The Developmental Atlas: Organ-Specific Genomic Architecture Across Development

The folding of DNA in the nucleus, 3D genomic architecture, is a major regulator of gene expression. Chromatin loops act like molecular bridges, bringing distal genomic sequences into proximity, facilitating interactions for gene expression. Variations in expression allow cells with identical genomes to differentiate into and function as different tissues. Given this role of genomic architecture, it is critical to explore these features comprehensively. This study explores the variation of genomic architecture across organs through development and aging. We investigate domains, compartments, and loops to characterize tissue- and stage-specific genomic architecture down to base pair resolution.

We obtained B6 x Castaneus F1 mouse tissues including heart, gastrocnemius, left cerebral cortex, adrenal gland, and hippocampus at multiple time points spanning post-natal day 4 (approximate to a 2nd trimester human fetus) through 20 months (approximately 65-year-old human age). We completed the intact Hi-C protocol established for the Encyclopedia of DNA Elements 4 (ENCODE4) consortium on each tissue, which were then analyzed using the Juicer pipeline.

These Hi-C maps reveal dynamic tissue- and developmental stage-specific variations in chromatin domains, compartments, and loop interactions. Specifically, gastrocnemius maps on chromosome 11 show high compartmentalization, important for discerning transcriptional activity affecting gene expression. Understanding these annotations will characterize how disruptions in these interactions can lead to developmental abnormalities and disease.

This work provides the first comprehensive atlas of spatiotemporal genome architecture to advance our understanding of tissue-specific regulatory mechanisms as well as important structural regulations across development. Future research will focus on dissecting the dependency of these chromatin loops on architectural proteins like CTCF and RAD21 in tissue-specific regulation and enhancer-promotor interactions. Paving the way for therapeutic strategies targeting genome organization while further elucidating the genetic blueprint of development and aging.

One image is permitted under **100KB, and format should be JPEG, PNG, or BMP. Your abstract is limited to 2500 characters (including spaces). Your title characters do not count against your max limit. The abstract submission form includes the following fields:**

• Title: The title should be brief, but long enough to identify clearly the nature of the study. Do not include authors in the title.

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• Background: Indicate the purpose and objective of the research, the hypothesis that was tested or a description of the problem being analyzed or evaluated.

Chromatin defects have been found to induce abnormalities in genomic regulation, including methylation and chromatin organization. Detailed annotations of the genome must be understood to discern crucial regulatory factors and underlying mechanisms of growth where gene expression can be modified. Exploring the epigenomic features that govern this regulation, specifically the three-dimensional structure of the genome during development. Some features include chromatin loops where genomic sequences on a single chromosome are in closer proximity than expected, by looping of a chromatin strand that can regulatory elements like enhancers and transcription factors binding sites; if defected chromatin loops are present, development and disease are affected. Annotate regions with altered interactions to understand their functional relevance and correlate changes in genome architecture with potential processes. Utilizing functional annotation tools to interpret the biological significance of genomic changes for a comprehensive understanding which will give us a detailed picture of the genetic wiring that takes place. Creating a more profound comprehension of organ development and the intricate interplay between genomic architecture and developmental processes.

• Methods: Describe the study period/setting/location, study design, study population, data collection and methods of analysis used.

Hi-C experiments show how DNA folds by measuring frequency of contact between different loci. The X-axis and Y-axis represent genomic positions, and the color intensity of the pixel indicates the frequency of contact. The closer two pieces of DNA are in 3D space, the stronger the signal between them. Utilizing formaldehyde tissue crosslinking followed by intact DNase Hi-C, to create high-quality 3D maps of the organ-specific genomes throughout development while generating annotations that bring distal elements in proximity and influence their regulation. Experiments were done on B6xCastaneus F1 mouse tissues; specifically, the heart,

gastrocnemius, left cerebral cortex, adrenal gland, and hippocampus. Timepoints range from mouse post-natal 4 days to 20 months, equivalent to human second trimester of pregnancy to old age.

• Results: Present the findings/outcome of the study as clearly and as detailed as possible. Please summarize any specific results.

When comparing the organs and timepoints, domains and compartments are seen to change at varying degrees depending on which chromosome is in view and at what scale. Further research will be done looking at specific enhancer and promoter regions, chromatin looping dependence. Results suggest various tissue-specific and developmental stage specific features of genomic architecture.

• Conclusions: Explain the significance of your findings/outcomes of the study, treatment, care and/or support, and future implications of the results.

This study underscores the dynamic nature of genomic architecture across tissues and developmental stages, highlighting its critical role in regulating gene expression. The findings advance our understanding of the interplay between 3D genome organization and organ-specific functions, with potential implications for developmental biology and disease mechanisms. Future work will delve deeper into enhancer-promoter dynamics and their regulatory dependencies to further elucidate the genetic blueprint of development.

• Keywords: Provide 3-5 keywords that will direct search queries to your abstract. Do not use words that are included in your abstract title.

differentiation, regulation, gene expression

This work provides the first comprehensive atlas of organ-specific genomic architecture across developmental stages, shedding light on the interplay between 3D genomic organization and biological processes. By correlating chromatin features with functional annotations, we advance our understanding of how chromatin loops influence gene regulation in a spatiotemporal manner for tissue-specific regulatory mechanisms in biological processes.

The folding of DNA in the nucleus, 3D genomic architecture, is a master regulator for gene expression. Chromatin loops act like molecular bridges, bringing distal genomic sequences into proximity, facilitating interactions between enhances and promoters for proper gene expression. Disruptions in these interactions, such as defective chromatin loops, can lead to developmental abnormalities and disease. This study dives into the dynamic shifts in genomic architecture across organ-specific genomes during critical developmental stages, unraveling the molecular mechanisms driving these changes and their biological significance. By investigating specifics such as domains, compartments, and loop dynamics, we can characterize tissue- and stage-specific genomic architecture down to base pair level.

Hi-C data reveals dynamic tissue- and developmental stage-specific variations in chromatin domains, compartments, and loop interactions. Initial correlations show specific dependency patterns emerging for organ development. Suggesting dynamic dependencies of architecture for these complex mechanisms. Chromosome-scale analyses could reveal regions of high interaction variability are enriched for regulatory elements, such that developmental transitions are accompanied by reorganization of chromatin loops and enhancer-promoter dynamics, with certain loops showing tissue-dependent reliance on architectural proteins. On the other hand, disruptions in these loops could be associated with potential shifts in gene expression networks, hinting at critical developmental and disease-related regulatory mechanisms.

The findings reveal a dynamic genomic landscape: chromatin domains, compartments, and loop interactions are anything but static. Instead, they evolve uniquely in each tissue and developmental stage. Regions with high interaction variability are enriched for regulatory elements, highlighting their role in orchestrating developmental transitions. Remarkably, chromatin loops often rely on specific architectural proteins in a tissue-dependent manner. Disruptions in these loops can ripple through gene expression networks, offering clues to the genetic underpinnings of development and disease.

how chromatin structure drives tissue-specific gene regulation