Topological domains in mammalian genomes identified by analysis of chromatin interactions.

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Public Summary:
Every cell in the human body contains an entire copy of the human genome, containing all the genetic material in the form of DNA that is necessary for proper cellular function. To compact this amount of DNA into a single cell is a great challenge. We sought to understand the principles of how entire chromosomes of DNA are folded up in both embryonic stem cells and differentiated cells. We have observed that each chromosome is made up of a series of regions we term “topological domains.” These are regions of the genome that self-associate, and are largely restricted in their associations with neighboring regions, leading to the idea a chromosome may be arranged with these domains like the beads along a necklace. The organization of these domains does not appear to change markedly from embryonic stem cells to more differentiated cells. Furthermore, these domains appear to be conserved through evolution, as similar structures at similar locations are also observed in the mouse genome. Lastly, we can observe that the regions in between the domains, which we term boundaries, are enriched for diverse factors, including proteins known to regulate nuclear structure. By understanding how the genome is organized in embryonic stem cells and differentiated cells, this will likely aid in our understanding of the processes that occur normally when an embryonic stem cell differentiates. Furthermore, chromosome structures are known to be altered when cells become cancerous, and this work will help lay the groundwork for future studies looking at how structures change in cancer cells.

Scientific Abstract:
The spatial organization of the genome is intimately linked to its biological function, yet our understanding of higher order genomic structure is coarse, fragmented and incomplete. In the nucleus of eukaryotic cells, interphase chromosomes occupy distinct chromosome territories, and numerous models have been proposed for how chromosomes fold within chromosome territories. These models, however, provide only few mechanistic details about the relationship between higher order chromatin structure and genome function. Recent advances in genomic technologies have led to rapid advances in the study of three-dimensional genome organization. In particular, Hi-C has been introduced as a method for identifying higher order chromatin interactions genome wide. Here we investigate the three-dimensional organization of the human and mouse genomes in embryonic stem cells and terminally differentiated cell types at unprecedented resolution. We identify large, megabase-sized local chromatin interaction domains, which we term 'topological domains', as a pervasive structural feature of the genome organization. These domains correlate with regions of the genome that constrain the spread of heterochromatin. The domains are stable across different cell types and highly conserved across species, indicating that topological domains are an inherent property of mammalian genomes. Finally, we find that the boundaries of topological domains are enriched for the insulator binding protein CTCF, housekeeping genes, transfer RNAs and short interspersed element (SINE) retrotransposons, indicating that these factors may have a role in establishing the topological domain structure of the genome.