Druggable\_nucleosome

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With dropping costs of sequencing technologies, tenths of thousands genomes get sequenced by private enterprises [1] and through NIH support (Trans-Omics for Precision Medicine (TOPMed) Program). Yet, the discovery of new genetic variants appears to be saturated at ~8,500 high-coverage genomes [1], highlighting the need to shift focus on a higher-level understanding the role of genomic variation.

The advent on chromatin conformation capture (3C) sequencing technology [**???**] marked the beginning of a new era in precision medicine. Its evolution into Hi-C technology allows an insight into the 3D structure of the human genome within the nucleus [2]. Numerous studies demonstrated highly conserved topologically associated domains (TADs) - spatially close units of chromatin bringing together enhancers, promoters of genes, and other regulatory elements . These TADs have well-defined boundaries marked by strongly interacting chromatin regions (chromatin loops) [3][4]. TADs harbor multiple active RNA polymerases anchored to a nuclear substructure, with genes within TADs showing co-expression patterns [5][6][7]. TADs are increasingly recognized as regulatory units orchestrating expression of thousands of genes, thus emerging a new "druggable nucleosome" paradigm.

Disruption of TAD boundaries due to copy number variants and even single nucleotide polymorphisms lead to fusion of TADs and/or formation of smaller TADs [8][9]. This is a frequent event in cancer, leading to coordinated expression of oncogenes [10]. These changes in TAD boundaries are now emerge as a hallmark of cancer [11]. With the dropping costs of sequencing using personalized TAD abnormalities for diagnostic prognostic and, potentially, treatment purposes will soon become a reality.

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