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Letter to Editor

Human Genome – Mysterious Kryptos In Biology: Decoding By Encode

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The twentieth century was the century of physics due to the successful interactions between theoretical and experimental physics, engineering principles and applications paved way for billion-dollar market in aircraft industry. Twenty first century is un-doubtfully the century of biology primarily because of the promise and achievements of genomics. Scientists aim to use variations within genes as disease biomarkers, drug responses, genome specific treatment, and treatment based on gene modulation. However, the increasing complexity of genome and unexplored functions resists us in fully exploit our discovery in clinical climate.The human genome is comprised of two sets of 23 chromosome contributed by a male and a female partner. About 97 percent of the genome consists of sequences that do not code for proteins and have no known function; these were previously referred as “Junk DNA” while now we call them as “Noncoding DNA”. About 70,000 genes are estimated in the rest 3% of the genome.

The goals of today’s genome biology is ambitious, Noncoding DNA (ncDNA) are sequences within a genome that does not code for a protein. It is a great puzzle for scientist around the world to accept the factual result of human genome project revealed that about 97% of the human genomes are composed of ncDNA. Nevertheless, scientists continue to be convinced that ncDNA must have certain functions and explored few of their functions until date that includes vital functions in the transcriptional and translational regulation of protein-coding sequences. Numerous classes of ncDNAhave been identified. This includenoncoding RNA specific gene, introns, unrelated regions of mRNA, pseudo-genes, regulatory DNAsequences, repetitive DNA sequences, and sequences related to mobile genetic elements.

After completing human genome project in 2003, to delineate all functional elements encoded in the human genome, project ENCODE (Encyclopedia of DNA Elements) was initiated. The aim of the project is identify the functional elements that encode a defined product such as protein or non-coding RNA. The map the function of ncDNA, ENCODE researchers approach the project in three different ways.

1. Biochemical approach
2. Evolutionary approach
3. Genetic approach

The biochemical approach is specific for cell type, condition, and molecular process derived from previous molecular studies of gene regulation and RNA metabolism. The noncoding functional elements are mapped to specific chromatin structures that display signature patterns of histone modifications, DNA methylation, endonuclease and transcription factor accessibility and/or occupancy. The results derived by ENCODE through biochemical assays(Kellis et al. 2014) shed light on transcribed and functional micro RNA’s (miRNA) and long non coding RNA’s (lncRNA) at nuclear and cytoplasmic level. Also, we have learned about theoccupancy of sequence-specific transcription factors and their binding domain, effector molecules that function at cis and trans mechanisms, other chromatin regulatory proteins and modifiers, DNA methylation and histone modifications, and trans

chromosomal interactions.

Evolutionary approach employs comparative genomics to study multispecies comparisons ranging from yeast to mammals. ENCODE have had success in recognizing protein-coding regions, structural RNAs, gene regulatory regions, regulatory motifs, and specific regulatory elements. Comparative genomic studies suggest that 3–8% of bases may be functional(Pennacchio 2003). After studying 1% of genome, The ENCODE project annotated 60% of mammalian genome has evolutionarily constrained bases and are potentially functional;they have also identified many additional putative functional elements without evidence of constraint. However, evolutionary approach has their own limitations such as identification of conserved regions depends on accurate multispecies sequence alignments that is challenging. In addition, owing to the fact that alignments are less effective for distal-acting regulatory regions, there could be sequence composition biases. Thus, comparative genomics is less efficient with own limitations and requires complementary studies.

Genetic approaches are often considered as gold standard method. They rely on sequence alterations. Briefly, a functional relation is mapped to a DNA segment by studying the mutation. Mutations can be either natural or induced using interference, once mutation occurred the phenotypes are screened by sequence variants. Transfection studies using reporter assays are used to identify regulatory elements and to measure their activities. This approach has a disadvantage in missingphenotype element that are specific to rare cells or a particular environment that are insensitive for current assay protocol. Nevertheless, this is one of the best methods available for practiced. Efforts are drawn in to improve the sensitivity of the assay techniques.

According to the ENCODE project consortium;

“The important features about the organization and function of the human genome are:

1. About 80.4% of the human genome participates in at least one biochemical RNA and/or chromatin associated event in at least one cell type. Much of the genome lies close to a regulatory event: 95% of the genome lies within 8kb of a DNA-protein interaction, and 99% is within 1.7kb.
2. Primate-specific elements as well as elements without detectable mammalian constraint show evidence of negative selection; thus, some of them are expected to be functional.
3. Classifying the genome into seven chromatin states suggests an initial set of 399,124 regions with enhancer-like features and 70,292 regions with promoter-like features, as well hundreds of thousands of quiescent regions.
4. It is possible to quantitatively correlate RNA sequence production and processing with both chromatin marks and transcription factor (TF) binding at promoters, indicating that promoter functionality can explain the majority of RNA expression variation.
5. Many non-coding variants in individual genome sequences lie in ENCODE-annotated functional regions; this number is at least as large as those that lie in protein coding genes.
6. SNPs associated with disease are enriched

within non-coding functional elements, with a majority residing in or near ENCODE-defined regions that are outside of protein coding genes. In many cases, the disease phenotypes can be associated with a specific cell type or TF".

Where is genomics leading us? The advent of computers coupled with genomics and 3-D printing has opened up the possibility of printing human body parts. Using custom-designed printer's researchers around globe are trying to create synthetic scaffold and materials for vital organs such as dental implant, endothelial structure, blood vessels, skin grafting, bone regeneration, artificial kidney and so on.Bonasser's lab at Cornell University had developed tissue injection molding and cell-mediated sintering technique, where living implants are formed under cell viable conditions. The ultimate aim is to fabricating composite tissues with heterogeneous structures and anisotropic properties by 3-D printing technology where genomics play a vital role in understanding the relationship of native cells and engineered cells. The group had succeeded in printing ear tissue in layers composed of ink with living cells(Cohen et al. 2006). Similarly, scientists are working on a cell-based hormone therapy – essentially an artificial ovary to deliver sex hormones in a more natural manner than drugs to simulate and regulate non-coding RNA mediated gene response triggered by binding of estrogen(Diaz-Garcia and Herraiz 2014). The exceptional number of functional elements identified by ENCODE provides the researcher a valuable database and knowledge to significantly find novel solution for major clinical disease.

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