In Search of Genomic Dark Matter: A Novel Method for the Global Identification of Active Regulatory Elements

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The human genome contains upwards of 20,000 genes that code for functional products, such as proteins. In addition to genes, the genome encodes regulatory elements that respond to specific stimuli to control which genes are transcribed. Identifying regulatory elements represents a critical endeavor because in any given cell many hundreds of genes may be turned on, and it is this combination of expressed genes that determines the characteristics of a particular cell type. This project describes a new method for the genome-scale identification of regulatory elements. While genes can be predicted via computational models, regulatory elements cannot be so easily identified, as most approaches are confounded by their widely varied sequence composition and location relative to genes. Therefore, a novel series of techniques that captures links between regulatory elements and genes during expression was developed. The method, termed “GRIP-seq” (Genomic Regulatory element Immunoprecipitation followed by high-throughput Paired-end Sequencing), marks an improvement over previous technologies by selecting for transcription-related protein-DNA complexes involved in active regulation and harnessing next-generation sequencing to create a genome-wide map of paired elements at high resolution. Employing the sea urchin Strongylocentrotus purpuratus as the first model system, analyses of five major developmental genes and associated regulatory modules—including Blimp1—have indicated a high signal-to-noise ratio and sensitive identification of functional elements. Implications of this method include developing regulatory maps of previously unstudied genomes, determining pathogeneses of genetic diseases on a predictive basis, and advancing therapeutic and individualized medicine.

Awards Won:

Second Award of $2,000