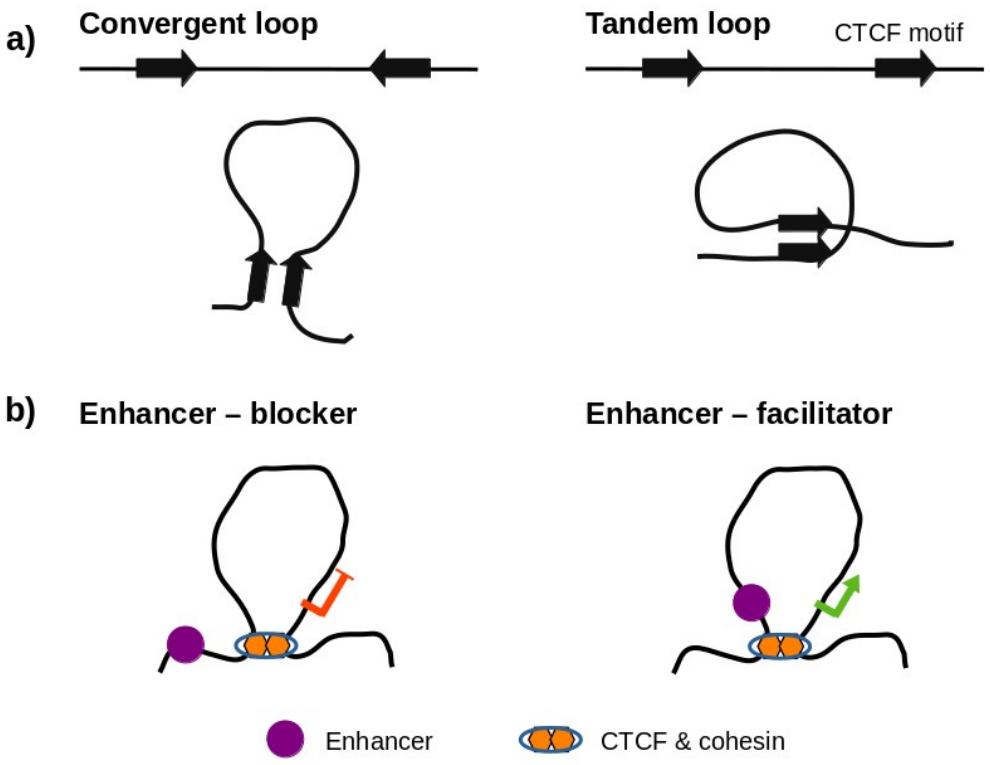

Figure 1.2.11 Types of loops based on (a) CTCF motif orientation, and (b) transcriptional activity.

Further, hierarchically nested sub-TAD substructures are present inside TADs (Figure 1.2.10). Like TADs, sub-TADs exhibit domain-like structures and have boundaries but with have lower insulating abilities than TADs. They are more likely to exhibit cell-type-specific characteristics (Phillips-Cremins et al. 2013; Rao et al. 2014; Bonev et al. 2017; Norton et al. 2018; Beagan and Phillips-Cremins 2020).

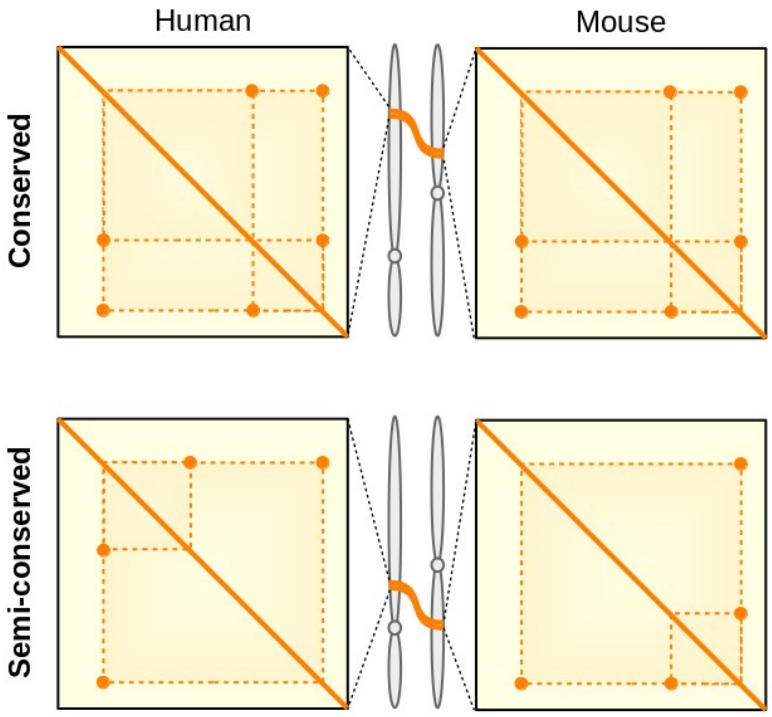

Figure 1.2.12 Different level of conservation of CTCF loops in the orthologous regions of human and mouse, such as conserved and semi-conserved.

The ultimate chromatin structures that are present inside TADs are the chromatin loops. Architecturally, most of the loops are anchored by CTCF motifs that are in a convergent orientation (Figure 1.2.11a) (Rao et al. 2014; Tang et al. 2015). Based on the activity, they can be broadly classified into two categories, such as enhancer facilitator and enhancer blocker (Figure 1.2.11b) (Ong and Corces 2014). The enhancer – linking ability of the chromatin loops to gene promoters is the key property of all higher-order genome architecture (Bonev and Cavalli 2016). The chromatin loops are conserved across evolution to some extent (Figure 1.2.12) (Rao et al. 2014; Vietri Rudan et al. 2015).

Therefore, the above structures summarize the different hierarchical level of the higher-order genome architecture and show the rapid progress in the field of 3D genomes. Some of the aspects regarding domain architecture and their role in gene expression are yet to be addressed.

Section - 2

Do insulated chromatin domains regulate the genome in an allele-specific manner?

2.1 Introduction

The mono-allelically expressed (MAE) genes, i.e., the genes that are expressed only from one of the alleles (Andrew Chess 2012; 2013; Eckersley-Maslin and Spector 2014; Reinius and Sandberg 2015), creates cellular heterogeneity, contributes to genetic diversity, and leads to adaptation (Andrew Chess 2012; Zwemer et al. 2012; Eckersley-Maslin and Spector 2014; Savova et al. 2016). It can be broadly classified into two categories based on how the choice of the allele is made, such as parent-of-origin dependent and stochastic (Figure 2.1.1) (Andrew Chess 2013; Reinius and Sandberg 2015; Massah, Beischlag, and Prefontaine 2015).

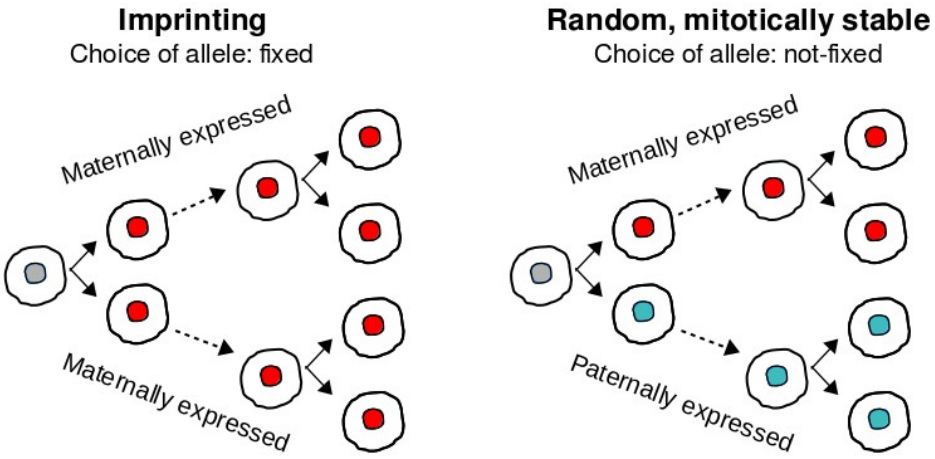

Figure 2.1.1 Broad classification of mono-allelic expression of genes.

i) Fixed: Parent-of-origin specific (Imprinting)

The term ‘imprinting’ was described in 1984 when the initial experiments involving uniparental disomy led to the discovery of unequal contributions from the parents to the embryo (Surani, Barton, and Norris 1984; McGrath and Solter 1984). Chromosomal deletions of imprinted regions from the maternal and the paternal chromosomes can lead to different phenotypes (Knoll et al. 1989). For example, maternal and paternal deletion of 15q11q13 leads to Angelman and Prader–Willi syndrome, respectively (Prader, Labhart, and Willi 1956; Angelman 1965; Knoll et al. 1989; Nicholls 1993; Falls et al. 1999). The imprinted genes have significant implications in growth and metabolism (Frost and Moore 2010). Loss of imprinting can also lead to cancer. For example, loss of imprinting at *H19-Igf2* associates with Wilms’ tumour (Moulton et al. 1994; Steenman et al. 1994). The parental-conflict theory of imprinting states that the imprinting evolved due to the differential interests of parental genomes (Trivers 1974; Iwasa 1998). While paternally-expressed genes tend to increase the growth and fitness of the offspring, maternally-expressed genes suppress the growth of the offspring to conserve the resources while giving sufficient to the offspring (Iwasa 1998). This theory is further supported by androgenetic (AG) and parthenogenetic (PG) chimeras. The AG embryos are larger with a larger placenta than normal (except the brain), and the PG embryos are smaller with a little or no placenta (Judson et al. 2002). A significant proportion of the imprinted genes is expressed in the brain (Davies, Isles, and Wilkinson 2005; Isles, Davies, and Wilkinson 2006). Paternally-expressed imprinted genes are found in the hypothalamus, amygdalas, and the other parts of the limbic or lower brain. Maternally-expressed imprinted genes are found in the prefrontal cortex (Allen et al. 1995; Keverne et al. 1996).

ii) Stochastic/random

When the choice of the allele is made randomly, it is called stochastic. It includes X-chromosome inactivation, random autosomal and allelic exclusion (confined to gene families such as olfactory and antigen receptors) (M. F. Lyon 1961; Pernis et al. 1965; A. Chess et al. 1994; Mostoslavsky, Alt, and Rajewsky 2004; A. Gimelbrant et al. 2007; Reinius and Sandberg 2015).

a) X-chromosome inactivation (XCI)

For dosage compensation, one of the X-chromosomes in females is randomly inactivated during development (example: E6.5 in mouse) and maintained through cell division (M. F. Lyon 1961; Martin et al. 1978). Individual cells inactivate independently of each other, and all the successors maintain the same X-chromosome inactivated (Martin et al. 1978; Boumil and Lee 2001). There is imprinted inactivation of the X-chromosome during the preimplantation stages from 2-cell to 16-cell stage (Sado et al. 2001; Huynh and Lee 2005; Okamoto and Heard 2006; Graves 2006; Massah, Beischlag, and Prefontaine 2015; Pinheiro and Heard 2017; Galupa and Heard 2018).

Non-coding *Xist* RNA mediates the silencing of X-chromosome (Brown et al. 1991; Marahrens et al. 1997; J. T. Lee, Davidow, and Warshawsky 1999; J. T. Lee and Lu 1999), while *Tsix* RNA, the anti-sense of *Xist*, antagonizes the function of *Xist* on the active-X. Few genes escape the X-inactivation and are proposed to have roles in phenotypic differences between the sexes (Carrel and Willard 2005; Johnston et al. 2008).

XCI is a complex mechanism that comprises of four major stages such as counting, choice, inactivation of one X chromosome and then, the maintenance of the same (Avner and Heard 2001; Monkhorst et al. 2008). During counting, a diploid cell assesses the number of X chromosomes present inside. In the case of abnormal chromosomal events such as XXX, XXY, XXXX, XXXY, or XXYY, counting is crucial as only one X chromosome remains active (Brown et al. 1991; Massah, Beischlag, and Prefontaine 2015). Pluripotency factors, such as *Oct4*, *Sox2*, *Nanog*, *CTCF*, and *YY1*, inhibits XCI by suppressing *Xist* expression (Donohoe et al. 2007; Navarro et al. 2008; Donohoe et al. 2009). Dosage-sensitive expression of *Rnf12* is also crucial, and it is the first identified dosage-dependent activator of XCI. Ectopic expression of *Rnf12* in males and females leads to the inactivation of the one and both X chromosomes, respectively (Jonkers et al. 2009). It initiates XCI and also helps in the transcriptional activation of *Xist* by proteasomal degradation of the pluripotency factor *Rex1* (Schulz, Nora, and Heard 2011; Barakat et al. 2011; Gontan et al. 2012). It is also suggested that counting involves a transient homologous pairing of some regions inside the X-chromosome Inactivation Centre (XIC) during S-phase (Bacher et al. 2006; Xu, Tsai, and Lee 2006; Xu et al. 2007; Augui et al. 2007). Following pairing, the inactive X chromosome is directed towards peri-nucleolar space for further silencing (L.-F. Zhang, Huynh, and Lee 2007). Once the choice is made, the chosen one is inactivated by *Xist* expression and other genes in the domain aid *Xist* expression. *Xist* ncRNAs spread, surround the X chromosome, and localize it to the nuclear lamina for inactivation (Nora and Heard 2009; C.-K. Chen et al. 2016). *Tsix* suppresses the activation of *Xist* by its transcription and keep the other X chromosome active (J. T. Lee, Davidow, and Warshawsky 1999).

b) Allelic exclusion

VDJ recombination in immune cells

The allelic exclusion was first discovered in the antigen receptors of the specialized immune cells such as B and T lymphocytes (Pernis et al. 1965; Cebra, Colberg, and Dray 1966; Mostoslavsky, Alt, and

Rajewsky 2004; Vettermann and Schlissel 2010; Brady, Steinel, and Bassing 2010). These immune cells express only one type of receptor to give specificity, which has variable-(diversity)-joining regions. These regions are coded by V, D, and J genes, respectively. From a pool of V genes, few V genes are selected randomly, and rest are deleted/excluded via DNA recombination. D and J genes also select their genes by the same mechanism and linked to form VDJ (Figure 2.1.2). Once a functional VDJ combination is made, it is expressed on the surface of the cell. Further, DNA recombination and expression of the functional receptor are only one of the homologous chromosomes. Once successful rearrangement is made, a feedback mechanism inhibits the rearrangement of the other allele (Nemazee and Hogquist 2003; Cedar and Bergman 2008). Bi-allelic expression of the receptors could lead to multiple specificities and deleterious phenotypes such as autoimmunity (Pelanda 2014). Allelic exclusion leads to the specificity and greater diversity of the immune cell receptors, which are required to counteract the pathogens (Brady, Steinel, and Bassing 2010; Andrew Chess 2013).

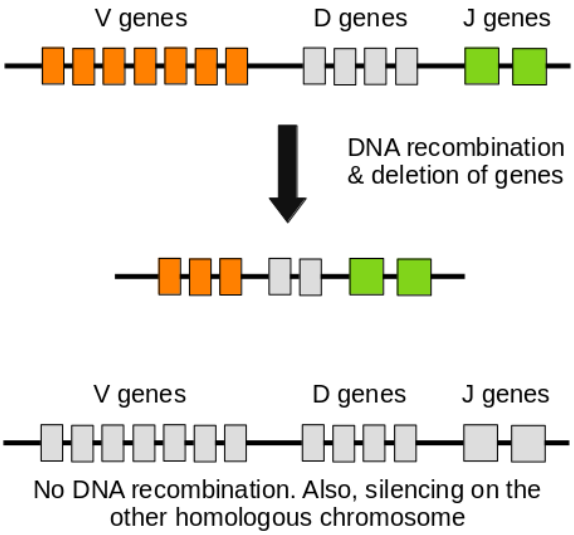

Figure 2.1.2 VDJ recombination of T-cell receptors.

Mono-genic and mono-allelic expression of Olfactory receptor genes

Olfactory receptors (OR) are present on the surface of the olfactory sensory neurons and responsible for the detection of smell (Buck and Axel 1991; Sullivan et al. 1996). Out of ~1000 OR genes in mouse, only one is randomly selected and expressed from only one of the two alleles (A. Chess et al. 1994; A. Chess 1998). Hence, they follow 'one neuron, one receptor' rule (Figure 2.1.3) (Nagai, Armelin-Correa, and Malnic 2016). The rest of the genes are inactivated and kept near the chromocenters at the center of the nucleus, which has a non-traditional 'inside-out' chromosome organization, but not as extreme as rod cells (Clowney et al. 2012; Tan et al. 2019).

Unlike antigen receptor cells, the choice of olfactory receptor genes in allelic exclusion is not through DNA recombination (Eggan et al. 2004; J. Li et al. 2004). Mice that were generated from the nuclear transfer using a neuron that expressed OR gene M71 as a donor was capable of choosing other OR genes (J. Li et al. 2004), suggesting that the choice of expressed OR is stochastic. Co-operative intra- and inter-chromosomal interactions among enhancers leads to such singular olfactory receptor expression (Lomvardas et al. 2006; Markenscoff-Papadimitriou et al. 2014; Monahan et al. 2017).

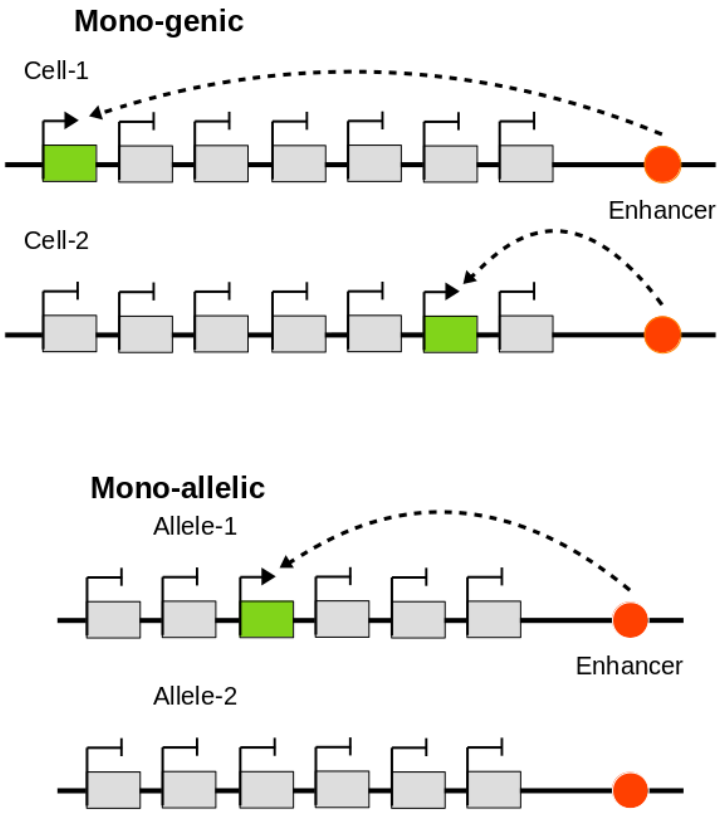

Figure 2.1.3 Mono-genic and mono-allelic expression of genes.

c) Random autosomal mono-allelic expression

Apart from sex-chromosomes and specialized gene families, mono-allelic expression is also seen among the autosomal genes (A. A. Gimelbrant et al. 2005; A. Gimelbrant et al. 2007; Zwemer et al. 2012; Nag et al. 2013; Gendrel et al. 2014; Q. Deng et al. 2014; Nag et al. 2015). It is classified into two sub-types, such as dynamic and fixed (Reinius and Sandberg 2015).

Dynamic: If the choice of the allele is switched over time in the same clonal population of cells, it is called dynamic (Reinius and Sandberg 2015). The dynamics of transcriptional bursting might explain this phenomenon (Q. Deng et al. 2014). Under the assumption of allelic independence and Poisson nature of transcription, many lowly expressed genes, which exhibit low frequency of transcriptional bursts, are expected to exhibit dynamic mono-allelic expression in single cells. On the other hand, the highly expressed genes, marked with a high frequency of bursts, often exhibit bi-allelic expression unless the gene had regulated fixed mono-allelic expression and not the dynamic one (Q. Deng et al. 2014; Reinius and Sandberg 2015; Larsson et al. 2019).

Fixed: Once the choice of allele is established, it is maintained through subsequent cell divisions. This type gives true global heterogeneity in cells across tissues. A gene can show mono-allelic expression in

one tissue and be bi-allelic in other tissues (A. Gimelbrant et al. 2007; Zwemer et al. 2012; Andrew Chess 2012; Eckersley-Maslin et al. 2014).

iii) Mechanisms establishing and maintaining mono-allelic expression

a) Domain regulation by a control element

Imprinted genes are known to locate in clusters for their coordinated regulation by cis-regulatory elements like Imprinting Control Regions (ICRs) and long noncoding RNAs (Figure 2.1.4) (Pfeifer 2000; Reik and Walter 2001; Sleutels, Zwart, and Barlow 2002; C. M. Williamson et al. 2004; Mancini-Dinardo et al. 2006; Edwards and Ferguson-Smith 2007; Koerner et al. 2009; Ferguson-Smith 2011). X-chromosome inactivation center (XIC) is also well-known for its role in chromosome-wide inactivation (Jeannie T Lee et al. 1996). Ectopic Insertion of these elements into a different region can initiate mono-allelic expression (Jeannie T Lee et al. 1996; Jeannie T. Lee and Jaenisch 1997; Matsuzaki et al. 2009). It has been proposed that linear clustering of imprinted and certain other mono-allelically expressed genes might have evolved under the constraint to access the imprinting control regions (Pfeifer 2000; Marisa S. Bartolomei 2009; Ohlsson, Paldi, and Graves 2001).

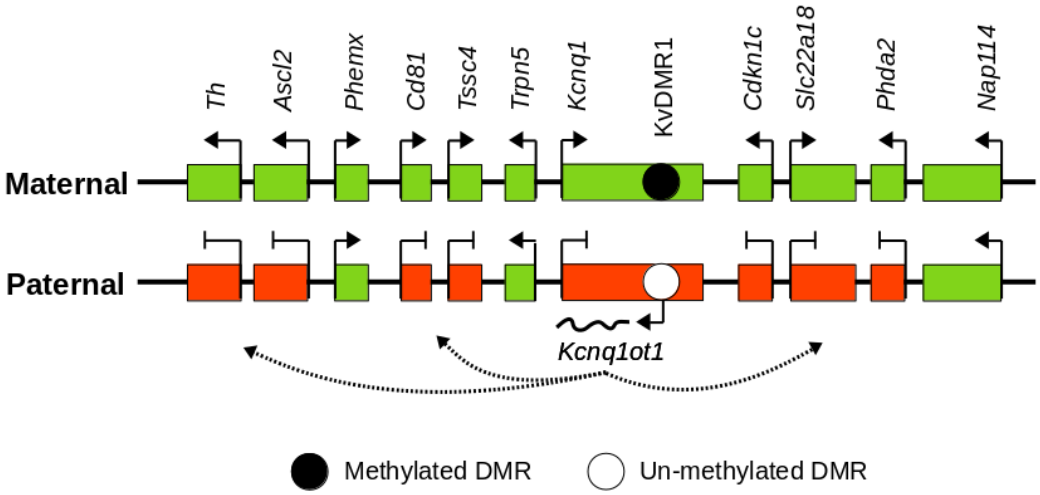

Figure 2.1.4 Domain regulation of imprinted loci by ICRs and ncRNAs.

b) Differentially Methylated Regions (DMRs)

Soon after the discovery of imprinted genes, few regions were found as differentially methylated between the alleles. They have a primary role as Imprinting Control Region (ICR) (Ferguson-Smith et al. 1993; Stöger et al. 1993; M. S. Bartolomei et al. 1993; E. Li, Beard, and Jaenisch 1993). They can be classified as primary/germline and secondary/somatic DMRs. Germline and somatic DMRs are established during gametogenesis and after fertilization, respectively (Figure 2.1.5) (Sasaki et al. 1995; Ohno, Aoki, and Sasaki 2001; Bhogal et al. 2004; Lees-Murdock and Walsh 2008; Ferguson-Smith 2011; Seisenberger et al. 2013). The de novo methyltransferases *DNMT3A* and *DNMT3B*, and regulatory factor *DNMT3L* are required for the establishment of methylation at DMRs (Kaneda et al. 2004; Bourc'his et al. 2001; Kato et al. 2007). Although there is a genome-wide erasing of epigenetic marks once the primordial germ cells enter the genital ridges during gestation, the establishment of methylation is during late fetal in males and early neonatal in females (Lucifero et al. 2004; Hajkova et al. 2008; Lees-Murdock and Walsh 2008).

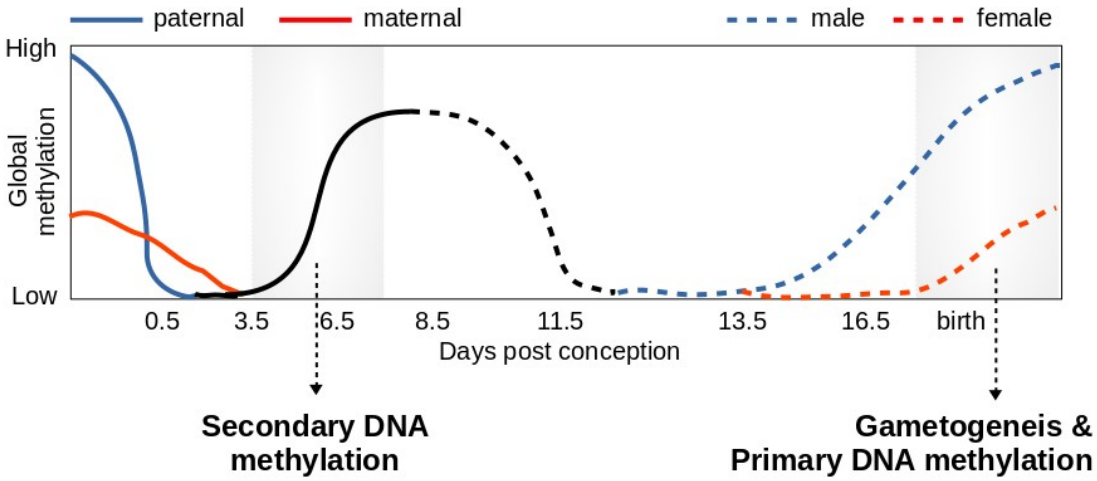

Figure 2.1.5 Maternal and paternal DNA methylation dynamics after fertilization.

c) Repression by non-coding RNA (ncRNA)

The role of non-coding RNA in mono-allelic expression is well-characterized in X-chromosome inactivation and imprinting (Brown et al. 1991; J. T. Lee, Davidow, and Warshawsky 1999; Sleutels, Zwart, and Barlow 2002; Pandey et al. 2008). In X chromosome inactivation, *Xist* is expressed from the inactivated chromosome, and *Tsix*, an antisense transcript to *Xist*, blocks the transcription of *Xist* in the active chromosome (Figure 2.1.6) (Brown et al. 1991; J. T. Lee, Davidow, and Warshawsky 1999; J. T. Lee and Lu 1999). *Xist*, further, surrounds and represses the entire X chromosome through polycomb repressive complex (Kohlmaier et al. 2004; J. Zhao et al. 2008; Maenner et al. 2010; Kaneko et al. 2010). It also brings the inactive X chromosome to the nuclear periphery for silencing through binding directly with Lamin B receptor (C.-K. Chen et al. 2016).

The imprinted domain *Igf2r* is one of the well-documented examples of showing the role of anti-sense ncRNA in repressing the entire domain of imprinted genes. The ncRNA *Air* is anti-sense to only *Igf2r*, and when it is expressed from the paternal copy, it silences other genes in the domains, such as *Slc22a2* and *Slc22a3*, via spatial proximity achieved through chromatin compaction, and recruiting PRC and *EHMT2*. In the maternal copy, the *Air* is silenced via DNA-methylation of the promoter. Premature termination of the transcription of *Air* also leads to the loss of repression (Wutz et al. 1997; Zwart et al. 2001; Sleutels, Zwart, and Barlow 2002; Andergassen et al. 2019).

At the imprinted domain *Kcnq1*, transcription of anti-sense *Kcnq1ot1* ncRNA leads to the repression of the entire domain by G9a, and PRC2, and methylation of somatic DMRs by *Dnmt1* in the paternal chromosome (Lewis et al. 2004; Umlauf et al. 2004; Lewis et al. 2006; Mancini-Dinardo et al. 2006; Pandey et al. 2008; Mohammad et al. 2010). Further, *Kcnq1ot1* has been shown to interact with PRC proteins and mediates the compaction of the domains for silencing (Terranova et al. 2008). Therefore, non-coding RNAs regulate allele-specific expression either by repressing the transcription of its antisense transcript or by recruiting repressive complexes (Yang and Kuroda 2007).

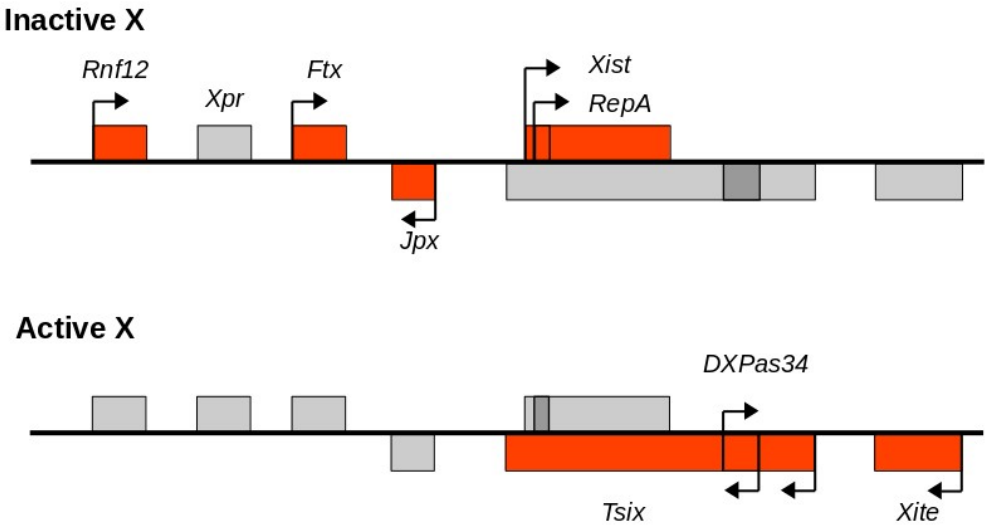

Figure 2.1.6 Expression of several non-coding RNAs in X-chromosome inactivation.

d) Allele-specific spatial localization

Due to differential nuclear localization of euchromatin and heterochromatin, distinct spatial localization of active and inactive alleles of MAE genes may help to maintain their contrasting transcriptional states, though the evidence for the causal relationships between spatial localization and mono-allelic expression remains limited (Heitz 1928; Takizawa et al. 2008; Yang and Kuroda 2007). The chromosome territories may also assort, though not necessarily, the active and inactivate alleles spatially because the transcription levels of gene positively correlate with their distance from the periphery of chromosomal territory (T. Cremer et al. 1993; T. Cremer and Cremer 2001; Mahy, Perry, and Bickmore 2002; Chaumeil et al. 2006; Clemson et al. 2006).

In X chromosome inactivation, the active and inactive chromosomes occupy distinct territories correlating with their transcriptional state (Barr and Bertram 1949; L.-F. Zhang, Huynh, and Lee 2007). The inactive X chromosome localizes at the nuclear periphery and known to interact with nuclear lamina via interactions between *Xist* and Lamin B (C.-K. Chen et al. 2016). *Xist* also form a highly repressive nuclear compartment, and chromatin regions inside it are silenced (Clemson et al. 2006; Chaumeil et al. 2006). Escapee genes are predominantly present outside this nuclear compartment and present in an outer-rim of active transcription (Clemson et al. 2006).

Besides chromosome-level spatial organization, individual genes and gene clusters are also shown to localize different nuclear positions (Dietzel et al. 2004; Yang and Kuroda 2007; Takizawa et al. 2008; Shachar and Misteli 2017; Tan et al. 2019). Mono-allelically expressed astrocyte-specific marker *GFAP* is shown to localize its inactive allele closer to the nuclear periphery compared to the active allele (Takizawa et al. 2008). The nuclear aggregation of the inactive OR genes at the nuclear center (whose nuclear organization is in inside-out configuration with heterochromatin at the center and euchromatin at the periphery) is also shown in mono-allelic and mono-genic expression of OR genes (Magklara et

al. 2011; Clowney et al. 2012; Tan et al. 2019). Therefore, allele-specific localization of active and inactive alleles are efficient in establishing and maintaining several types of mono-allelic expression.

e) Allele-specific chromatin conformation

At chromosome level: The inactive X-chromosome can be seen as a highly compact 'Barr body' near the nuclear periphery, and its higher-order architecture is entirely different from the active one (Barr and Bertram 1949; Eils et al. 1996; Mary F Lyon 2003; Teller et al. 2011; X. Deng et al. 2015; Giorgetti et al. 2016). Broadly, it is divided into two mega-sized domains, and it is called the bipartite structure of the inactive X-chromosome (Figure 2.1.7) (X. Deng et al. 2015; Giorgetti et al. 2016). A small, highly conserved element DXZ4 is crucial for the bipartite structure (Horakova et al. 2012; McLaughlin and Chadwick 2011; Darrow et al. 2016; G. Bonora et al. 2018). Deleting that sequence leads to the disruption of the bipartite structure (Figure 2.1.7) (Darrow et al. 2016; Giorgetti et al. 2016). It is hypothesized that the bipartite structure exposes this macro-satellite repeats for their binding to the nuclear periphery and nucleolus via CTCF binding (Giancarlo Bonora and Disteche 2017). The inactive X chromosome further shows no higher-order chromatin architectures such as compartments and TADs (Figure 2.1.7) (X. Deng et al. 2015; Giorgetti et al. 2016).

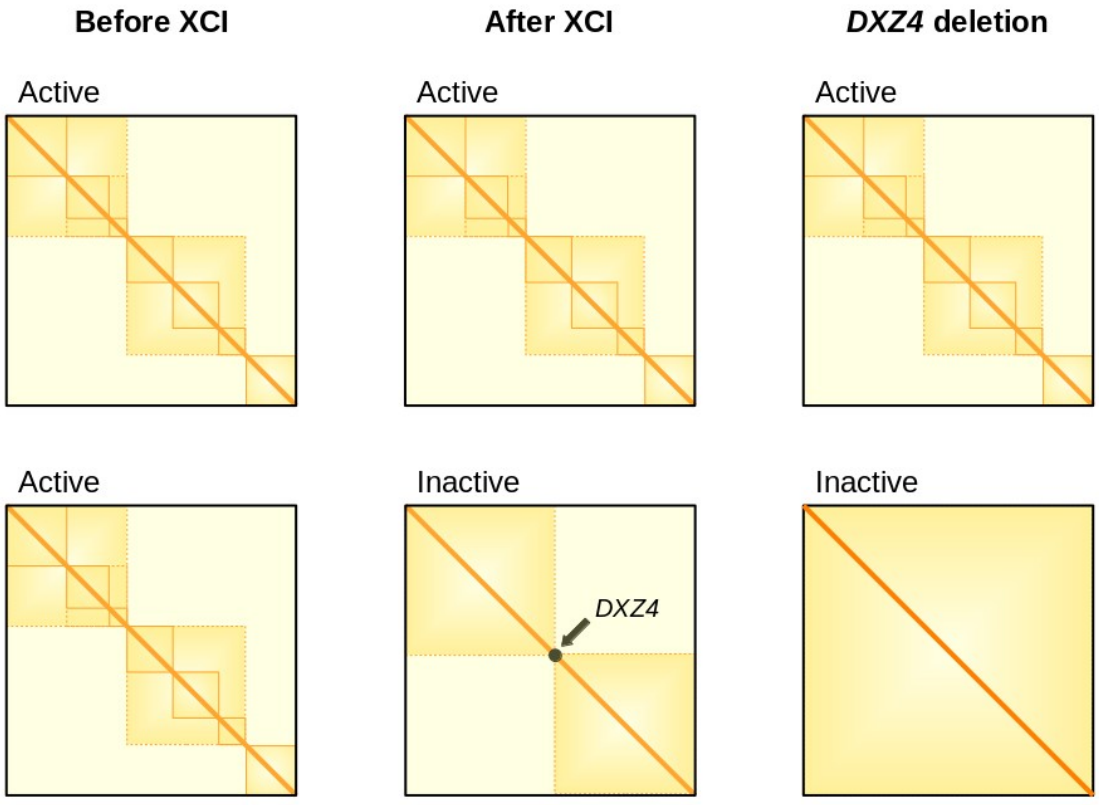

Figure 2.1.7 3D organization during XCI and after deletion of *DXZ4* element.

At domain level: Allele-specific chromatin looping is well-characterized at the imprinted domain *Igf2-H19* (Murrell, Heeson, and Reik 2004; Kurukuti et al. 2006; Nativio et al. 2009; Massah, Beischlag,

and Prefontaine 2015). *Igf2* and *H19* are expressed from the paternal and maternal alleles respectively (DeChiara, Efstratiadis, and Robertson 1990; DeChiara, Robertson, and Efstratiadis 1991; M. S. Bartolomei, Zemel, and Tilghman 1991; Y. Zhang and Tycko 1992; Rachmilewitz et al. 1992; Jinno et al. 1995). They are insulated from each other in two distinct chromatin domains via chromatin looping by CTCF and cohesin (Murrell, Heeson, and Reik 2004; Kurukuti et al. 2006; Nativio et al. 2009). While the chromatin loop between unmethylated *H19*-DMR and *Igf2*-DMR1 in the maternal chromosome prevents *Igf2* to the enhancer, *H19* is an active domain. In the paternal chromosome, methylated DMRs that prevent CTCF binding lead to the spatial proximity of *Igf2* to the enhancer. *H19* is silenced via DNA methylation of its promoter (Figure 2.1.8) (Ferguson-Smith et al. 1993; Kurukuti et al. 2006; Massah, Beischlag, and Prefontaine 2015).

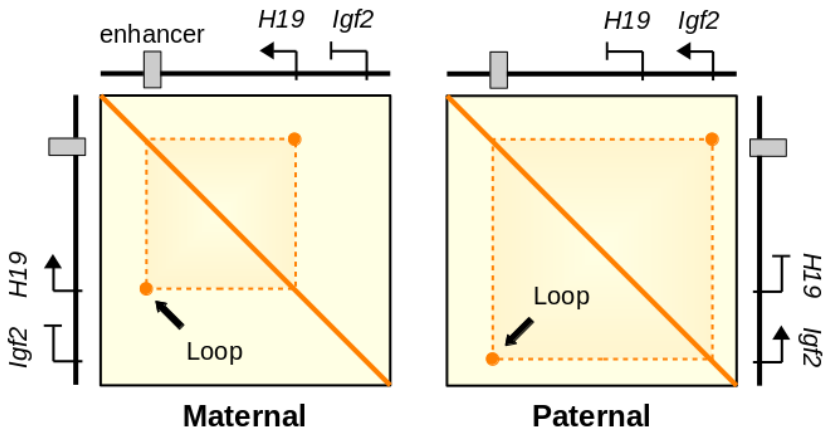

Figure 2.1.8 Allele-specific chromatin looping at H19/Igf2 loci as seen in Hi-C contact maps.

f) Genetic mechanism

When one of the functional copies of a gene is damaged either due to point mutations or abnormal chromosomal events, it leads to loss-of-function, mono-allelic expression and severe phenotypic conditions. For examples, mutations in *TBX5* lead to Holt-Oram syndrome and mutations in *MECP2* lead to Rett syndrome (Basson et al. 1997; Amir et al. 1999; Huang et al. 2002; Gui, Slone, and Huang 2017). Further, SNPs can also lead to allele-specific chromatin interactions (Tang et al. 2015).

iv) Methods to detect the mono-allelic expression

1. DNA-RNA FISH (Figure 2.1.9) (Takizawa et al. 2008; Eckersley-Maslin et al. 2014),
2. cDNA sequencing (Figure 2.1.10) (J. Wang et al. 2007),
3. Allele-specific gene expression analysis using microarray or RNA sequencing (A. Gimelbrant et al. 2007; Rozowsky et al. 2011; Zwemer et al. 2012; Gendrel et al. 2014; Eckersley-Maslin et al. 2014),
4. Computational prediction based on the equal appearance of active (H3K36me3) and inactive (H3K27me3) on the gene body (Nag et al. 2013; 2015).

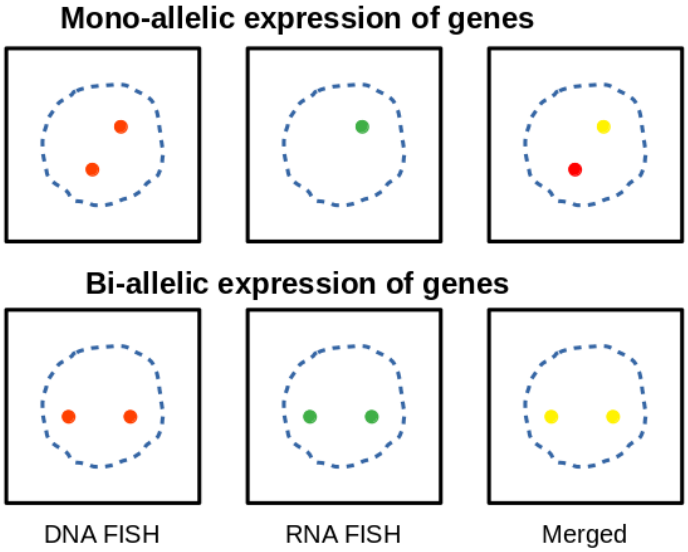

Figure 2.1.9 DNA-RNA FISH inferring mono and bi-allelic expression of genes.

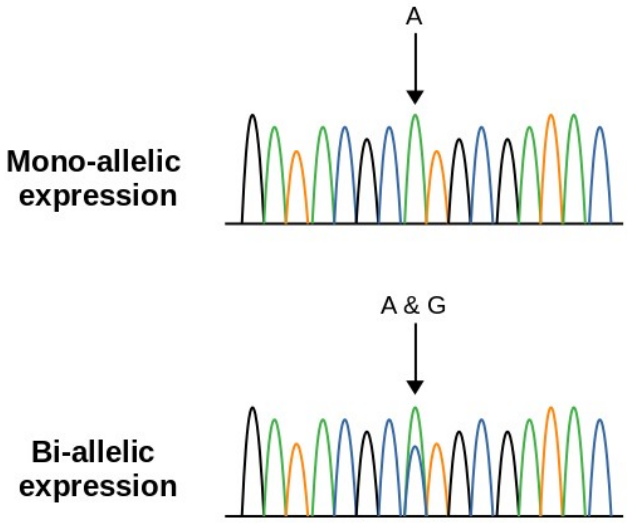

Figure 2.1.10 Sanger sequencing of reverse transcription PCR product of mono-allelic and bi-allelic expression of genes.

v) Aim & motivation

Establishment and maintenance of mono-allelic expression is vital for development and protection against pathogens. Understanding how the mechanisms that govern mono-allelic expression, therefore, gains more importance for human health and precision medicine in future. While it has been more than a decade since the identification of widespread expression of the random autosomal mono-allelic expression, the presence or absence of mechanisms that aid and govern the other forms of mono-allelic expression have not been explored in random autosomal mono-allelic expression. Due to the availability of genome-wide mono- and bi-allelically expressed gene lists and allele-specific chromatin interaction maps, it is now possible to address whether some of the mechanisms that govern imprinting, such as linear clustering and allele-specific chromatin conformation, also govern random mono-allelic expression.

2.2 Materials & Methods

Data-sets of random MAE and BAE genes

Table 2.2.1 List of datasets used in the study

Type	Species	Cell types	Source
Inferred	Human	Lymphoblastoid (hLCL), K562	(Nag et al. 2013)
	Mouse	Lymphoblastoid (mLCL), mESC	(Nag et al. 2015)
Experimentally identified	Human	Lymphoblastoid (hLCL)	(A. Gimelbrant et al. 2007)
	Mouse	Lymphoblastoid (mLCL)	(Zwemer et al. 2012)
		mESC	(Gendrel et al. 2014)

Clustering of genes

We performed this analysis to elucidate if MAE genes clustered among themselves (just like imprinted genes) and got assorted from BAE genes. Clustering of MAE genes would give a benefit of controlling those genes with a single regulatory element. Due to low number of experimentally identified MAE genes (A. Gimelbrant et al. 2007; Gendrel et al. 2014), they were not used for the analysis. Observed gene pairs such as MAE-MAE, BAE-BAE, and mix (MAE-BAE and BAE-MAE) were calculated by counting the number of instances when an MAE gene followed another MAE genes; a BAE gene followed another BAE gene and the cases when they did not respectively. The expected number of above pairs was calculated by an equation Pij = Pi * Pj [‘i’ and ‘j’ were the allelic status of pairs. Pi and Pj were the frequencies of each type of gene (MAE or BAE)]. Density (number of genes per 100kb) of MAE and BAE genes was calculated. Bins were designated as MAE and BAE bins when they were at least two MAE (no BAE) and two BAE (no MAE) genes, respectively. As a control, the gene labels were randomized, and bins were designated as MAE and BAE as above. The number of original and randomized MAE/BAE bins were plotted as barplots for the cell-lines. P-values were calculated using binomial tests.

Kronecker delta calculation

We performed this analysis to check if CTCF was at boundaries of MAE and BAE domains. Due to low number of experimentally identified MAE genes (A. Gimelbrant et al. 2007; Gendrel et al. 2014), they were not used for the analysis. Six genes upstream (gene designations: -g6, -g5, -g4, -g3, -g2, -g1) and five genes downstream (gene designations: +g1, +g2, +g3, +g4, +g5) were mapped to each insulator CTCF site from ChromHMM (Ernst and Kellis 2012). CTCF sites that did not have genes as per condition were removed. From the left side to the right side, considering two genes at a time, Kronecker delta was assigned using the formula below (For example: -g6 & -g5 leads to -5, -g5 & -g4 leads to -4 and so on).

$$\delta(x_{i-1}, x_i) = \begin{cases} 0 & \text{if } x_{i-1} = x_i \\ 1 & \text{otherwise} \end{cases}$$

It was done for all insulator CTCF sites. Then the average values at each corresponding position (i.e., average of all values at -5 leads to final value at -5 in the figure and so on) were plotted. As a control, we randomized the positions of insulator sites in the genome 100 times and plotted the mean.

ChIA-PET gap-loop-gap analysis

We performed this analysis to check if MAE genes were insulated from BAE genes in higher-order genome architecture via CTCF-mediated chromatin loops. Insulation of MAE genes would prevent transcriptional interference with highly expressed BAE genes. CTCF ChIA-PET loops for human lymphoblastoid and mESC were taken from (Tang et al. 2015) and (Handoko et al. 2011), respectively. Loops that were having at least three PET counts, intra-chromosomal, and length of less than 1mb, were filtered according to (Fullwood et al. 2009). Both anchors of CTCF ChIA-PET loops that overlapped with ChromHMM insulator sites (Ernst and Kellis 2012; Shen et al. 2012) in respective species were filtered and used for further analyses. These loops and with their flanking regions on either side of the loops, having lengths the same as those of respective loops, were assessed for the enrichment of MAE and BAE genes from various studies. Average aggregation values for all loops were normalized with total gene count accordingly. These final values were then scaled to 0-1 using [(x-min(x))/(max(x)-min(x)], where x is the vector of values. P-values were calculated using the Mann-Whitney U test for the normalized enrichment of genes inside the loop anchors (20% of the total loop length on both anchors).

Conserved and variable status of MAE genes

We performed these analyses to check if conserved MAE genes (i.e., genes that were expressed mono-allelically in two different cell-types in an organism or in same cell-type of two different species) maintained similar epigenetic features.

Between different human cell-types: Genes were categorized as conserved MAE (mono-allelic expression in both hLCL and K562), conserved BAE (bi-allelic expression in both hLCL and K562), MAE in hLCL but BAE in K562, and BAE in hLCL but MAE in K562. Their normalized enrichment inside insulator CTCF loops was calculated separately in hLCL and K562 by gap-loop-gap analyses and plotted as solid and dashed lines, respectively. Normalized enrichment of insulators and enhancers was calculated in the CTCF loops enclosing the above categories of genes separately in hLCL and K562. Log2 ratio of insulators to enhancers in hLCL and K562 were plotted as solid and dashed lines, respectively. P-values were calculated using the Mann-Whitney U test for the normalized enrichment of genes inside the loop anchors (20% of the total loop length on both anchors).

Between human and mouse lymphoblastoid cells: Orthologous gene information was taken from Ensembl. By comparing MAE/BAE genes in lymphoblastoid cell-lines, genes were classified as conserved MAE (mono-allelic expression in both human and mouse), conserved BAE (bi-allelic expression in both human and mouse), MAE in human but BAE in mouse, and BAE in human but MAE in mouse. Orthologous ChromHMM insulator CTCF sites of human (hg19) in mouse (mm10) were obtained by using UCSC liftover (with a minimum ratio of bases that must remap as 0.1) and checked for CTCF binding in mouse by mapping CTCF ChIP-seq peaks from GSE36030. Percentage of genes having at least one insulator CTCF site and CTCF site overlapping with CTCF ChIP-seq peaks within 20kb of gene TSS was calculated separately for the above-mentioned genes. P-values were calculated using Fisher's exact test.

CTCF depleted transcriptome, insulation and neighborhood analysis
We performed the analyses to check the effects of CTCF depletion on MAE genes.

Gene expression changes: SRA files for LPS induced CTCF depleted B-cells in mLCL were downloaded from GSE98507 (Pérez-García et al. 2017). They were converted into 'fastq' format using 'fastq-dump' (SRA Toolkit). Differential gene expression was calculated using tophat and cufflinks without new gene/transcript discovery (Trapnell et al. 2012). RPKM values for control (no auxin) and CTCF depleted (2days auxin-treated) of mESC were downloaded from GSE98671 (Nora et al. 2017). Log2 fold change of CTCF depletion to control was calculated, and density plots were made for MAE and BAE genes.

Changes in domain boundary insulation: Hi-C data (.cool format) and dip prominence scores (resolution: 20kb, mm9) were taken from GSE98671 (Nora et al. 2017). Higher the dip prominence, the higher the locally insulating boundaries. Gene coordinates for inferred and experimentally identified mESC MAE and BAE genes were converted into mm9. Dip prominence values were mapped upstream to the transcription start sites (TSS) of genes, and unique values were used for the analysis. Hi-C data (.cool format) was extracted using Cooler (Abdennur and Mirny 2019). The ratio of the CTCF depleted to control contact matrices were visualized using R.

Neighborhood of MAE genes that got affected upon CTCF depletion: Up-regulated and down-regulated MAE genes (1.5 fold higher in CTCF depletion with respect to control) were mapped into CTCF ChIA-PET loops of mouse embryonic stem cells (Handoko et al. 2011). These loops were anchored by insulator CTCF sites in mESC. RPKM of nearest neighbors on both sides in control were plotted as neighbors of MAE up- and down-regulated genes.

Allele-specific virtual 4C analysis:
We performed these analyses to check if there is an allele-specific chromatin conformation between two alleles of MAE genes. As a control, we also performed this on the two alleles of BAE genes.

In hLCL: Processed maternal and paternal Hi-C data ('.hic') files of hLCL were downloaded from GSE63525 (Rao et al. 2014). They were extracted using 'Juicer tools' from Aiden's lab (https://github.com/aidenlab/juicer/wiki/Download). RNA-pol2 ChIA-PET loops of hLCL were taken from GSE72816 (Tang et al. 2015), and anchors of the loops were overlaid onto Hi-C pairs to get loop interaction frequencies in the maternal and paternal genome. The average interaction frequency of all RNA-pol2 loops within the 5kb of gene promoter was calculated for paternal and maternal alleles. A ratio of maternal to paternal enrichment was calculated. MAE genes with ratio more than quartile Q3 of the distribution were classified as maternally expressed and less than Q1 as paternally expressed genes. BAE genes within Q1 and Q3 were used as control.

In mESC: The 'fastq' files of allele-specific promoter capture Hi-C and RNA-seq of mESC were downloaded from GSE107421 (Rivera-Mulia et al. 2018). SNP information of 'Cast' and '129' was taken from Ensembl. Allele-specific Hi-C processing with ICED normalization was done using 'HiC-Pro' (Servant et al. 2015). Log2 fold change (129/Cast) of expression was calculated. Genes with log2 FC >10 and log2 FC < -10 were used to define the active and inactive alleles of MAE genes respectively. BAE genes with -0.1 < log2 FC < 0.1 were used as control. All the interacting bins within 10mb of the gene promoters were filtered, and log2 ratio of active to inactive interaction frequencies

were calculated (in the case of BAE genes, log2 ratio of active to active interaction frequencies was calculated).

Allele-specific RNA-seq analysis

We performed this analysis to check if the inactive allele of MAE gets activated (Nag et al. 2015) after CTCF depletion. SRA files of control and 2-days auxin-treated (CTCF depleted) RNA-seq were downloaded from GSE98671 (Nora et al. 2017). They were converted into 'fastq' files by 'fastq-dump' of NCBI SRA Toolkit and processed by the in-house pipeline. Briefly, paired-end reads were aligned to indexed mouse mm10 reference genome by using bowtie2 with default parameters. The output 'sam' files were converted into 'bam' files by using 'samtools'. Then, pairs were fixed, sorted, removed duplicates, and indexed by using 'fixmate', 'sort', 'markdup' and 'index' of 'samtools' respectively.

'ASEQ' (http://demichelislab.unitn.it/ASEQ) was used to genotype and get the number of read counts to SNPs from control and CTCF depleted RNA-seq experiments. Then, 'GeneiASE' (https://github.com/edsgard/geneiase) with the parameter 'individual condition-dependent ASE' was used to call the genes which have allele-specific changes between control and CTCF depleted. The active and inactive alleles of the MAE genes ($p<0.05$) were defined when read counts were >5 and <=2 in the control experiment respectively. Then, the log2 ratio of CTCF depleted to control read counts in the active and inactive alleles were plotted.

2.3 Results

Insulation of MAE genes from BAE genes

Functional differences between MAE and BAE genes prompted us to check if there were domains of MAE genes (Nag et al. 2013; 2015), similar to imprinted genes. We calculated the percentage change of observed gene pairs from the expected number of gene pairs, such as MAE-MAE, BAE-BAE, and mix (MAE-BAE and BAE-MAE) in multiples cell-lines of human and mouse (Nag et al. 2013; 2015) (Figure 2.3.1a). We observed around 25% increase of MAE-MAE and BAE-BAE gene pairs, but a 20% decrease of mix pairs to expected gene pairs. We further defined 100kb bins exclusively containing only the MAE or only the BAE genes (Nag et al. 2013; 2015). As a control, we randomized the allelic status of all the genes and re-assigned the 100kb bins. Figure 2.3.1b showed that the MAE/BAE bins were 1.56 fold more in number than the randomized set in hLCL. The above observations suggested that there were domains of MAE and BAE genes, which were assorted from each other.

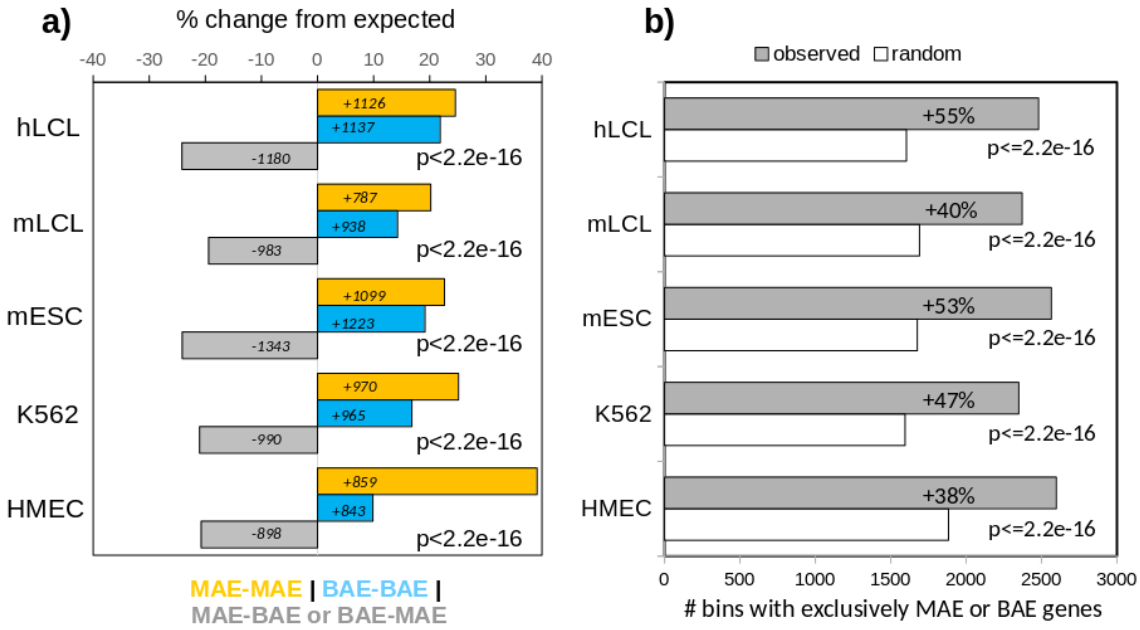

Figure 2.3.1 (a) Percentage change of observed from expected number of gene pairs. (b) Number of 100kb domains in observed (grey) and randomized (white) datasets.

Then, we hypothesized that the domains of MAE genes were epigenetically insulated from the domains of BAE genes. We assessed this by analyzing the presence of an epigenetic insulator protein. CTCF is currently known as the best insulating agent, and we checked its presence between the domain borders by calculating Kronecker delta for every CTCF marked insulator site with six genes upstream and five genes downstream of the insulators and averaged their values (Figure 2.3.2). The drop in the Kronecker delta values after encountering the insulator site clearly suggested that the CTCF was marking the domain borders in the linear genome.

Role of higher-order genome architecture in regulating MAE genes

The presence of CTCF at the domain borders hinted at the involvement of chromatin loops in regulating mono-allelic expression. We, therefore, tested if the CTCF-mediated chromatin loops (Tang

et al. 2015; Handoko et al. 2011) insulated MAE genes from the BAE genes (Figure 2.3.3). In general, MAE genes showed higher preference inside insulator CTCF loops when compared to BAE genes.

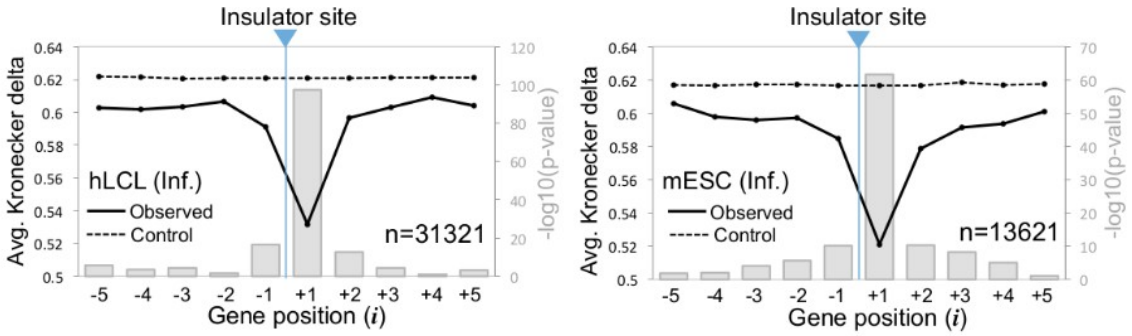

Figure 2.3.2 Average profile of Kronecker delta, δ(i-1, i), values as a function of gene position i from the CTCF insulator site (a) for the inferred set in hLCL (Nag et al. 2013), and (b) for the inferred set in mESC (Nag et al. 2015). Control data was obtained by randomly shuffling the positions of CTCF sites in the genome 100 times.

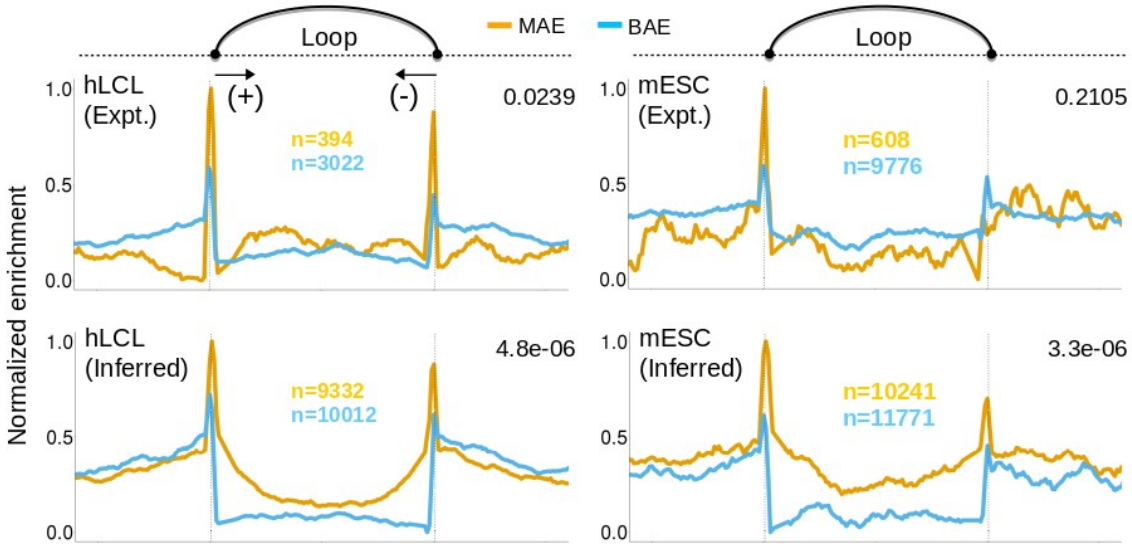

Figure 2.3.3 Gap – loop – gap analysis of experimental (A. Gimelbrant et al. 2007; Gendrel et al. 2014) and inferred (Nag et al. 2013; 2015) MAE/BAE genes inside insulator CTCF – mediated chromatin loops from CTCF ChIA-PET in hLCL and mESC.

On the other hand, BAE genes were located, preferably inside enhancer-linking loops (Figure 2.3.4). We then calculated the density of genes inside the insulator CTCF loops in hLCL. The average densities of MAE and BAE genes were comparable (1.68 and 1.67 respectively), but the number of loops containing only MAE genes was 2.6 fold more than the number of loops containing only BAE genes despite the similar total number of MAE (n=9332) and BAE (n=10012) genes (Nag et al. 2013). We also ruled out the possibility of the association of chromatin loops with gene expression by sampling MAE and BAE of similar expression levels (Figure 2.3.5). Therefore, we suggested that the

domains of MAE genes were insulated from the neighborhood the domains of BAE genes through insulator CTCF-mediated chromatin loops, as depicted in Figure 2.3.6.

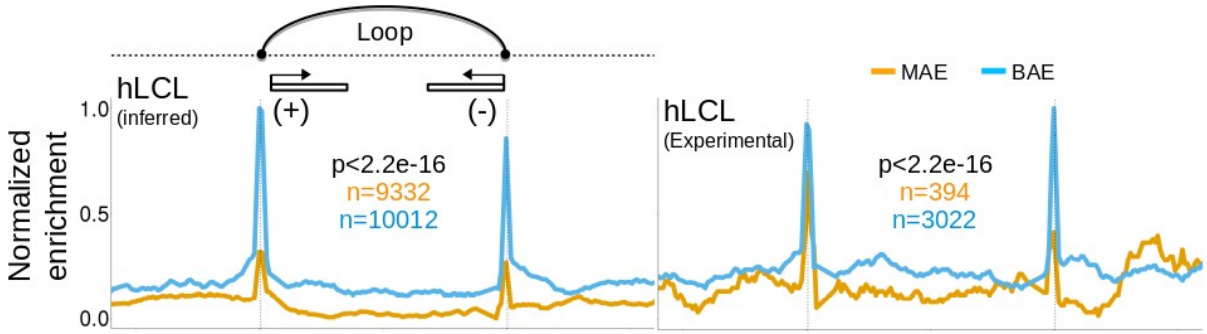

Figure 2.3.4 Gap – loop – gap analysis of experimental (A. Gimelbrant et al. 2007) and inferred (Nag et al. 2013) MAE/BAE genes inside enhancer-linking chromatin loops from CTCF ChIA-PET.

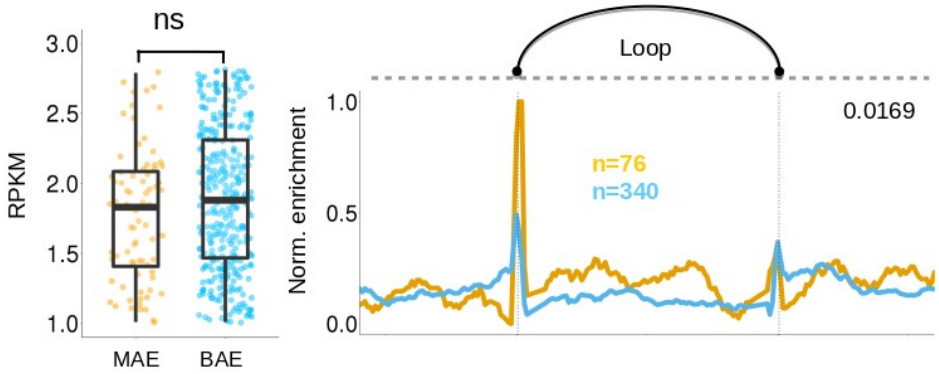

Figure 2.3.5 Gap – loop – gap analysis of MAE/BAE genes (A. Gimelbrant et al. 2007) of similar expression level inside insulator CTCF-mediated chromatin loops in hLCL.

Dynamics of mono-allelic expression with insulator CTCF loops

To further scrutinize the association of MAE genes with insulator CTCF loops, we checked the cell-type-specific association of mono-allelic expression with insulator CTCF loops. MAE/BAE genes from different human cell types, such as hLCL and K562 (Nag et al. 2013), were tested for their association with CTCF loops (Figure 2.3.7). While the genes that maintained mono-allelic expression between two cell types maintained their association with CTCF loops, genes that did not maintain mono-allelic expression (i.e., bi-allelic expression) showed weaker association with CTCF in both the cell types. Genes that had mono-allelic expression in hLCL but bi-allelic expression showed association with insulator CTCF loops in hLCL but not in K562. The converse was also true (Figure 2.3.7). The gain and loss of mono-allelic expression, therefore, coincided with the gain and loss of CTCF associated insulating chromatin loops. The loss of association with insulator loops might be either related to loss of insulator CTCF loops or change in the role of CTCF loops. Towards this, we performed the following two analyses: 1) We checked the percentage of genes with conserved loops, cell-type-specific loops, and no loops (Figure 2.3.8a). The genes that switched status from mono- to bi-allelic expression and vice-versa between the two cell-lines showed an increase in the percentage of cell-type-

specific loops and a decrease in the percentage of conserved loops when compared to the genes that maintained mono-allelic expression.

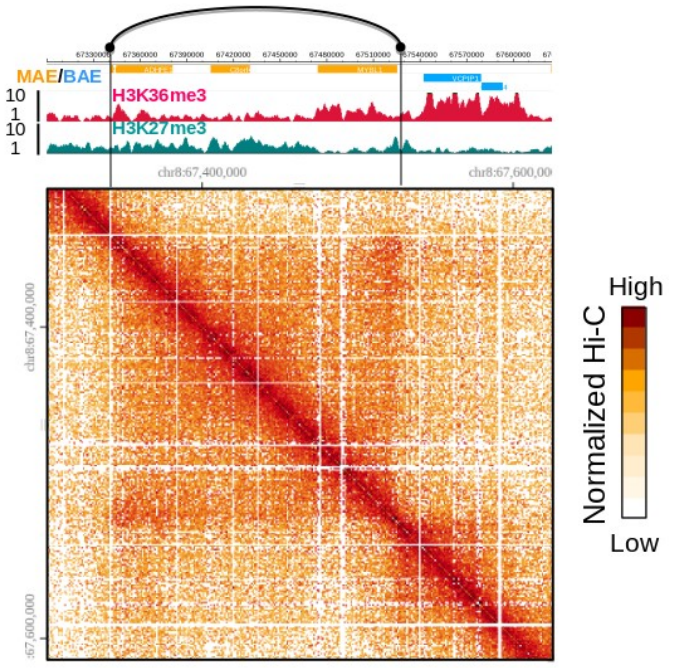

Figure 2.3.6: Example showing the segregation of the domain of MAE from BAE genes.

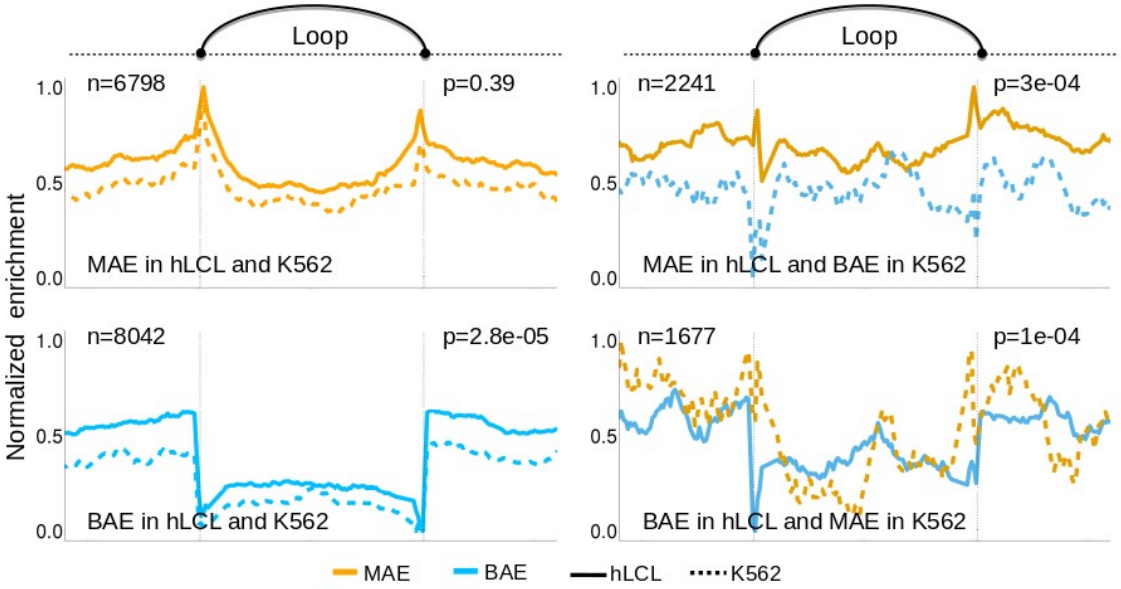

Figure 2.3.7: Gap – loop – gap analysis of MAE/BAE genes (Nag et al. 2013) which maintained and switched their status between hLCL and K562 inside insulator CTCF – mediated chromatin loops in hLCL and K562.

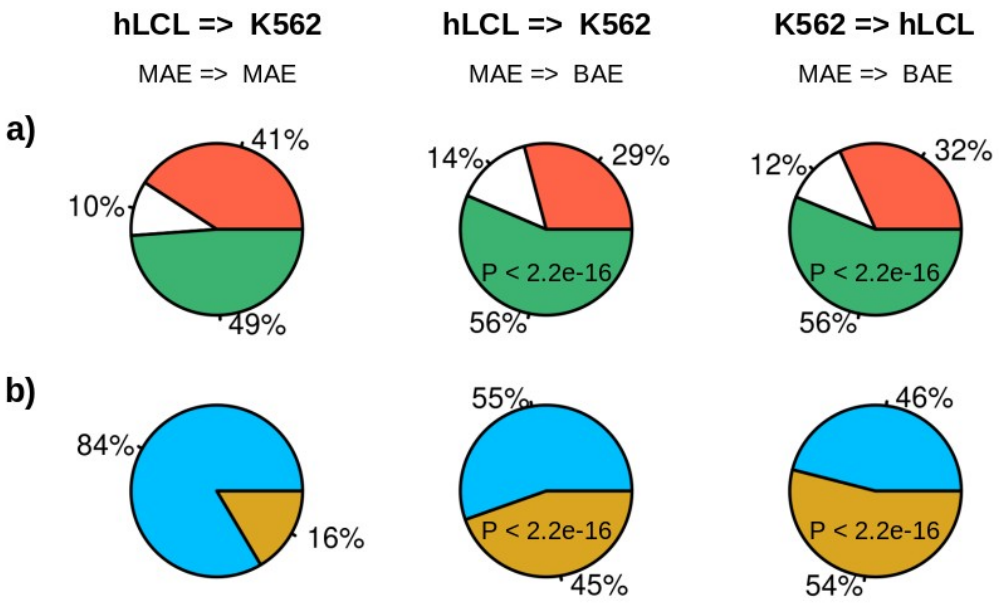

Figure 2.3.8 (a) Percentage of conserved (red), cell-type-specific (green), and no loops (white). (b) Percentage of conserved insulator (blue) and insulator => enhancer-linking loops (yellow).

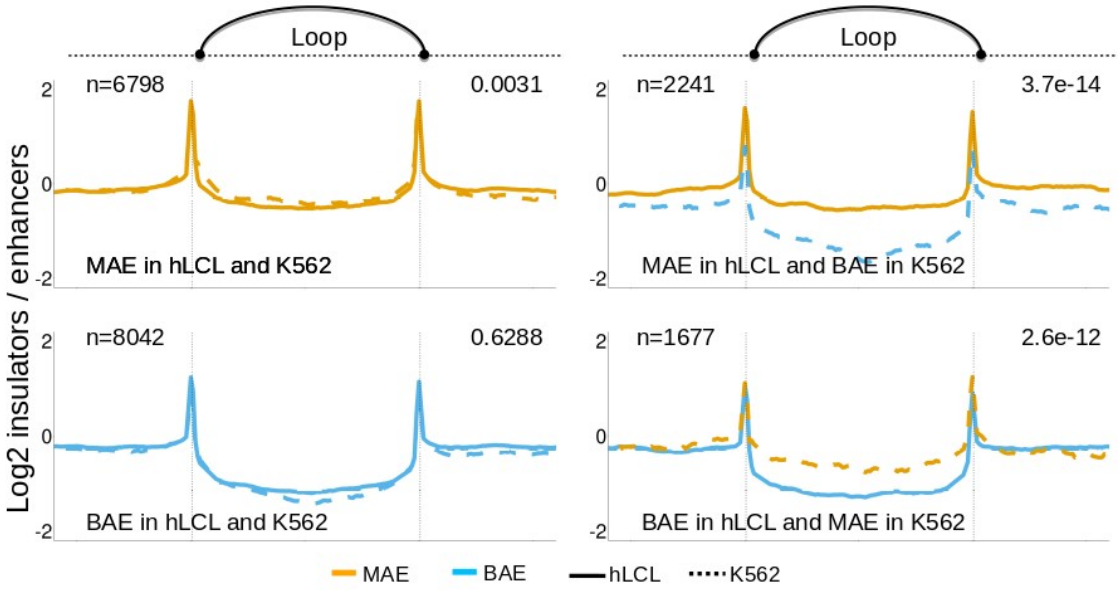

Figure 2.3.9 Log2 ratio of insulators to enhancers in the loops that enclose genes as mentioned.

2) We calculated the percentage of genes with loops that switched its activity from insulator to enhancer-linking (Figure 2.3.8b). The genes that switched from mono- to bi-allelic expression showed an increase in the loops that switched their activity when compared to the genes that maintained mono-allelic expression between the two cell lines. This was also confirmed by plotting the log2 ratio of enrichment of insulators to that of enhancers around the coordinates of loops that contained the genes in the above-mentioned categories (Figure 2.3.9). Genes when showed mono-allelic expression in a

tissue, the loops that enclosed them in that tissue were associated with insulators. Same genes when they were expressed bi-allelically in a different tissue, the loops that enclosed them in that tissue were associated with enhancers. Therefore, when genes showed mono- and bi-allelic expression between cell-lines, their loops were associated with insulators and enhancers, respectively.

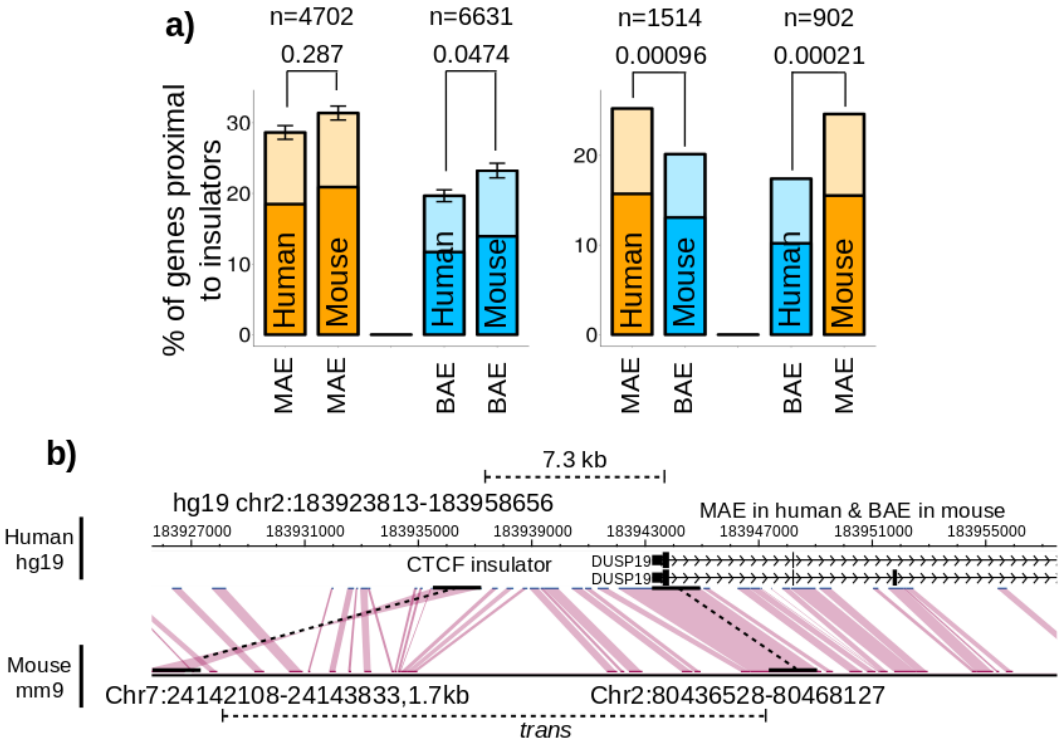

Figure 2.3.10 (a) Insulator CTCF association to MAE and BAE genes which maintained and switched their status between human and mouse. Dark and light portions in the bars represent CTCF sites that are bound and not bound with CTCF, respectively. (b) An example showing loss of CTCF site through an inversion to a gene which is MAE in human but BAE in mouse.

Further, we checked the evolutionary association of MAE genes with insulator CTCF sites by comparing MAE/BAE genes from the lymphoblastoid cell-lines of human and mouse (Nag et al. 2013; 2015) (Figure 2.3.10). Genes that maintained mono-allelic expression between human and mouse maintained their association with insulator CTCF sites and genes which maintained bi-allelic expression showed lesser association (Figure 2.3.10a). When genes switched their status from mono- to bi-allelic expression between human and mouse, they lost their association with insulator CTCF sites and vice-versa. We concluded that the evolutionary gain and loss of mono-allelic expression coincided with the gain and loss of association with insulator CTCF sites, respectively (Figure 2.3.10b). Altogether, these observations highlighted genetic and epigenetic association of CTCF insulators with the mono-allelic expression of genes.

Dosage sensitivity of mono-allelic expression to CTCF depletion

While CTCF knockout is embryonic lethal (Moore et al. 2012), the role of CTCF in genome organization is being studied by induced-degradation experiments (accessions: GSE98507 & GSE98671) (Nora et al. 2017; Pérez-García et al. 2017). Such datasets allow us to assess the status of mono-allelic expression before and after CTCF depletion. Loss of domain insulation (dip prominence) following CTCF depletion was more pronounced at MAE loci than at BAE [genes analyzed: (Nag et al. 2015; Gendrel et al. 2014)] (Figure 2.3.11). We further observed that the dosage of MAE genes was significantly affected when compared that of BAE genes (p<2.2e-16, Figure 2.3.12). In general, MAE genes were up-regulated after CTCF depletion [genes analyzed: (Nag et al. 2015; Gendrel et al. 2014) (Figure 2.3.12a). We confirmed the above observations by comparing MAE and BAE gene datasets with the same sample size, and expression-matched MAE and BAE gene datasets (Figure 2.3.12b).

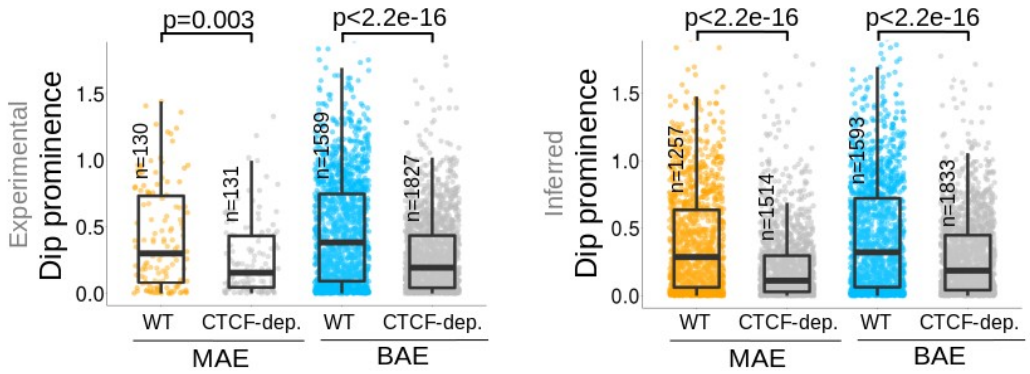

Figure 2.3.11 Insulation (Dip prominence) before and after CTCF depletion at MAE and BAE loci.

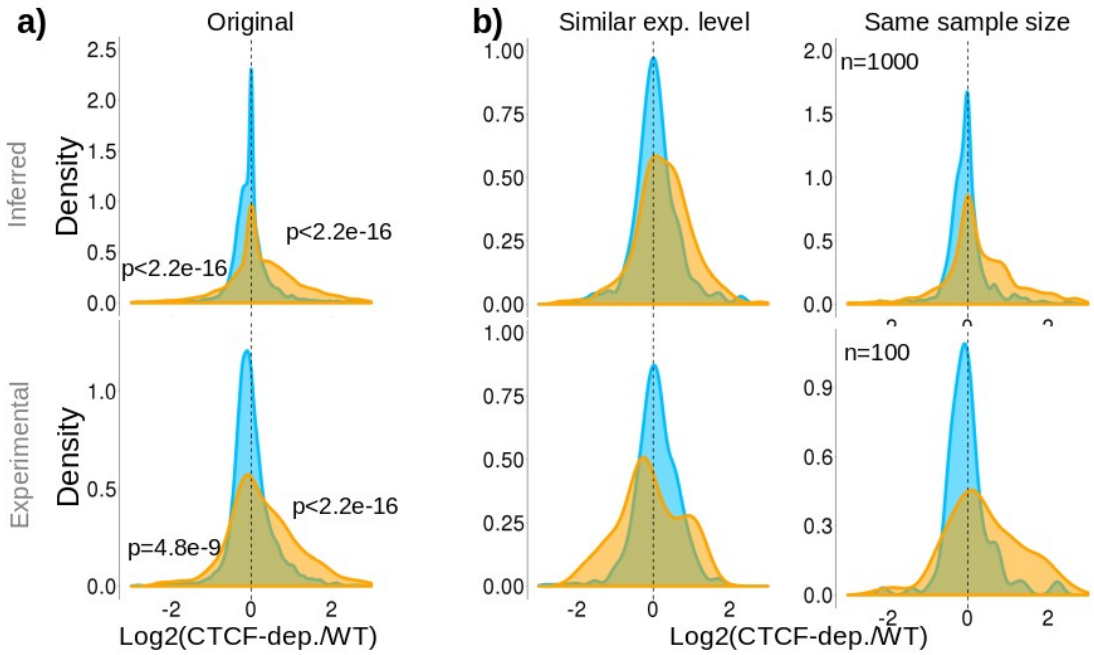

Figure 2.3.12 (a) Log2 fold change (CTCF depleted / control) of expression of MAE (yellow) and BAE (blue) genes. (b) Left: genes with similar expression level & right: genes with same N as denoted.

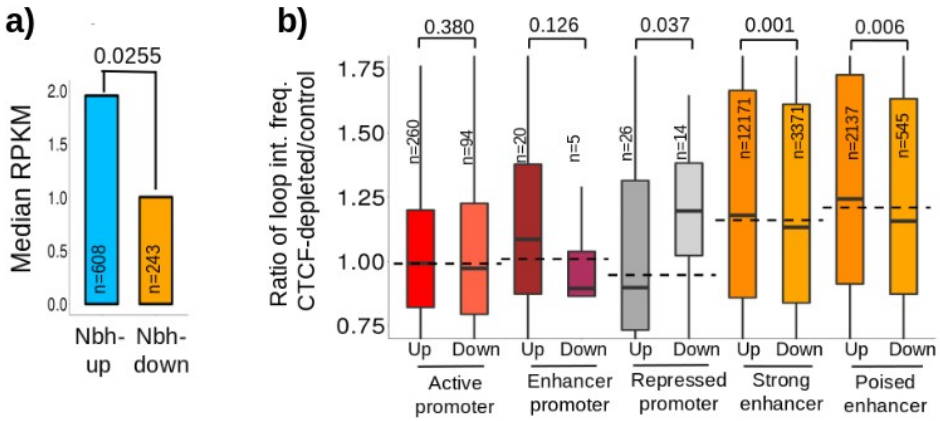

Figure 2.3.13 (a) Exp. of neighbors to up- and down-regulated MAE genes. (b) Ratio of CTCF dep. to control int. freq. of up- and down-regulated MAE with different kinds of promoters and enhancers.

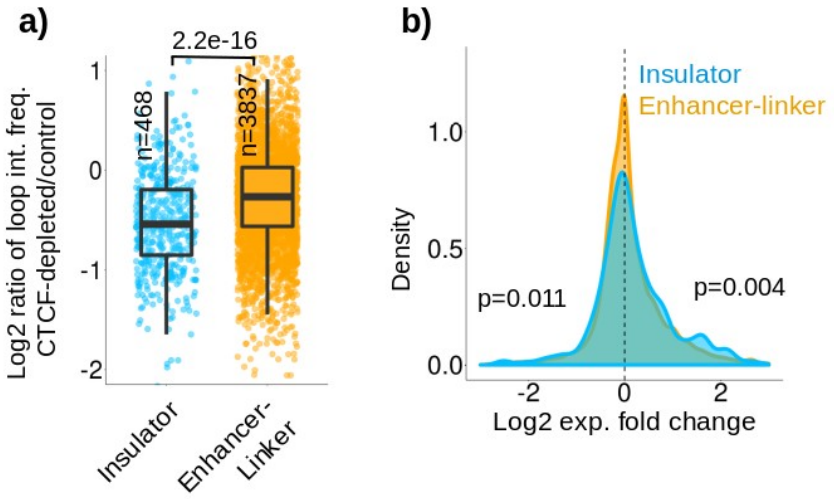

Figure 2.3.14 (a) log2 ratio of interaction freq. of CTCF depletion to control. (b) Log2 fold change (CTCF depleted / control) of expression of genes enclosed by insulator and enhancer-linking loops.

Further, we looked at the neighborhood of MAE genes [genes analyzed: (Nag et al. 2015)]. MAE genes that were up-regulated were flanked with highly expressed genes when compared to MAE genes, which were down-regulated (Figure 2.3.13a). While up-regulated MAE genes gained interactions with the enhancer-like promoters, down-regulated MAE genes gained interactions with the repressed promoters (Figure 2.3.13b). Hence, spatial interference with the active transcribing neighborhood might have raised the expression of MAE genes. We further observed that insulator loops were more sensitive to CTCF depletion than enhancer-linking loops, and the genes enclosed by insulator loops experienced increased dosage sensitivity when compared to the genes enclosed by enhancer-linking loops (Figure 2.3.14). Since insulator and enhancer-linking CTCF loops enclosed MAE and BAE genes respectively, we concluded that the loss of CTCF depletion affected MAE genes more than BAE genes.

Allele-specific regulation of MAE genes

The observations, such as the loss of insulator CTCF loops coincided with the loss of mono-allelic expression and MAE genes were mostly up-regulated after CTCF depletion, hinted at the functional role of insulator CTCF loops at the inactive alleles. To test this, we conducted the following three analyses. 1) We performed allele-specific virtual 4C with active and inactive alleles of inferred MAE genes (Nag et al. 2013; 2015) in hLCL (accession: GSE63525) and mESC (accession: GSE107421). By plotting the log2 ratio of active to inactive (for BAE genes, active to active) allelic interaction frequencies with their neighborhood, we observed that the inactive allele had short-range interactions with higher-interaction frequencies when compared to the active allele (Figure 2.3.15).

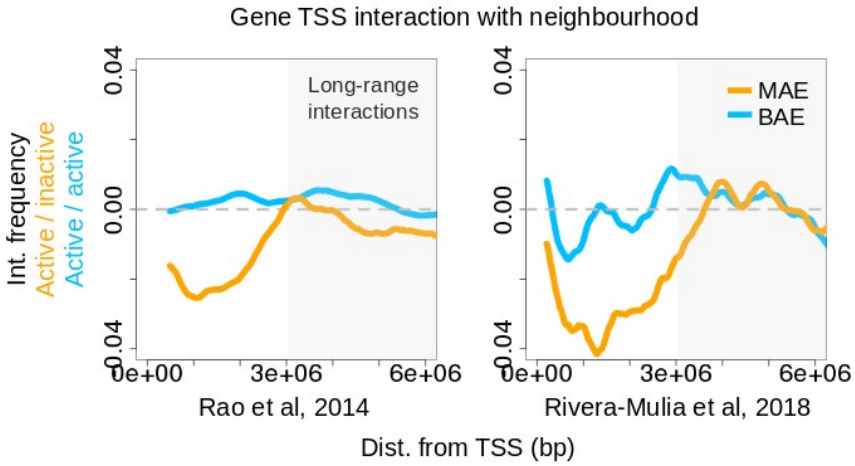

Figure 2.3.15 Log2 ratio of active to inactive allele of MAE gene interaction with neighborhood by virtual 4C analysis in hLCL and mESC. For BAE, the ratio is between active and active allele.

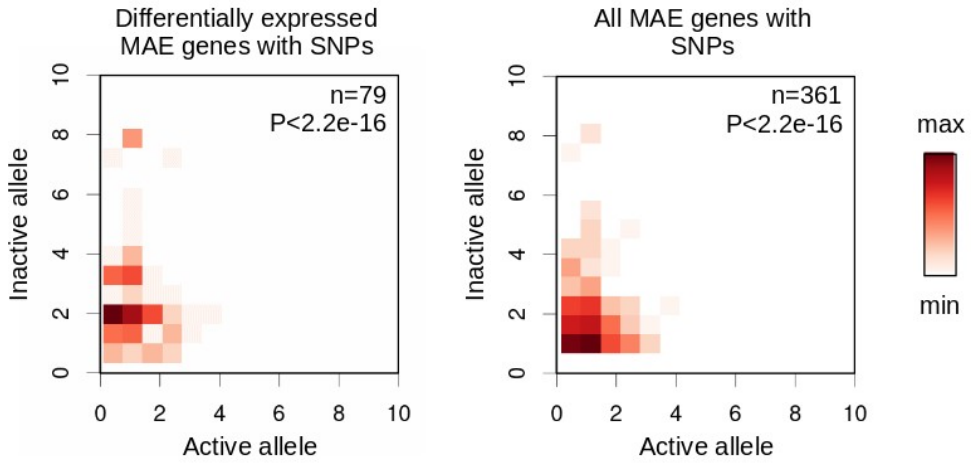

Figure 2.3.16 Ratio of CTCF depleted to control in the active and inactive alleles of MAE gene.

The above observation suggested that there was an allele-specific chromatin conformation, and the inactive allele was being more compact when compared to the active allele. This interpretation was in agreement with a recent observation that the active (early replicating) and inactive (late replicating) alleles had long- and short-range interactions, respectively (Rivera-Mulia et al. 2018).

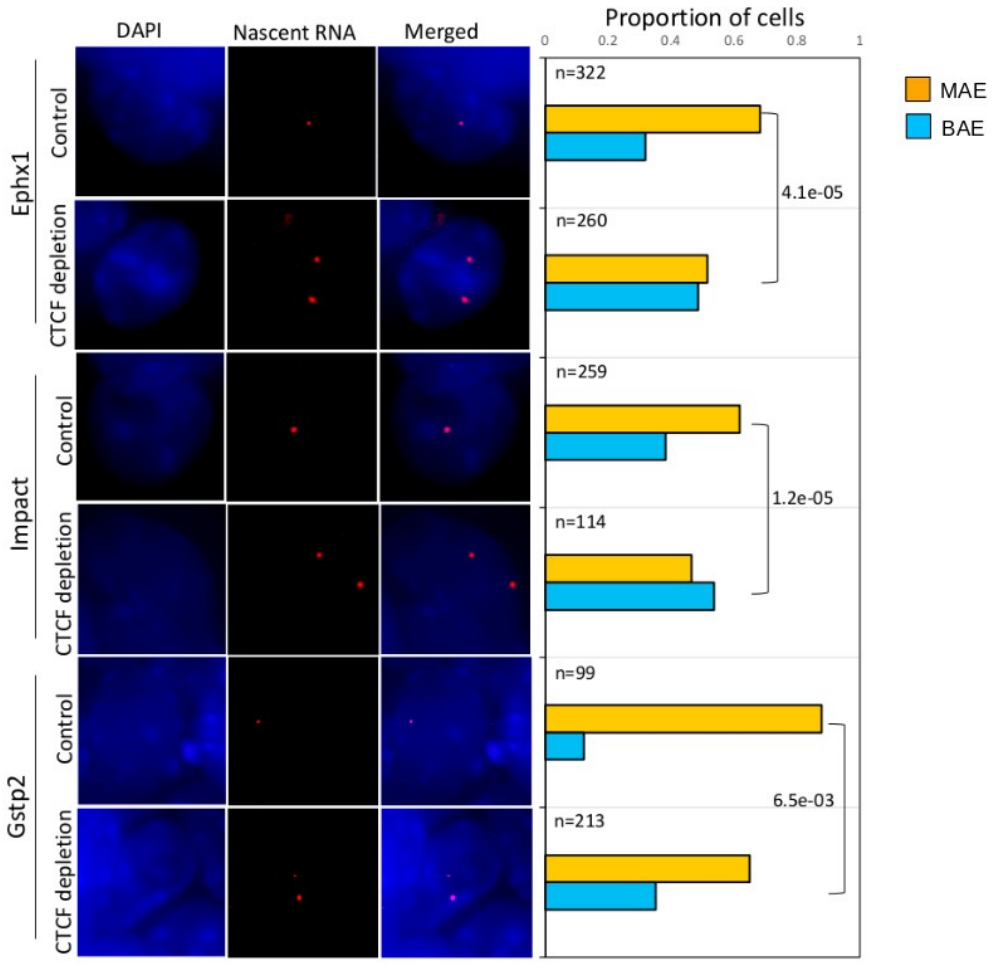

Figure 2.3.17 Single molecule RNA FISH before and after CTCF depletion at *Ephx1*, *Impact* and *Gstp2*.

2) We performed an allele-specific analysis of RNA-seq experiments before and after CTCF depletion (accession: GSE98671). First, we performed the genotype analysis of RNA-seq reads to obtain SNP containing reads. Then, we plotted the log2 ratio (CTCF depletion to control) of SNP containing reads mapping to MAE genes (Nag et al. 2015). We observed that the inactive allele was up-regulated/activated after CTCF depletion (Figure 2.3.16). 3) We performed single-molecule RNA FISH experiments at candidate loci, such as *Ephx1*, *Impact*, and *Gphx1*, before and after CTCF depletion (Figure 2.3.17). Through the incorporation of multiple short (20 bp) probes targeting the same transcript, the single-molecule RNA FISH can monitor the expression level at single mRNA level, which has been exemplified by measuring the spatial distances among multiple probes with different fluorophores tiled on the very same transcript (Femino et al. 1998; Raj et al. 2008). We observed that there was an increase in the percentage of cells with bi-allelic expression after CTCF depletion. These observations together highlighted the role of insulating CTCF loop at the inactive allele of MAE genes and suggested that the up-regulation/activation of the inactive allele after CTCF depletion was likely due to the loss of domain insulation and increased spatial interference with the neighborhood.

2.4 Discussions

The role of allele-specific chromatin architecture in regulating gene expression has been studied at individual loci. In particular, CTCF is shown to be involved in allele-specific chromatin looping (Kurukuti et al. 2006; Llères et al. 2019). However, there is a lack of a genome-wide link between CTCF-mediated genome architecture and allele-specific expression. Here, we show the genome-wide regulatory role of CTCF-mediated allele-specific chromatin architecture in maintaining mono-allelic expression. CTCF insulates the domains of MAE genes from the domains of BAE genes both in the linear and 3D genome. While CTCF links the gene promoters to enhancers at the active allele, CTCF insulates the inactive allele from the neighborhood via chromatin loops. Therefore, loss of CTCF leads to the loss of insulation at the inactive allele and its activation via spatial interference with the active neighborhood, as shown by computational analysis and single-molecule RNA FISH. Enhancer-linkers are less unaffected than insulators after CTCF depletion, as there are multiple transcription factors that could reinforce the interactions and residual amount of CTCF could be left with chromatin. Therefore, the active allele of MAE genes and BAE genes, which are associated with enhancer-linkers, are less affected by the loss of CTCF (Figure 2.4.1).

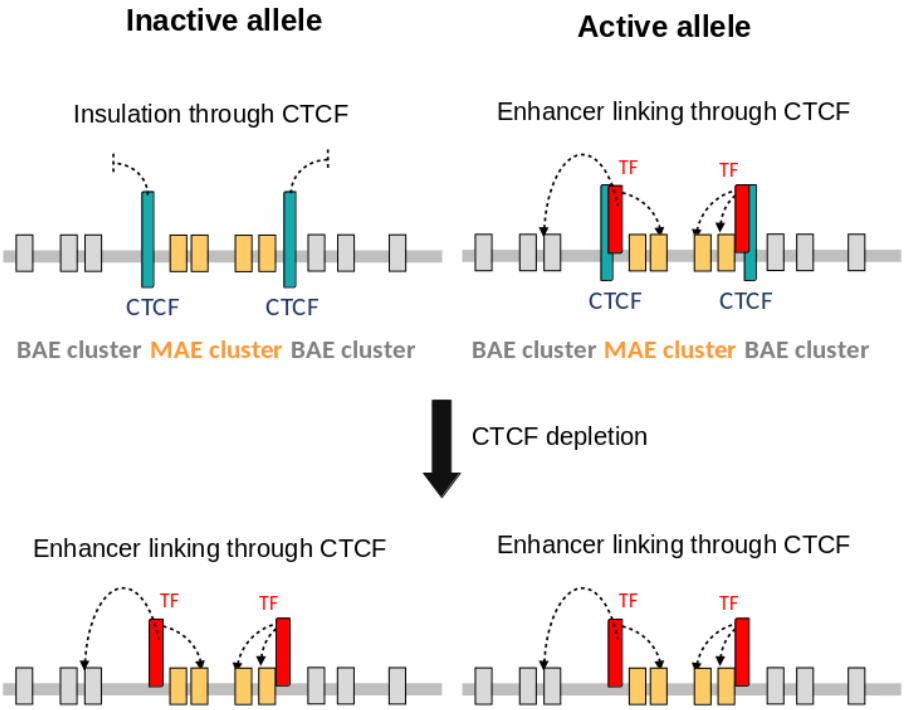

Figure 2.4.1 Loss of domain insulation due to CTCF degradation creates spatial interference with the neighborhood at the inactive allele and it is activated.

When genes switch from mono- to bi-allelic expression between cell-types, they lose association with insulator CTCF. With quantitative analyses, we observed the cell-type-specific role of CTCF. When genes are expressed mono-allelically in a cell-type, CTCF acts as insulators. However, when they are expressed bi-allelically in a different cell-type, CTCF acts as enhancer-linkers. Therefore, the role of CTCF in regulating mono-allelic expression is largely epigenetic. We also checked if the role of CTCF

was genetic in nature. To test this, we checked the association of loops with allele-specific SNPs. Loops that exhibited allele-specific chromatin conformation and loops that did not exhibit conformation showed 56% and 47% respectively, confirming the association of CTCF with mono-allelic expression is mostly epigenetic in nature.

Most of the above observations are reconciled by analyzing MAE/BAE gene datasets from multiple tissues/cell-lines. While the use of inferred MAE/BAE gene datasets (Nag et al. 2013; 2015) could be criticized, we emphasize that we have shown most of the observations through both experimentally-identified (A. Gimelbrant et al. 2007; Gendrel et al. 2014) and inferred gene datasets (Nag et al. 2013; 2015). Further, we argue with the following points: 1) Nag et al. have shown experimental validation of their approach through RNA-seq and AST-seq (Nag et al. 2013). 2) Although bi- and multi-valent chromatin marks have been shown, H3K36me3 and H3K27me3 cannot be present on the same allele because active chromatin inhibits H3K27me3 (Roh et al. 2006; Alder et al. 2010; Dahl et al. 2010; Vastenhouw et al. 2010; Schmitges et al. 2011; Brookes et al. 2012). Therefore, H3K36me3 and H3K27me3 should be present on different alleles. 3) The cell-to-cell variation could lead to the presence of H3K36me3 and H3K27me3 in different cells (Toyooka et al. 2008; Hayashi et al. 2008). If it were true, we would see higher gene expression noise of MAE genes. So, we checked expression noise and observed that MAE genes showed less gene expression noise than BAE genes (Figure 2.4.2a). 4) The key observation, i.e., the activation of the inactive allele after CTCF degradation, from the computational analysis, is validated by single-molecule RNA-FISH experiments at three candidate loci. Therefore, we again emphasize that the observations are from both inferred (Nag et al. 2013; 2015) and experimentally-identified (A. Gimelbrant et al. 2007; Gendrel et al. 2014) gene datasets. And the observations that are exclusively from inferred gene datasets (Nag et al. 2013; 2015) are also reliable.

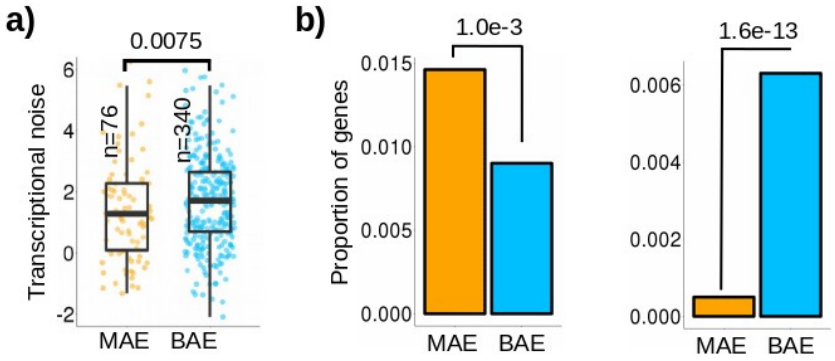

Figure 2.4.2 (a) Gene expression noise of MAE and BAE genes. (b) Percentage of overlap of MAE and BAE genes with dosage-sensitive genes (left) and copy number variations (right).

Earlier, it has been hypothesized that MAE genes are dosage-sensitive (Jeffries et al. 2013; Eckersley-Maslin et al. 2014; Gendrel et al. 2014). To test this, we checked the overlap of MAE/BAE gene datasets (Nag et al. 2013) with dosage-sensitive genes. MAE genes had a higher overlap than BAE genes (Figure 2.4.2b). On the other hand, BAE genes are less sensitive to dosage as they have a higher overlap with genes that show copy number variations (Figure 2.4.2b). Therefore, these MAE genes are likely to be dosage-sensitive, and this constraint might have shaped the CTCF-mediated genome architecture to maintain their appropriate dosage.

Section - 3

How are distinct transcriptional states of TADs concurrently regulated genome-wide during development?

3.1 Introduction

i) Enhancer – promoter interactions in gene activation

Recent studies suggest that the genome organization is non-random, and different cell-types express the cell-type-specific genes by maintaining appropriate 3D conformation (Bonev and Cavalli 2016). In general, individual genes switch their transcriptional states by switching their compartment (Figure 3.1.1) and spatial localization (Figure 3.1.2) (Lin et al. 2012; Therizols et al. 2014; Dixon et al. 2015).

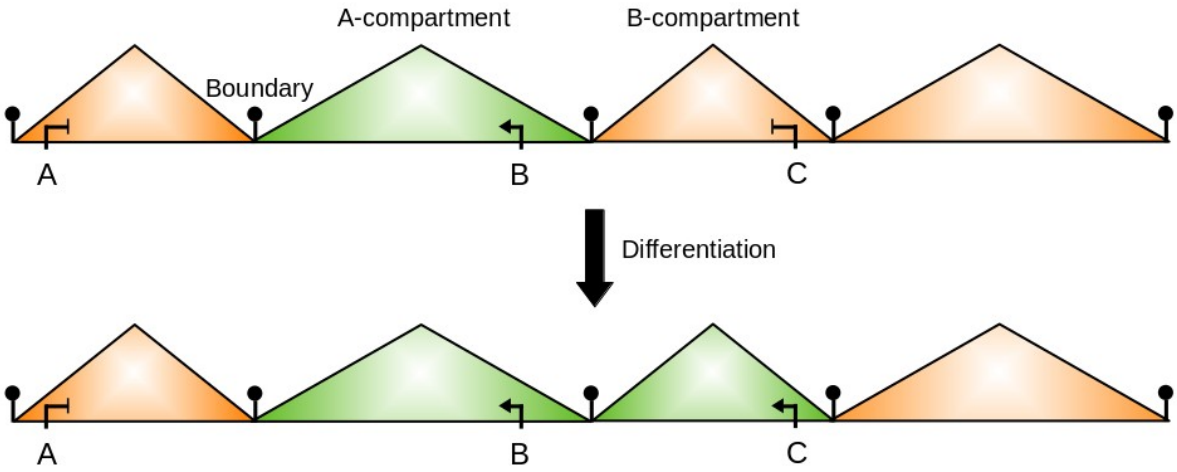

Figure 3.1.1 Compartment switch during gene activation.

Figure 3.1.2 Nuclear localization of gene during gene activation.

It is often accompanied by the spatial proximity between the enhancer and its target gene promoter via chromatin loops, and no spatial proximity when the gene is not expressed (Figure 3.1.3) (Vernimmen and Bickmore 2015; I. Williamson et al. 2016; Bonev and Cavalli 2016; Bonev et al. 2017). A well-characterized example is the spatial proximity between the Locus Control Region (LCR) and its target genes in the β-globin cluster via long-range chromatin contacts when they are expressed in the erythroid cells (Palstra et al. 2003). CTCF, cohesin, and mediator that are present both at the enhancers and promoters of the actively transcribed genes are known to aid in physical proximity (Kurukuti et al. 2006; Splinter et al. 2006; Rubio et al. 2008; Hadjur et al. 2009; Kagey et al. 2010; Lai et al. 2013;

Seitan et al. 2013; Sofueva et al. 2013; Rao et al. 2014; Tang et al. 2015). Some of the interactions mediated by CTCF are present during mitosis and also preserved from gametes to early mouse embryo, suggesting the inheritance of the enhancer – promoter interactions (Burke et al. 2005; Jung et al. 2019). The orientation of CTCF motifs also plays a significant role in establishing enhancer – promoter interactions. The famous 'loop extrusion' model states that the molecular motors, such as cohesin, extrude the chromatin until they encounter CTCF motifs in convergent orientation (Fudenberg et al. 2016). Therefore, chromatin loops are established between two convergent CTCF motifs, and any change in the orientation can lead to a change in gene expression (Rao et al. 2014; de Wit et al. 2015; Tang et al. 2015).

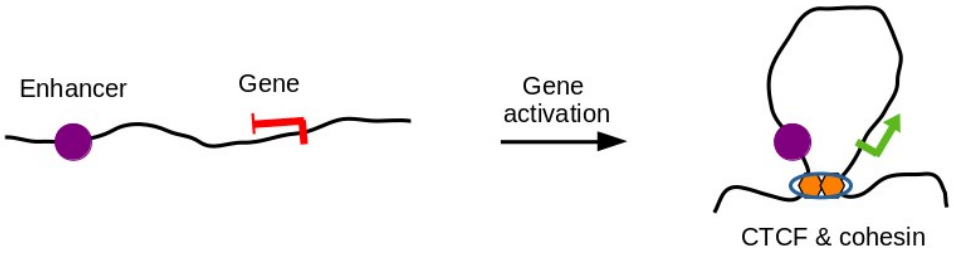

Figure 3.1.3 Enhancer – promoter loop.

Loss of the chromatin looping between the enhancer and its target promoter by removing the structural factors usually results in the loss of gene expression and consequently, the associated phenotype (Phillips-Cremins et al. 2013; Lai et al. 2013). On the other hand, a forced loop between an enhancer and its target gene is sufficient for the transcription of the gene via the recruitment of RNAPII in the absence of the required transcription factor (W. Deng et al. 2012). Sometimes, the enhancer – promoter interactions seem to be preset, and they are present even when the genes are not transcribed (Amano et al. 2009, 2; Montavon et al. 2011; Andrey et al. 2013). These preset interactions are usually set by paused RNAPII, and the release of RNAPII is crucial for gene activation (Ghavi-Helm et al. 2014). These studies further highlight the importance of enhancer – promoter interactions and their spatial proximity in gene activation.

Further, the loop extrusion also establishes TAD boundaries to insulate the domains from each other and guide enhancer – promoter interactions (Dixon et al. 2012; Rao et al. 2014; Lupiáñez et al. 2015; Narendra et al. 2015; Symmons et al. 2016; Valton and Dekker 2016). At the *HoxA* domain, the deletion of two CTCF sites in motor neurons leads to the activation of three *HoxA* genes through the loss of insulation and the spread of active histone modification (Narendra et al. 2015). *Epha4* is regulated by a cluster of limb enhancers, and the deletion of a domain boundary leads to the activation of another gene in the locus (Lupiáñez et al. 2015). These studies suggest that the loss of domain insulation, in general, leads to the rewiring of enhancer – promoter contacts and non-specific activation of genes. However, the loss of TAD boundaries genome-wide due to the deletion of cohesin-loading factor *Nipbl* did not result in genome-wide transcriptional changes with reinforced compartments (Figure 3.1.4). Only a small significant number of genes was affected due to the loss of long-range enhancer – promoter interactions and enhancers were rewired to the nearby genes (Schwarzer et al. 2017). Another study involving the degradation of CTCF also have observed the genome-wide loss of TAD boundaries with no immediate TAD-wide transcriptional changes and preservation of compartments. It is hypothesized that the exposure of the promoters to new enhancers due to the loss of

insulation might require time and additional factors for global transcriptional changes (Nora et al. 2017).

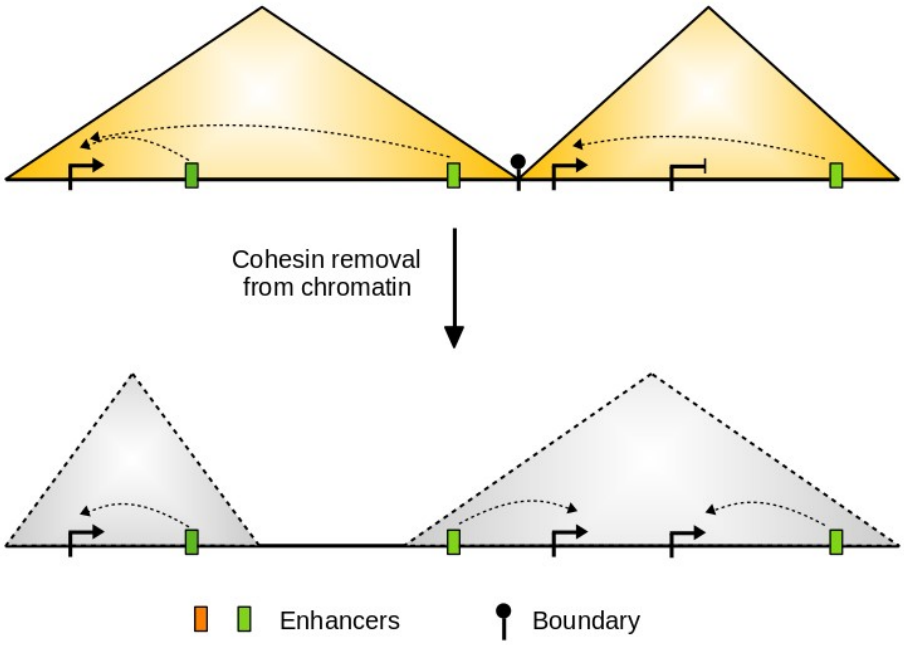

Figure 3.1.4 Loss of long-range interactions and enhancer-promoter rewiring after cohesin removal.

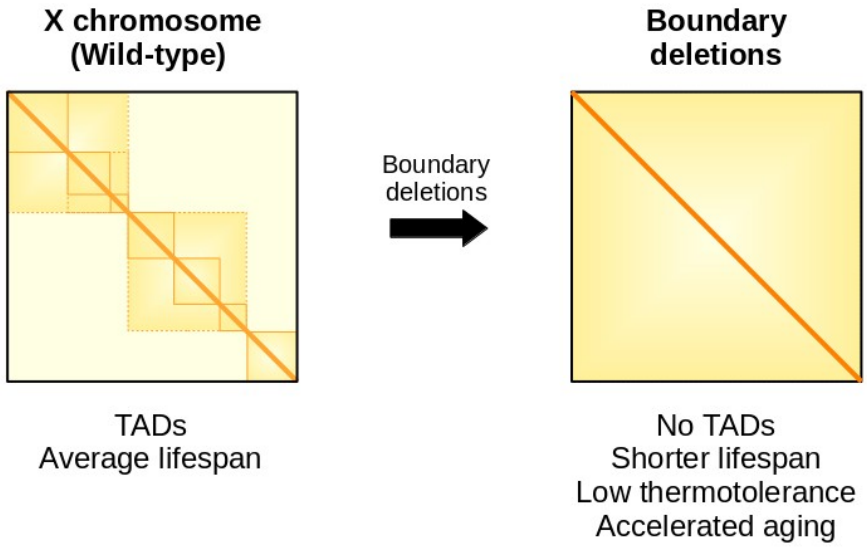

Figure 3.1.5 Loss of TADs leads to abnormal phenotypes in adults.

Indeed, a recent study in the X chromosome of worms observed that the deletion of TAD boundaries was not sufficient to change the dosage of the genes drastically in the X chromosome as Dosage-compensation Condensin Complex (DCC) establishes other short- and long-range interactions independent of TAD boundaries. However, the long term effects in adults were observed as shorter life

span, reduced thermo-tolerance, and accelerated aging due to the change in gene expression of few genes next to the domain boundaries, highlighting the underlying complexity (Figure 3.1.5) (Anderson et al. 2019). Altogether, these studies suggest that the appropriate expression of genes is regulated by their enhancer – promoter interactions via increased spatial proximity and by their insulation from the neighboring domains. Loss of insulation could lead to locus-specific effects via rewiring enhancer – promoter interactions and other higher-order structures, such as compartments, could maintain the overall genome structure with minimal genome-wide transcriptional changes.

ii) Unconventional decreased enhancer – promoter spatial proximity

While all of the above studies establish a stable relationship between the enhancers and gene activation via increased spatial proximity, recent studies challenge the stable formation of enhancer – promoter interactions. While transcription bursts exclude the possibility of stable loops, live-cell imaging of *Sox2* shows its transcription in the absence of spatial proximity to its enhancer *Sox2* Control Region (SCR) (Fukaya, Lim, and Levine 2016; Alexander et al. 2019). Using super-resolution 3D-FISH and 3C techniques, a more recent study observed that the decreased spatial proximity between a gene and its enhancer led to the activation of the gene (Figure 3.1.6) (Benabdallah et al. 2019). These studies hypothesized that the enhancers might be involved in nucleation and spreading of transcription factors, activators, and co-activators, and increase chromatin accessibility as super-enhancers, such as SCR, have long-range communication systems (Bulger and Groudine 2010; Whyte et al. 2013; Alexander et al. 2019; Benabdallah et al. 2019). Indeed, several studies support the hypothesis as many components of transcription machinery have intrinsically disordered low-complexity sequence domains (LCDs) to form condensates that could aid in phase separation (Chong et al. 2018; Sabari et al. 2018; Boija et al. 2018; Cho et al. 2018). Therefore, a new conceptual framework is emerging that connects the nature and behaviour of their interactions to their functions in the regulation of transcription (Plys and Kingston 2018; Chong et al. 2018; Sabari et al. 2018; Cho et al. 2018). Transcription factors EWS/FLI1 have been shown to interact among themselves via dynamic, multivalent, and specific LCD-LCD interactions to form local high-concentration hubs at regulatory regions. These hubs stabilize their binding to chromatin, recruit RNA Polymerase II, and activate transcription. They also have the potential to phase-separate at higher concentrations. Any defects in forming strong, dynamic, and transient contacts between EWS and FLI1 lead to Ewing's sarcoma (Chong et al. 2018).

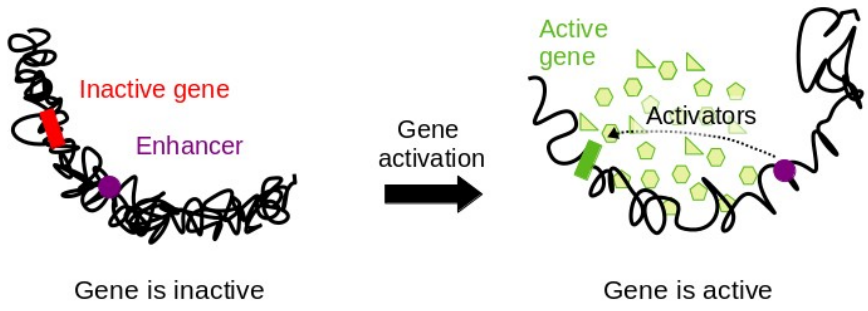

Figure 3.1.6 Separation of enhancer from gene and its activation via condensates of activators.

Another study showed that transcription factors, BRD4, MED1, and RNA polymerase II form liquid-like condensates at super-enhancers through their Intrinsically Disordered Regions (IDRs), which compartmentalize and aggregate the transcription machinery to maintain the expression of genes

(Figure 3.1.7) (Sabari et al. 2018). These condensates have the capacity to push chromatin, and the dynamic interactions of these condensates further initiate transcription elongation (Cho et al. 2018; Shin et al. 2018). These condensates also show sensitivity to selective transcriptional inhibitors (Cho et al. 2018). Collectively, these studies lead to a liquid-liquid phase separation model through the accumulation of transcription factors, activators, co-activators, and other transcription machinery to form dynamic condensates, and it aids in gene activation. These condensates could push chromatin out to increase the spatial distance between the enhancer and its target gene, in turn, could facilitate liquid-liquid phase separation and activate the gene (Hnisz et al. 2017; Boija et al. 2018; Sabari et al. 2018; Chong et al. 2018; Cho et al. 2018; Shin et al. 2018; Benabdallah et al. 2019). Therefore, increased spatial distance between the enhancer and promoter could lead to gene activation.

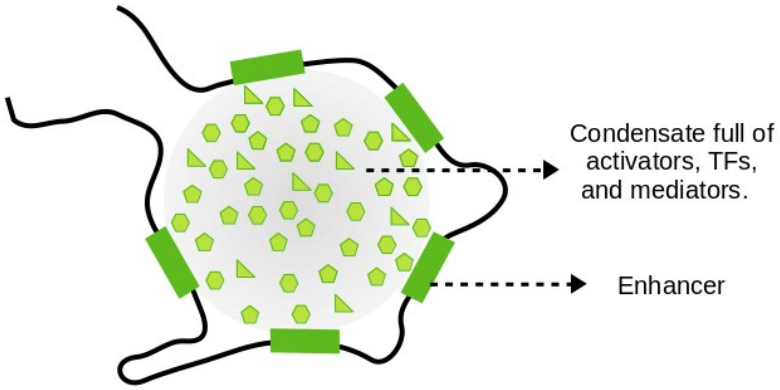

Figure 3.1.7 Formation of phase-separation at super-enhancers.

iii) Aim & motivation:

Currently, there are two mutually exclusive mechanisms that involve chromatin compaction in gene expression and we have also observed the compaction of inactive allele in the previous chapter. Therefore, we attempt to investigate the discrepancies in the role of chromatin compaction in transcription. Often, the decondensed (open chromatin) and condensed states are identified by a variety of techniques such as DNase-seq, FAIRE-seq, and ATAC-seq (Giresi et al. 2007; Song and Crawford 2010; Buenrostro et al. 2015). The nucleases that are used in the above-mentioned assays digest the nucleosome-free accessible DNA, and therefore, these are suitable to identify the narrow transcriptional factor binding sites only. On the other hand, very few authors have used restriction endonuclease to quantitate the chromatin compactness (P. B. Chen et al. 2014). Instead, restriction endonucleases are extensively used in 3C-based techniques to identify domains (i.e., TADs) and study their role in gene activation, assuming that the restriction digestion is uniform in the genome (Lieberman-Aiden et al. 2009; Rao et al. 2014). Further, transcriptional regulation of genes happens at domain-level via the concurrent deposition and maintenance of similar epigenetic marks (Orlando and Paro 1993; de Wit et al. 2008; Filion et al. 2010; Bickmore and van Steensel 2013; Sexton and Cavalli 2015; Dekker and Heard 2015; Dixon, Gorkin, and Ren 2016). Such domain-wide is possible only via concurrent opening and closing of chromatin (Chambeyron and Bickmore 2004; Therizols et al. 2014; Rafique et al. 2015; Benabdallah et al. 2019). Therefore, by analyzing publicly available Hi-C datasets, we intend to test if the restriction digestion in 3C techniques is uniform, and if not, we will use it to identify the condensed and decondensed domains to understand their role in gene regulation and propose a computational method to correct the non-uniform restriction digestion in contact maps.

3.2 Materials & methods

List of datasets used in this study

Table 3.2.1 List of datasets used in the study

Accession	Cell-type	Experiment	RE	Processing
GSE96107	mESC, NPC, CN	*In-situ* Hi-C	DpnII	HiCUP/bowtie
GSE89520	mESC (lamin KO)	*In-situ* Hi-C	BgIII	Pre-processed
ENCSR032JUI	mESC	H3K4me1 ChIP-seq		Pre-processed
ENCSR000CGQ		H3K27ac ChIP-seq		Pre-processed
ENCSR000CGO		H3K4me3 ChIP-seq		Pre-processed
ENCSR253QPK		H3K36me3 ChIP-seq		Pre-processed
ENCSR857MYS		H3K9me3 ChIP-seq		Pre-processed
ENCSR059MBO		H3K27me3 ChIP-seq		Pre-processed
GSE96107		CTCF ChIP-seq		Pre-processed
GSE96107	NPC	H3K4me1 ChIP-seq		Pre-processed
		H3K27ac ChIP-seq		Pre-processed
		H3K4me3 ChIP-seq		Pre-processed
		H3K36me3 ChIP-seq		Pre-processed
		H3K9me3 ChIP-seq		Pre-processed
		H3K27me3 ChIP-seq		Pre-processed
		CTCF ChIP-seq		Pre-processed
GSE96107	CN	H3K4me1 ChIP-seq		Pre-processed
		H3K27ac ChIP-seq		Pre-processed
		H3K4me3 ChIP-seq		Pre-processed
		H3K36me3 ChIP-seq		Pre-processed
		H3K9me3 ChIP-seq		Pre-processed
		H3K27me3 ChIP-seq		Pre-processed
		CTCF ChIP-seq		Pre-processed
Repeats	Mouse	UCSC browser		Pre-processed
GSE96107	mESC, NPC, CN	RNA-seq		Pre-processed

Hi-C 1D read counts

If pre-processed files by authors were available, we obtained the SRA files from respective accessions and converted them into fastq files using NCBI SRA toolkit. Hi-C processing was done by two different approaches such as traditional Hi-C processing using HiCUP (Wingett et al. 2015). Briefly, paired-end reads were mapped separately using bowtie2 on to the indexed reference genome. They were further filtered for invalid and duplicated read pairs. Then, the forward and the reverse reads were mixed together and read counts were calculated at 10kb resolution genome-wide. Then, the read count was calculated at 10kb resolution genome-wide. Constitutive LADs and constitutive inter-LADs were downloaded from GSE17051 (Peric-Hupkes et al. 2010).

Correction of 1D read counts: To remove biases in 1D read counts

The 1D raw read count at 10kb resolution was corrected for restriction site density (RE-density) and GC content by using the loess regression. Since the RE-density influences the 1D raw read count as observed through a negative correlation between RE-density and 1D raw read count, we removed the observed correlation between RE and raw read count by loess regression. We obtained the RE corrected read count as the loess residuals of read counts after regression against RE-density. Differential GC content of chromatin fragments could lead to their differential amplification during PCR steps and that is observed through a correlation between GC content and RE corrected read count. Therefore, we corrected the RE corrected read counts for the bias due to GC content by the obtaining the loess residuals from the loess regression of the RE corrected read counts against GC content. Finally, the correlation between GC RE corrected reads and mappability was diminished by filtering out genomic regions with <0.8 mappability. The corrected read count follows a Gaussian distribution and we transformed it to Z-scale for plotting purposes.

Domain calling: To call condensed and decondensed domains in 1D corrected read count

Algorithm of domain calling was adopted from (Guelen et al. 2008) to identify condensed and decondensed domains from the 1D corrected read count. Briefly, corrected 1D data were scaled using Z-score and binarized as +1 (if Z>=0) and -1 (if Z<0). For every genomic region, the difference in the binarized data between 20 bins upstream and 20 bins downstream was calculated. Then, the regions with significant difference were identified through bootstrapping with FDR 5% (randomization of the binarized values and calculating the above-mentioned difference for every genomic region; n=1000). These regions were used as domains boundaries. Further, the regions between the boundaries were classified as condensed and decondensed if the proportion of the binarized values exceeded 0.8 in the negative and positive scales, respectively.

Analysis of different histone modifications and CTCF during differentiation in 1D domains: To check the transcriptional activity in condensed and decondensed domains

ChIP-seq read density of CTCF and different histone modifications such H3K4me1, H3K4me3, H3K27ac, H3K9me3, and H3K36me3 of mESC, NPC and CN were downloaded from GSE96107, binned at 10kb resolution, and brought into same scale by using the function ‘normalize.quantiles’ of the R package “preprocessCore”. Mean enrichment of these different histone modifications and CTCF was checked around the boundaries (+/- 1mb) between the condensed and decondensed regions, which were at least 200kb in length. Dynamics of the condensed and decondensed regions between mESC to NPC was checked by plotting the histone modifications in 2D hexagon plots with mESC and NPC in the x and y axes respectively.

3.3 Results

Condensed regions are less accessible to restriction endonuclease in *in-situ* digestion

Restriction endonuclease is widely used in Hi-C. To test if the visibility bias (i.e., the inability of restriction enzymes to digest highly condensed domains in restriction digestion of Hi-C protocol) was present in Hi-C datasets, we converted the raw interaction frequencies of Hi-C experiments into one-dimensional read counts and corrected for biases, such as GC content, RE density and mappability. We plotted the corrected read counts in the LAD (known condensed domains) and iLAD (known decondensed domains) in multiple cell-types, such as mouse embryonic stem cells (mESC), neural progenitor cells (NPC), and cortical neurons (CN), and observed the cLADs had lower read counts (Refer the associated manuscript). We also identified domains using our in-house pipeline in the corrected read counts and observed that 70% of the identified condensed domains were overlapping with known LADs, and rest 30% was within iLAD. This marked the identification of condensed domains outside the known condensed domains (Figure 3.3.1).

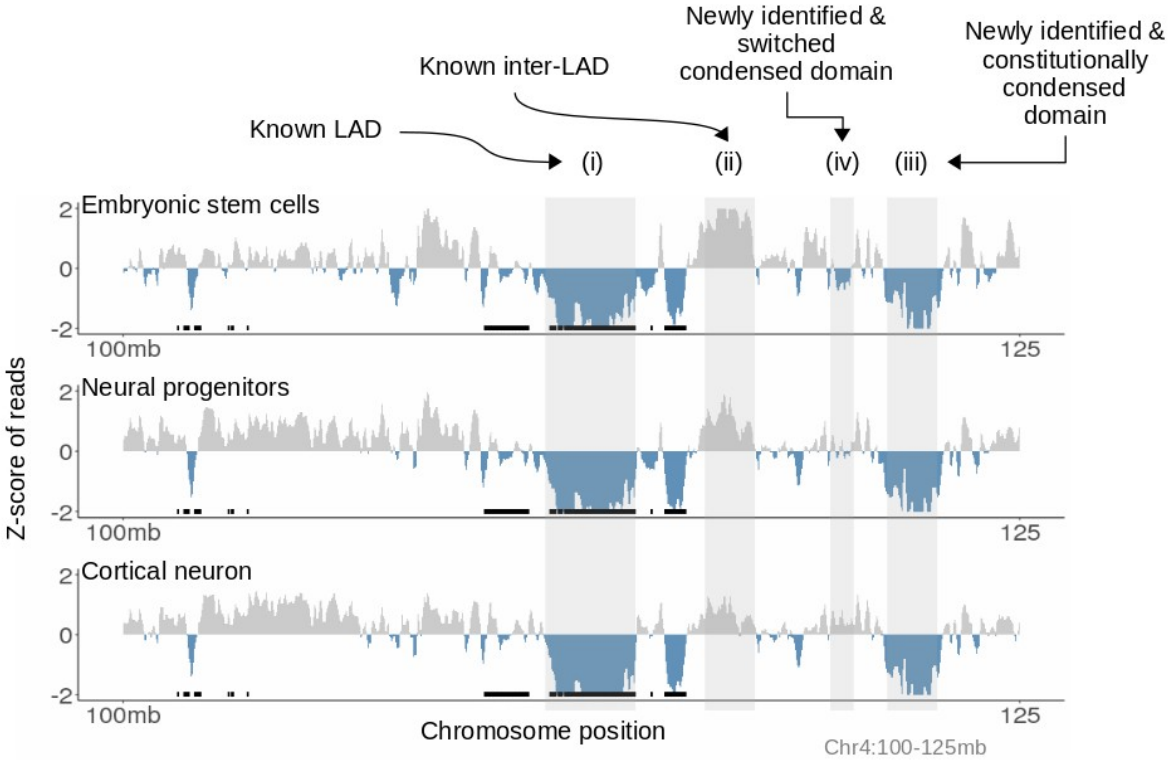

Figure 3.3.1 Example of condensed and decondensed domains. (i) and (ii) are known condensed and decondensed domains, respectively. (iii) and (iv) are newly identified domains.

Dynamics of newly identified domains

We analyzed the dynamics of newly identified condensed and decondensed domains between mESC and NPC to access their underlying functional significance. First, we checked the enrichment of active (H3K4me1, H3K27ac, K3K4me3, and H3K36me3) and inactive (H3K9me3) histone marks (see 'Materials & Methods' for complete list of data-sets that are used) across all condensed and decondensed domains by aligning the domain boundaries with the condensed downstream and decondensed regions upstream (Figure 3.3.2). The average aggregation plots of different histone

modification around the domain boundaries showed that the enrichment of active and inactive histone marks over the decondensed and the condensed, respectively, with transitions around the domain boundaries. We also observed the enrichment of epigenetic insulators, such as CTCF (accession: GSE96107) and MIR, at the boundaries between the condensed and decondensed domains (Figure 3.3.3).

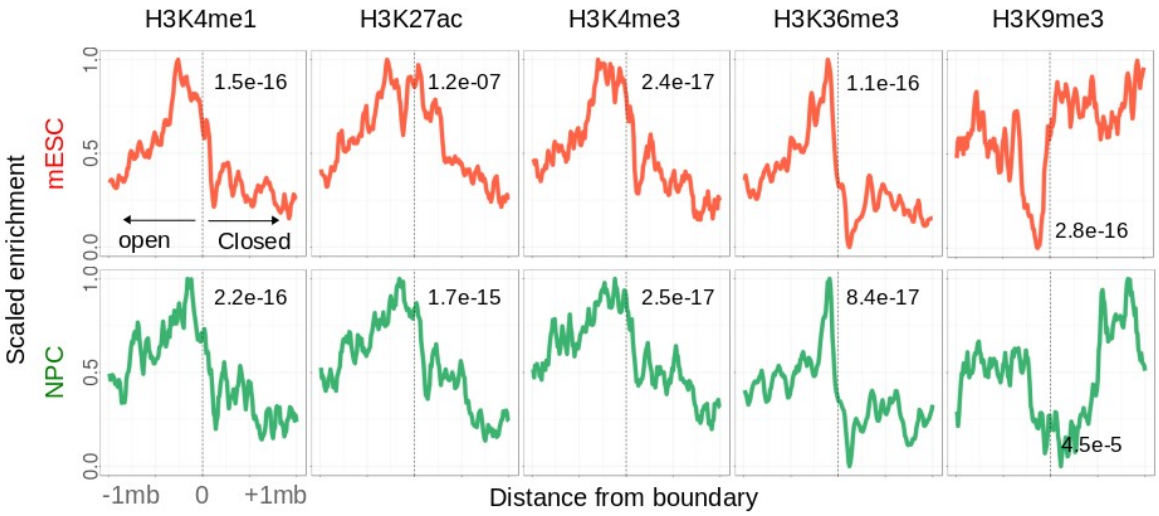

Figure 3.3.2 Enrichment of different histone modifications around the boundaries of condensed and decondensed regions.

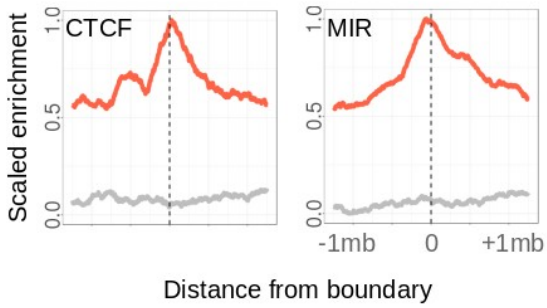

Figure 3.3.3 Enrichment of CTCF and MIR at the boundaries of condensed and decondensed regions.

Then, we checked the enrichment of active and inactive marks over the domains that switched their status during differentiation from mESC to NPC via 2D scatter-plots (Figure 3.3.4). While the domains that did not switch during the differentiation did not show significant skew between the two axes, the domains that switched the status between mESC and NPC showed skew towards one of the axes. For the domains that were decondensed in mESC and condensed in NPC, the active histone marks showed skew towards X-axis that represented the decondensation in mESC and the inactive histone mark showed skew towards Y-axis that represented the condensation in NPC. Likewise, for the domains that were condensed in mESC and decondensed in NPC, the active histone marks showed skew towards Y-axis that represented the decondensation in NPC and the inactive histone mark showed skew towards X-axis that represented the condensation in mESC.

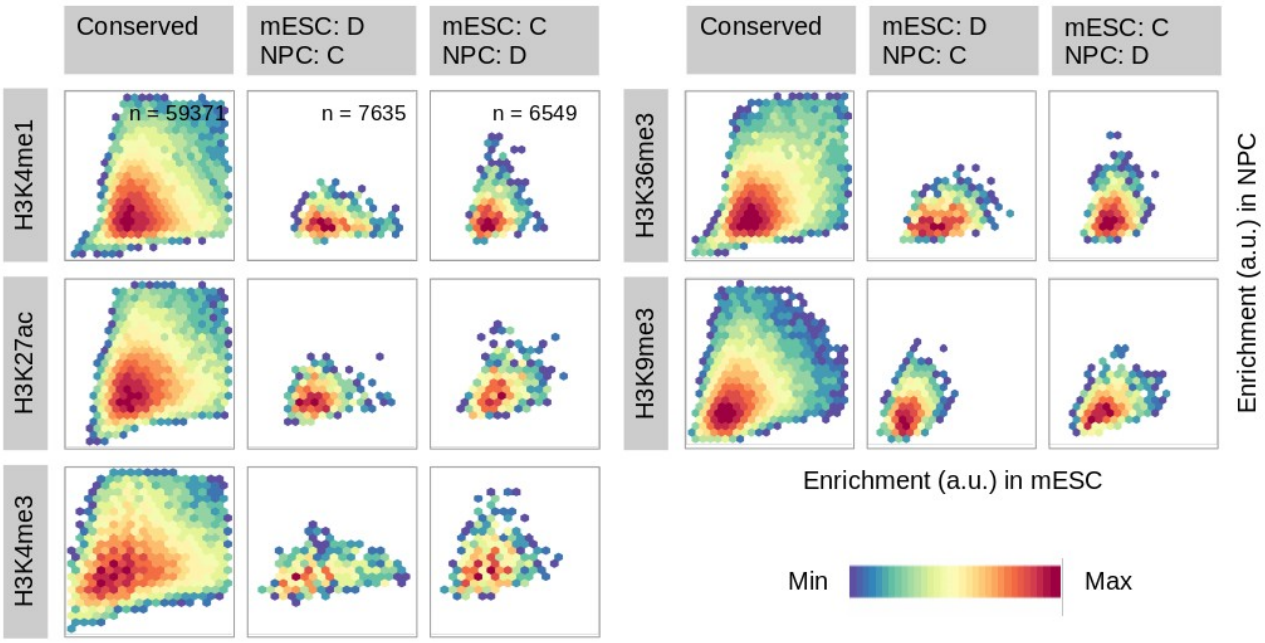

Figure 3.3.4 Dynamic of histone marks in conserved and switched domains in mESC and NPC. D – Decondensed; C – Condensed domains.

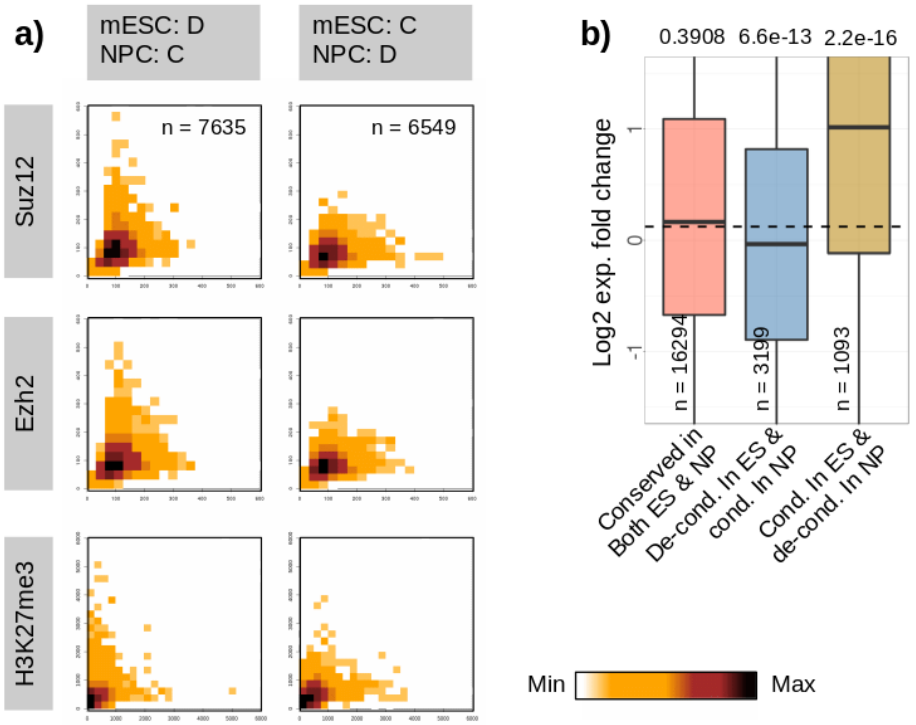

Figure 3.3.5 (a) Dynamic of SUZ12 and EZH2 in switched domains. D – Decondensed; C – Condensed domains. (b) Gene expression changes in conserved and switched domains.

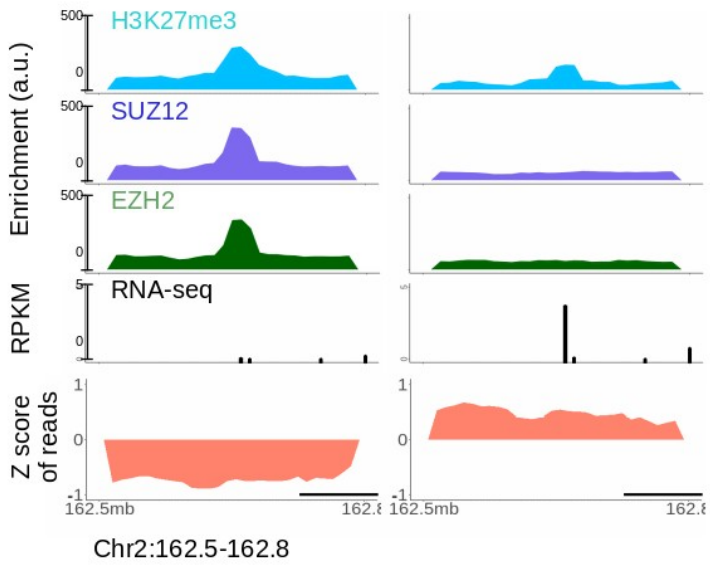

Figure 3.3.6 Example depicting the loss of polycomb repressive complex factors SUZ12 and EZH2, and H3K27me3 during gene activation. Left panel: mESC, right panel: NPC.

Therefore, the domains that switched the status showed enrichment of active histone marks when they were decondensed and loss of active histone marks when they were condensed. On the other hand, the inactive H3K9me3 showed subtle changes during domain switching. This was in agreement with another study that suggested the subtle changes of H3K9me3 during mESC differentiation (Dixon et al. 2015). We further observed that the domain-switch was associated with the polycomb repressive complex associated factors/marks, such as EZH2, SUZ12, and H3K27me3 (Figure 3.3.5a). For the domains that were decondensed in mESC and condensed in NPC, the inactive histone factors/marks showed skew towards Y-axis that represented the condensation in NPC. Likewise, for the domains that were condensed in mESC and decondensed in NPC, the inactive histone factors/marks showed skew towards X-axis that represented the condensation in mESC. The dynamic switch from condensed to decondensed and vice-versa were also associated with gene expression change (accession: GSE96107) (Figure 3.3.5b). The domains that did not switch between mESC and NPC did not show any change in gene expression. When condensed domains switched to decondensed, they got activated and vice-versa when they switched from decondensed to condensed. These results are shown through examples in the figures 3.3.6-7. Figure 3.3.6 shows the switch from condensation to decondensation between mESC and NPC, which is accompanied by the loss of polycomb repressive complex factors/marks and activation of the gene in the domain. Figure 3.3.7 shows the two scenarios: 1) Conserved domain (left panel): active histone marks and gene expression with less inactive histone marks are maintained between mESC and NPC; 2) Switch from decondensation to condensation (right panel), which accompanies with loss of active histone marks and gain of inactive histone marks with gene inactivation between mESC and NPC. Collectively, these results suggest the concurrent deposition and removal of active histone modification (also, removal and deposition of inactive histone modifications) in the decondensed and condensed domains, respectively.

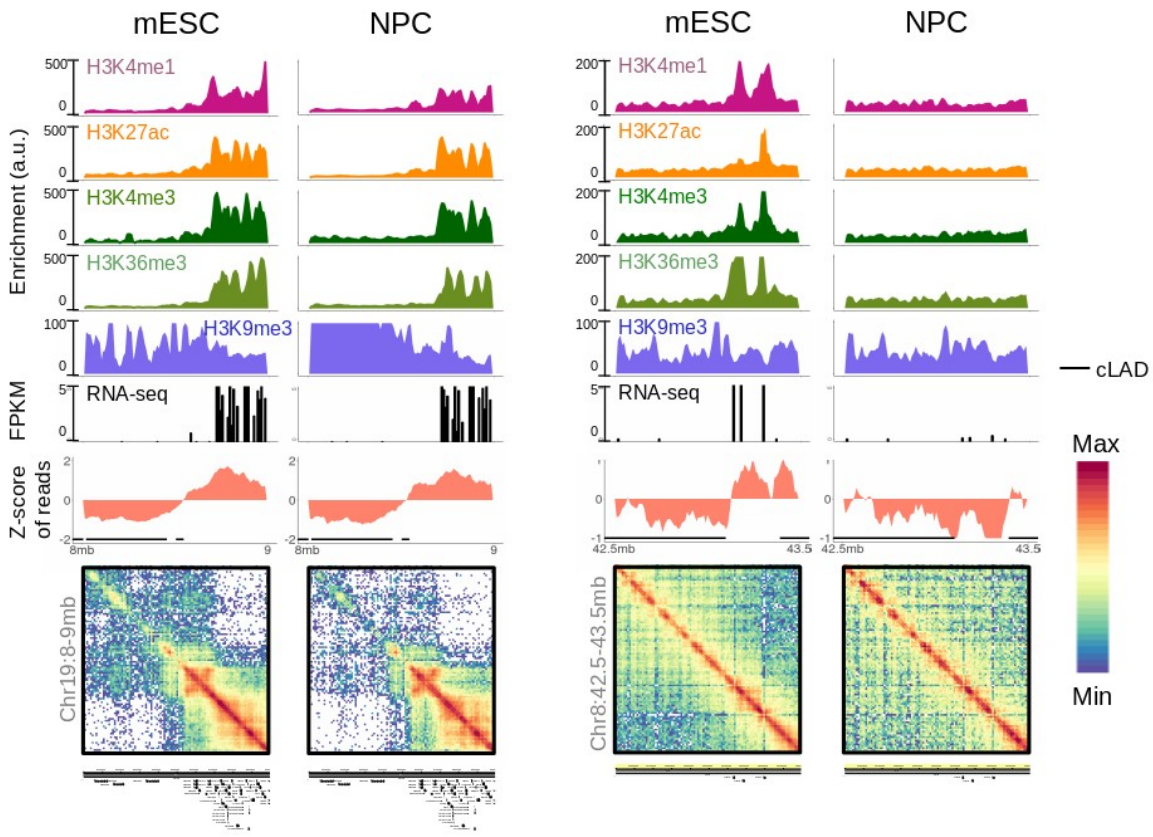

Figure 3.3.7 Examples depicting the dynamic of histone marks in conserved (left panel) and switched (right panel) domains between mESC and NPC.

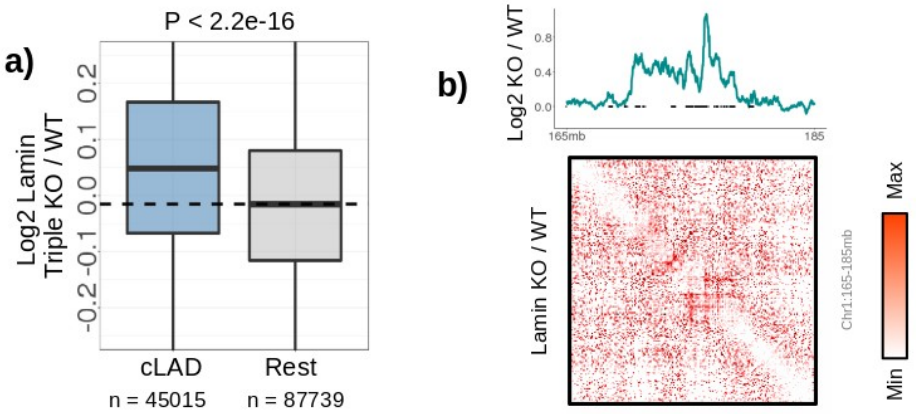

Figure 3.3.8 (a) Log2 ratio of 1D read count in Lamin triple KO to WT in cLAD and rest of the genome. (b) Examples of cLAD regions being decondensed in Lamin KO.

Lamin (*Lmnb1*, *Lmnb2*, *Lmna*) triple KO results in the decondensation of LADs in mESC (X. Zheng et al. 2018) and we hypothesized that the decondensed form would be more accessible to restriction endonuclease. Therefore, we analyzed Lamin knockout (KO) (accession: GSE89520) data in mESC. By comparing LADs and rest of the genome through ratio of reads in Lamin KO to control, we

observed that the condensed regions were more accessible to restriction endonuclease after Lamin KO (Figure 3.3.8).

3.4 Discussions

We have identified condensed outside the known condensed domains. In general, these condensed domains are repressive, and they are regulated by polycomb repressive complex factors, such as SUZ12 and EZH2. On the other hand, the decondensed domains are active in nature, as seen through the enrichment of several active histone modifications. These domains are also insulated by known epigenetic insulators, such as CTCF and MIR. When the condensed domains become decondensed during differentiation, the genes inside them are activated, as seen through the change in gene expression and histone modifications. Decondensation of LADs upon Lamin KO is also readily captured by our 1D read counts. Therefore, these observations reinforce our claims and dismiss the arguments that the visibility bias is just a hoax. Further, we understand the concurrent domain-wide opening and closing of chromatin regulates the expression of genes through different epigenetic modifiers.

Previously, several other studies found discrepancies between 5C/Hi-C and FISH results (I. Williamson et al. 2014; Fraser et al. 2015). In particular, 5C and Hi-C suggested that the locus *HoxD* remained condensed during differentiation, but DNA FISH showed the decondensation of the locus upon differentiation (I. Williamson et al. 2014). Another study corroborated that the discrepancy is due to the differential efficiency in restriction digestion between the condensed and the decondensed forms (Fraser et al. 2015). Indeed, our data (accession: GSE59027) captured the condensed and the decondensed status in mESC and NPC, respectively, at both *HoxA* and *HoxD* loci (Figure 3.4.1).

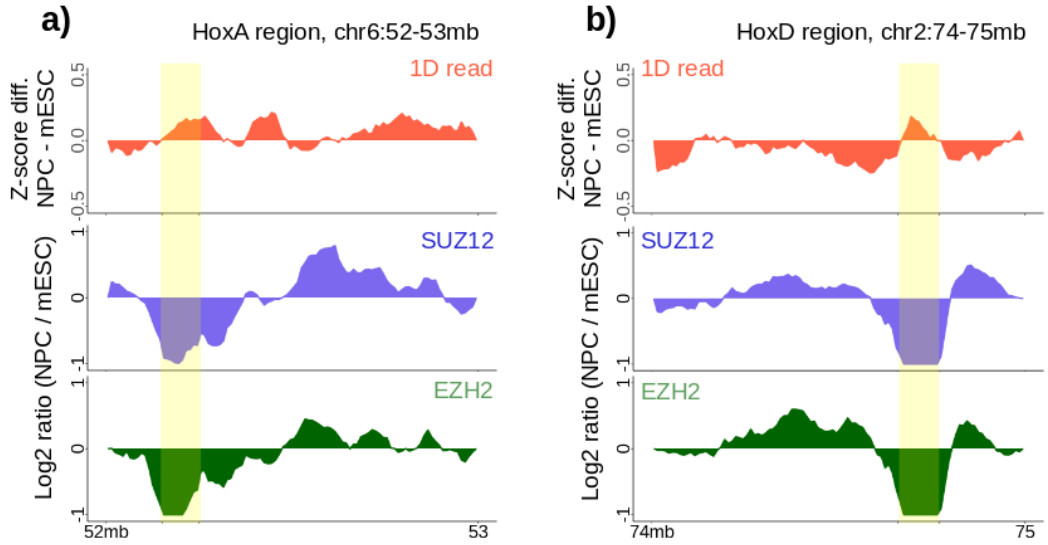

Figure 3.4.1 Z-score difference in corrected read count between NPC and mESC with log2 ratio of polycomb repressive complex factors (SUZ12 and EZH2) in NPC to mESC.

Section - 4
Conclusions

4.1 Widespread allele-specific regulatory role of insulated CTCF domains

By analyzing MAE/BAE gene datasets in multiple cell-lines of human and mouse, we have shown that the domains of MAE genes are segregated and insulated by CTCF from the domains of BAE genes. CTCF also has an allele-specific role in maintaining mono-allelic expression. While at the active allele, it acts as an enhancer – linker and promotes its expression, it insulates the inactive allele from the neighborhood of active transcription. Therefore, we propose a model that explains the genome-wide allele-specific regulatory role of CTCF in maintaining mono-allelic expression (Figure 4.1.1).

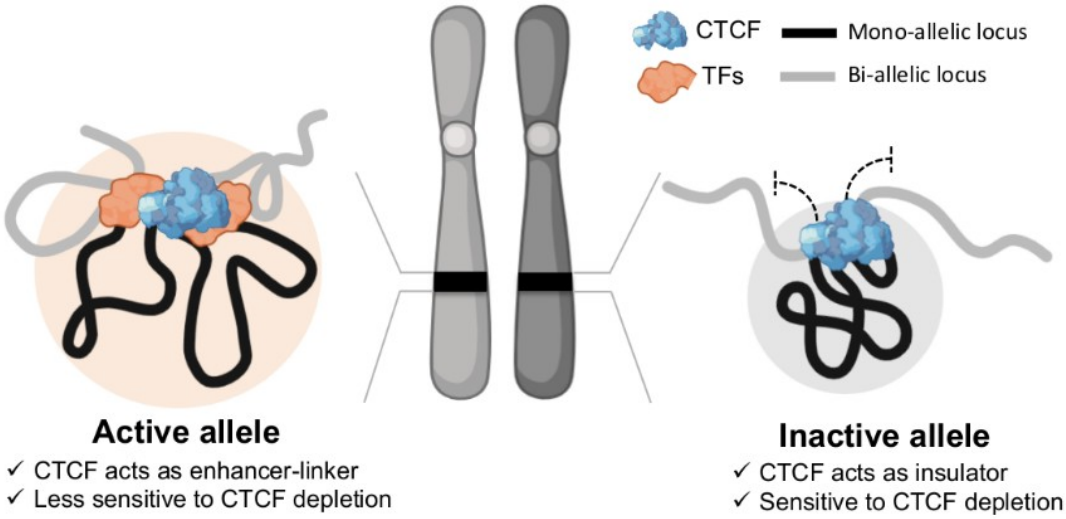

Figure 4.1.1 Genome-wide regulatory role of insulated CTCF domains in allele-specific expression.

4.2 The dynamic role of chromatin compaction in transcription

By analyzing multiple Hi-C, we have established that the restriction digestion is not uniform across the genome. The condensed regions are less accessible to restriction endonuclease, and that leads to the presence of visibility bias in Hi-C datasets. Then, we have repurposed the visibility bias (1D corrected read count) to quantitate chromatin compaction genome-wide and have identified novel condensed domains outside the known condensed domains, which are demarcated by CTCF and dynamically regulated via concurrent deposition of epigenetic marks during development.

Altogether, the thesis presents non-trivial insights to allele-specific and domain-wide transcriptional regulation guided through CTCF-mediated genome architecture.

Section - 5
Appendix

(a) List of abbreviations

1D	One-dimensional
3C	Chromosome Conformation Capture
3D	Three-dimensional
4C	Circular Chromosome Conformation Capture
5C	Chromosome Conformation Capture Carbon Copy
BAE	Bi-Allelically Expressing genes
ChIA-PET	Chromatin Interaction Analysis by Paired-End Tagged sequencing
ChIP	Chromatin ImmunoPrecipitation
ciLAD	constitutive inter Lamina Associated Domains
cLAD	constitutive Lamina Associated Domains
CN	Cortical Neurons
DiSCO	Distance Sorted Contact Optimization
DMR	Differentially Methylated Region
DNA	De-oxy ribo Nucleic Acid
GAM	Genome Architecture Mapping
H3K4me1	Histone-3-lysine-4-methylation
H3K4me3	Histone-3-lysine-4-tri-methylation
H3K36me3	Histone-3-lysine-36-tri-methylation
H3K9me3	Histone-3-lysine-9-tri-methylation
H3K27ac	Histone-3-lysine-27-acetylation
H3K27me3	Histone-3-lysine-27-tri-methylation
Hi-C	High-throughput Chromosome Conformation Capture
HiCUP	Hi-C User Pipeline
ICE	Iterative Correction and Eigenvector decomposition
ICR	Imprinting Controlling Region
IDR	Intrinsically Disordered Region
KO	Knock Out
LAD	Lamina associated Domain
MAE	Mono-Allelically Expressing genes
mESC	mouse Embryonic Stem Cell
MIR	Mammalian-wide Interspersed Repeats

NPC	Neuronal Progenitor Cell
RE-Density	Restriction Endonuclease site density
RED-seq	Restriction Endonuclease Digestion coupled with sequencing
RNA	Ribo Nucleic Acid
SRA	Sequence Read Archive
TAD	Topologically Associating Domain
TF	Transcription Factor
UCSC	University of California Santa Cruz
WT	Wild-Type

(b) Links of all online tools and other sources

S.no.	***Name***	***Link***
1.	ASEQ	http://demichelislab.unitn.it/ASEQ
2.	bedtools	https://bedtools.readthedocs.io/en/latest/
3.	bowtie2	http://bowtie-bio.sourceforge.net/bowtie2/index.shtml
4.	Cooler	https://github.com/mirnylab/cooler
5.	dbMAE	https://mae.hms.harvard.edu/
6.	Epigenome Roadmap	http://www.roadmapepigenomics.org/
7.	ENCODE	https://www.encodeproject.org/
8.	Ensembl	https://asia.ensembl.org/index.html
9.	GEO	https://www.ncbi.nlm.nih.gov/geo/
10.	GeneiASE	https://github.com/edsgard/geneiase
12.	HiCUP	https://www.bioinformatics.babraham.ac.uk/projects/hicup/
13.	HiCNorm	https://github.com/ren-lab/HiCNorm
14.	hiclib (ICE)	https://bitbucket.org/mirnylab/hiclib/src/default/
15.	HOMER	http://homer.ucsd.edu/homer/interactions/
16.	Imprinted genes	http://www.geneimprint.com/
17.	Juicer tools	https://github.com/aidenlab/juicer/wiki/Download
18.	NCBI SRA Toolkit	https://www.ncbi.nlm.nih.gov/sra/docs/toolkitsoft/
19.	SAMtools	https://github.com/samtools/samtools
21.	UCSC genome browser	https://genome.ucsc.edu/
22.	WashU Epigenome browser	https://epigenomegateway.wustl.edu/

Section - 6
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