|  |  |
| --- | --- |
| **Master in Omics Data Analysis** | **Gene regulation exercise** |
| Universitat de Vic | Teacher: J.M. Serrat |
| Name and Surname: Pierre Wensel | |

**How the authors of the article** *Enhancers: five essential questions* **answer the following questions? Write no more than five sentences for each question.**

|  |
| --- |
| **1. What are the challenges in identifying all enhancers and their functions?** |
| (1) The relatively high, scattered distribution of enhancers in 98% of the non-protein-coding DNA of the human genome results in a large (billions of bp) search region. (2) Cis-regulating enhancers can regulate multiple genes, adding complexity. (3) Enhancer location relative to such target gene (or genes) is highly variable and hard to predict (e.g. upstream or downstream of genes, within introns, proximate or distant to promoters, etc.). (4) Enhancers cannot be identified computationally from DNA sequence alone with high confidence as with protein-coding genes because the general sequence code of enhancers, if one exists at all, is poorly understood. (5)Enhancer activity is difficult to predict or understand, as it can be restricted to a particular tissue or cell type, a time point in life, or to specific physiological, pathological or environmental conditions. |

|  |
| --- |
| **2. How do enhancers bring about gene expression?** |
| Enhancers are DNA cis-regulatory elements that from a distance activate transcription of a gene or genes to higher levels than would be the case in their absence. Enhancers form chromatin loops that can be established, activated, or stabilized via, potentially, their own eRNA transcription, all to (a)bring themselves and target gene into proximity, (b) recruit and increase the local and focal concentration of interacting transcription machinery components (e.g. DNA-binding general transcription factors (GTFs) bound to promoters and enhancers, RNA polymerase II (Pol II), Mediator co-activator complexes) in the target gene(s) vicinity, (c) centrally host the assembly of pre- initiation complex (PIC) that it then can ‘deliver’ to a promoter or activated gene, (d) enable nuclear relocation of the enhancer–promoter pair to a neighborhood that is favourable for transcription, (e) influence both Pol II initiation and elongation via direct participation of transcription machinery components in looping. enhancer looping on a genome-wide scale may organize active regions of the genome and may determine the destiny of certain genes for transcription factories. I |
| **3. How do mutations and variants in enhancers influence human disease?** |
| Genetic variation due to rare or common mutations, etc. in pre-existing (as well as newly-formed via gain-of-function) distant gene-regulatory enhancers has been linked to small and large phenotypic effects, such as several human Mendelian disorders and complex disease traits. Such variants may have an impact on the risk for more than one disease. Whereas mutations in protein-coding sequences may alter broader aspects of gene expression like RNA processing, RNA stability, and protein folding, etc., mutations in enhancers are largely limited to cis effects on transcription thereby affecting subset of the quantitative, temporal and spatial expression of that corresponding gene. The modularity of enhancers and their functional compartmentalization imply that regulatory mutations will often have a lower burden on fitness than will coding mutations and may reach high frequency in populations. |

| **4. How important are changes in enhancers for evolution?** |
| --- |
| An adaptive genomic mutation may manifest itself by improving fitness in at least one context that the locus is used in while not perturbing function too much in any other context of its use. Gene sequence mutation may perturb the organism in all contexts where the transcript is in use, increasing the likelihood of a detrimental effect. Enhancer modifications and gene duplication probably have driven evolution of specific phenotypes, including insect body and wing pigmentation and larval trichome formation, butterfly wing patterning, fish pelvic fin loss, brain expansion, vibrissae loss, loss of vibrissae, and adaptations like lactase persistence. Because of their old age, high scattered distribution throughout the non-coding genomes, their aforementioned “modularity”, low-likelihood of deletion, slow mutation rate, and the highly probabilistic interaction between mobile elements and long, overlapping stretches of almost identical ‘repeats’ throughout the genome, the neutral and non-neutral changes in gene-regulating enhancers are likely to have driven much of evolution under purifying selection. Such gene-regulatory mutations account for the over 80% of loci carrying the genomic hallmarks of adaptive evolution. |