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Regulatory Element Study Guide Analysis of the Cis-regulatory Element Lexicon in Upstream Gene Promoters of Arabidopsis Thaliana and Oryza Sativa Sterol Regulatory Element Binding Proteins—Advances in Research and Application: 2012 Edition The RGBarrier Assay Computational Genomics with R The Analysis of Regulatory DNA: Current Developments, Knowledge and Applications Uncovering Gene Regulation The Study of the Regulatory Elements of the Human {221}-Globin Gene Analysis of the Posttranscriptional Regulatory Element of the Mammalian Hepatitis B Viruses Basic Helix-Loop-Helix Leucine Zipper Transcription Factors—Advances in Research and Application: 2012 Edition Machine Learning Approaches for Genome-wide Cis-regulatory Element Discovery and Transcription Factor Binding Sites Modeling Basic Helix-Loop-Helix Leucine Zipper Transcription Factors—Advances in Research and Application: 2013 Edition Computational Analysis of the Mammalian Cis-regulatory Landscape Understanding Trait Evolution at the Levels of a Cis-regulatory Element and a Gene Regulatory Network Gene Expression and Regulation in Mammalian Cells Cis-regulatory elements underlying Prdm15 gene during brain development Sheep CIS-Regulatory Element Polymorphisms Confer Resilience in Ovine Lentivirus Infection IDENTIFICATION OF

NOVEL DISTAL Identification of Novel Cis-acting DNA Regulatory Elements Involved in the Tissue-specific Regulation of Matrix Metalloproteinase 13 Gene Expression Analysis of Simian Virus 40 Early Transcriptional Regulatory Element in Mouse L Cells Multiple Approaches to the Study of Steroidogenic Factor 1 A Regulatory Element for Interneuron Progenitors in the Developing Vertebrate Central Nervous System Gene Transfer to Plants Genome-wide Analysis of Regulatory Element Sequence Evolution in Cichlid Fishes Functional Analysis of a Regulatory Element Controlling Spatial and Temporal Expression of Hoxc8 in Mouse Development Identification and Analysis of the Cis-regulatory Element for the AID-mediated Somatic Hypermutation and Application of this Process for the Artificial Protein Evolution in Chicken B-cell Line DT40 Cis-regulatory Evolution in Heliconius Butterflies Androgen-Induced Activation of Sterol Regulatory Element-Binding Proteins (Srebps) & Enhanced Lipogenesis in Tumor Cells 3' UTR Sequences and Syntax Functional Analysis of the Murine Upstream Regulatory Element Homolog Within the Context of the Human Chorionic Gonadotropin Alpha-subunit Promoter Identification and Analysis of a T-Box Regulatory Element Controlling the Expression of the Enzymes Involved in the TRNA-dependent Synthesis of Asparagine in Clostridium Acetobutylicum Analysis of the Cell Cycle Regulatory Element of a Hamster Histone H3.2 Promoter and Its Interaction with Nuclear Factors Plant Systems Biology Long-Range Control of Gene Expression Computational Biology and Applied Bioinformatics Preparing for Future Products of Biotechnology In Vivo Analysis of Human LHX3 Gene Regulation Identification of a Novel Regulatory Element in the Promoter of AJ18 Comparative Analysis of Ciliary Gene Regulation in Nematodes Gene Regulatory Sequences and Human Disease RNA

Motifs and Regulatory Elements

Bachelor Thesis from the year 2018 in the subject Biology - Genetics / Gene Technology, grade: 2.5, University of Cape Coast (Department of biochemistry - University of Cape Coast), course: Biochemistry, language: English, abstract: The interaction between transcriptional factors and cis-regulatory DNA element has given rise to the diversity in the expression of eukaryotic gene. Prdm15 gene is known to be expressed in the brain throughout development of mouse and zebrafish however; there are no known enhancer(s) for this gene in the brain. The aim of this study was to identify brain specific enhancer(s) for the gene Prdm15 during brain development. The VISTA enhancer browser and Encyclopedia of DNA Elements (ENCODE) data were used in this study to determine our candidate brain enhancer. The VISTA enhancer browser was used to quest for cis-regulatory element(s) in the environs of Prdm15 by comparative genomics and only one candidate enhancer we designated Prdm15 control element 1(PCE1) was identified downstream of the gene. PCE1 was found to be conserved in organisms such as chicken, zebrafish, rhesus, chimp, dog and cow. To ascertain if PCE1 is a brain enhancer, we delineated PCE1 using brain-specific enhancer chromatin modification signatures H3K4me1 and H3K27ac in the ENCODE data and they showed enrichment for PCE1. In conclusion, our data set revealed that only one brain candidate enhancer (PCE1) exist for Prdm15 and that this brain enhancer for Prdm15 will help in identifying important upstream specific transcription factors of PrdmI5 during brain development. Sterol Regulatory Element Binding Proteins—Advances in Research and Application: 2012 Edition is a ScholarlyPaper™ that delivers timely, authoritative, and

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developmental expression (5' ε-γ-γ-δ-β 3'). All five genes are regulated by an element located far upstream of the locus called the Locus Control Region (LCR). High level of β-globin gene expression is regulated by the LCR which consists of erythroid specific hypersensitive sites HS1 to HS5. Transcriptional regulation of the globin genes occurs through the cooperation of the LCR, the promoters of the globin genes and the interactions of trans-acting proteins. Recent studies show that activation of the β-globin locus involves the spatial formation of a LCR holocomplex that directly interacts with the transcribed genes. This complex is called the Active Chromatin Hub (ACH) (Palstra et al., 2003;Drissen et al., 2004). The objective of this project is to study the functional roles of two regulatory elements, namely, hypersensitive site 5 (HS5) of the LCR and the (AC) (AT) T motif n x y at the promoter of the β-globin gene. We study the enhancer blocking function of HS5 in transgenic mice by analyzing the conformational change in the context of the β-gene locus using the Chromatin Conformation Capture (3C) technique. The results show that HS5 functions as an enhancer blocking element in embryonic blood but not in adult erythroid cells. Interestingly, when HS5 is deleted form the locus, elements located upstream of the LCR are able to interact with the downstream regulatory elements within the β-globin gene locus. These results suggest that HS5 is a developmental stage specific border element. We determine whether CTCF, the only defined insulator protein in mammalian cells, binds to HS5 by using the CTCF-Chromatin immunoprecipitation (ChIP) assay. Our results demonstrate that CTCF binds to human HS5 and may mediate enhancer blocking activity in erythroid cell in vivo. In the second part of the thesis, we have examined the (AC) (AT) T motif n x y residing -530bp 5'

upstream of the β-globin gene in Chinese thalassaemic patients. This motif is a putative binding site for a repressor protein, namely beta protein 1 (BP1) (Berg et al., 1989). It has been shown that variations in the (AC) (AT) T n x y repeats affect the binding affinity of BP1 thereby altering the expression of the β-globin gene. Eight different configurations of this repeat motif are identified in our population of Chinese β-thalassaemia patients in Hong Kong. A novel (AC) (AT) T 3 7 5 motif is identified among the thalassaemia patients and its influence in β-globin gene expression is studied using stable transfection assay in murine erythroleukemia (MEL) cells. Our results demonstrate that this motif has moderately strong repressor effect on the expression of the cis-linked β-globin gene. This may be due to the higher affinity of BP1 for the motif resulting in the suppression of the transcription of the β-globin gene. We conclude that the proper developmental expression pattern of the β-like globin gene cluster is absolutely dependent on the presence of both the LCR and the proximal cis-regulatory elements of the globin gene. DOI: 10.5353/th_b

Improvements in DNA sequencing technologies have made it possible to determine the genetic makeup of many organisms. Computational analyses of the massive amounts of sequence data available have produced many insights into evolutionary and developmental biology. For example, comparison of the full genome sequences of human and mouse discovered that the majority of functional sequence in the human genome does not code for protein. Much of this functional non-coding sequence appears to act in a regulatory role, dictating the precise tissues and developmental time points in which each protein should be produced. This dissertation describes three major contributions to the computational analysis of regulatory elements. First, I describe the Genomic Regions

Enrichment of Annotations Tool (GREAT), a novel statistical method and associated web-based tool developed to infer the biological functions of regulatory elements based on the functions of their putative target genes. I demonstrate its marked improvement over current methods at interpreting functional enrichment signals for a variety of regulatory element types. Next, I discuss a computational methodology developed to identify medium- to large-scale (10-100,000 nucleotide) genomic deletions from whole genome sequences of multiple mammals. Using this methodology, I quantify the dispensability of highly conserved non-coding elements (CNEs) as their likelihood to be deleted in a subset of species. Despite their genomic prevalence and apparent redundancy in function, CNEs are very rarely lost in extant species. Even more surprisingly, there is a very weak relationship between dispensability and nucleotide conservation level. Sequences under purifying selection at moderate levels of nucleotide conservation are lost at a rate similar to those at perfect sequence conservation. Instead, evolutionary resistance to loss is more strongly correlated with depth of sequence homology, as ancient enhancers are more resistant to deletion than ones that arose more recently in evolution. Finally, I present the discovery and analysis of human-specific genomic deletions. By comparing the genome sequences of five species including human and our nearest ape relative, the chimpanzee, I identified 583 regions present in non-human species that contain highly-conserved sequence but are surprisingly deleted in humans. Statistical analyses indicate that these deletions occur preferentially near steroid hormone receptor genes and brain-expressed genes that are known to inhibit proliferation. Experimental results provide particular examples that may have contributed to unique human traits: the loss of an AR

enhancer is correlated with the human loss of penile spines and sensory vibrissae, and the loss of a GADD45G enhancer is correlated with the human expansion of the cerebral cortex. A major goal of integrative research is understanding regulatory networks to such an extent as to allow researchers to model developmental and stress responses. Regulatory networks of living systems include complex and vast interactions between proteins, metabolites, RNA, various signaling molecules and DNA. One aspect of systems biology is understanding the dynamics of protein-DNA interactions affecting gene expression that are caused by transcription factors (TFs) and chromatin remodeling factors. This e-book provides a resource for summarizing current knowledge eukaryotic transcription and explores cis-elements and methods for their analysis, prediction and discovery. The book also presents an overview of exploring gene regulatory networks, chromatin, and miRNAs. Information about state-of-the-art techniques for the determination of TF - cis-element interactions in vivo and in silico give cutting edge insights on how genomic-scale research is being approached. The Analysis of Regulatory DNA provides readers with both the necessary background knowledge and provocative, up-to-date insights aimed at sparking new and vibrant experimental designs for understanding and predicting cis-elements in the eukaryotic genome. Basic Helix-Loop-Helix Leucine Zipper Transcription Factors—Advances in Research and Application: 2012 Edition is a ScholarlyBrief™ that delivers timely, authoritative, comprehensive, and specialized information about Basic Helix-Loop-Helix Leucine Zipper T in a concise format. The editors have built Basic Helix-Loop-Helix Leucine Zipper Transcription Factors—Advances in Research and Application: 2012 Edition on the vast information

databases of ScholarlyNews.™ You can expect the information about Basic Helix-Loop-Helix Leucine Zipper T in this eBook to be deeper than what you can access anywhere else, as well as consistently reliable, authoritative, informed, and relevant. The content of Basic Helix-Loop-Helix Leucine Zipper Transcription Factors—Advances in Research and Application: 2012 Edition has been produced by the world's leading scientists, engineers, analysts, research institutions, and companies. All of the content is from peer-reviewed sources, and all of it is written, assembled, and edited by the editors at ScholarlyEditions™ and available exclusively from us. You now have a source you can cite with authority, confidence, and credibility. More information is available at http://www.ScholarlyEditions.com/. The T-box control system is a very common mechanism that Gram+ bacteria use to regulate the transcription of a variety of genes, like those involved in tRNA aminoacylation, in response to amino acid starvation. This regulation system is based on the stabilization of an antiterminator structure by the interaction with a cognate uncharged tRNA. Analysis of Gram+ Clostridium acetobutylicum (Cac) genome revealed an aberrant redundancy for the genes putatively involved in asparagine (Asn) and AsntRNAAsn synthesis. Through our investigations using various approaches, we showed that Cac only uses the indirect pathway to form Asn and Asn-tRNAAsn. We demonstrated that an entire transamidation pathway is organized as an operon under the control of a tRNAAsn-dependent T-Box riboswitch. One of our important findings gave some explanation to the function of this gene redundancy, which might be interconnected to control tRNA-dependent Asn synthesis, which might in turn be involved in controlling Cac metabolic switch from acid to solvent production. Moreover, we gave

new exciting explanations on how the T-Box recognizes its cognate tRNA. Our work brought some evidences that a T-Box can use more than one codon to control gene expression and that; therefore, they have more than one tRNA ligand. Finally, we demonstrated that one antitermination event can be reprogrammed through a synchronization mediated by a protein effector, and guided by another T-Box. Thanks to this process, a T-Box would be able to adequately respond to the level of two metabolically related amino acids. This finding paves the way for a better understanding of the antitermination mechanism in Gram+ bacteria. Between 1973 and 2016, the ways to manipulate DNA to endow new characteristics in an organism (that is, biotechnology) have advanced, enabling the development of products that were not previously possible. What will the likely future products of biotechnology be over the next 5â€"10 years? What scientific capabilities, tools, and/or expertise may be needed by the regulatory agencies to ensure they make efficient and sound evaluations of the likely future products of biotechnology? Preparing for Future Products of Biotechnology analyzes the future landscape of biotechnology products and seeks to inform forthcoming policy making. This report identifies potential new risks and frameworks for risk assessment and areas in which the risks or lack of risks relating to the products of biotechnology are well understood. The development of the central nervous system (CNS) is regulated by non-protein coding gene regulatory elements that control the expression of neural stem cell genes via the interaction of protein trans-acting factors. As a result of recent progress in neuroscience and biotechnology, valuable insight into neural cell growth has been attained from important components of the neural stem cell protein expression profile. However, the role of cis-

regulatory elements (non-protein coding genomic DNA on the same molecule) in neural stem cells remains confounded. A cis-regulatory element of neural progenitors during vertebrate development has been identified and characterized. This regulatory element is a conserved, non-protein coding region located within the established neural stem cell gene, Notch1. Notch1 is expressed in radial glia, which are self-renewing, neural stem/progenitor cells with long processes that serve as scaffolds for neuronal migration. A conserved non-coding region in the Notch1 locus (i.e., Notch1CR2) is active exclusively in the ventral CNS during neurogenic periods. On a cellular level, it is active in asymmetrically dividing cells that give rise to GABAergic interneuron progenitors and interneurons. Notch1CR2 is a novel regulatory element for interneuron progenitors. In this thesis, four studies of Notch1CR2 are presented. In the first study, CNS-specific regulatory activity of Notch1CR2 is revealed during chick embryonic development using in ovo electroporation. Second, the temporal-spatial profile of Notch1CR2 activity is determined to be present in cells with an interneuron progenitor phenotype using a transgenic mouse model. Third, the molecular mechanism of Notch1CR2 is investigated, and potential binding trans-acting factors of Notch1CR2 are identified. Finally, Notch1CR2 reveals a change in the interneuron progenitor population in the reeler mutant mouse compared to the wildtype. Reeler is a mutant mouse with deficiencies in neuronal migration and lamination. The discovery and characterization of Notch1CR2 contributes to the current knowledge of gene regulatory elements involved in the neural stem cell decision-making process. Notch1CR2 has the potential to serve as a tool for studying interneurons in other neurodegenerative models or as a platform for engineering cells for transplantation in

patients with interneuron deficiencies. Nowadays it is difficult to imagine an area of knowledge that can continue developing without the use of computers and informatics. It is not different with biology, that has seen an unpredictable growth in recent decades, with the rise of a new discipline, bioinformatics, bringing together molecular biology, biotechnology and information technology. More recently, the development of high throughput techniques, such as microarray, mass spectrometry and DNA sequencing, has increased the need of computational support to collect, store, retrieve, analyze, and correlate huge data sets of complex information. On the other hand, the growth of the computational power for processing and storage has also increased the necessity for deeper knowledge in the field. The development of bioinformatics has allowed now the emergence of systems biology, the study of the interactions between the components of a biological system, and how these interactions give rise to the function and behavior of a living being. This book presents some theoretical issues, reviews, and a variety of bioinformatics applications. For better understanding, the chapters were grouped in two parts. In Part I, the chapters are more oriented towards literature review and theoretical issues. Part II consists of application-oriented chapters that report case studies in which a specific biological problem is treated with bioinformatics tools. Sixty years after the "central dogma," great achievements have been developed in molecular biology. We have also learned the important functions of noncoding RNAs and epigenetic regulations. More importantly, whole genome sequencing and transcriptome analyses enabled us to diagnose specific diseases. This book is not only intended for students and researchers working in laboratory but also physicians and pharmacists. This volume

consists of 14 chapters, divided into 4 parts. Each chapter is written by experts investigating biological stresses, epigenetic regulation, and functions of transcription factors in human diseases. All articles presented in this volume by excellent investigators provide new insights into the studies in transcriptional control in mammalian cells and will inspire us to develop or establish novel therapeutics against human diseases. In this authoritative guide, expert investigators provide cutting-edge chapters dealing with modern plant systems biology approaches. This work provides the kind of detailed description and implementation advice that is crucial for getting optimal results. Regulating the precise rate of protein production from each protein-coding gene is a fundamental process of all cellular life. While transcriptional regulation plays a large role in determining final protein levels, post-transcriptional events can also make substantial contributions. In mammals, the majority of the cis-regulatory information that controls post-transcriptional events is located within a transcript's 3′ untranslated region (3′ UTR). The cis-regulatory sequence elements (cis-elements) found within 3′ UTRs are bound by trans-acting factors, mainly RNA binding proteins and non-coding RNAs, which in turn interact with the core decay and translation machineries to modulate mRNA decay or protein synthesis rates. Though a large number of cis-elements have been identified, many questions remain about their distribution and interactions. In addition, the contribution of parameters whose function is independent of their sequence, such as the length of the 3′ UTR, to gene regulation is poorly understood. Numerous studies have established that typical 3′ UTRs contain multiple discrete cis-elements, yet the typical density of elements within 3′ UTRs is unclear. Moreover, examples exist describing consequential interactions between cis-

elements, either cooperative or inhibitory. However, the extent to which such interactions are a general paradigm for cis-elements remains to be determined. By performing a systematic study of the regulatory sequences within two conserved mammalian 3′ UTRs, those of Hmga2 and PIM1, I determined that both 3′ UTRs contain a high density of cis-elements (at minimum 6 and 12 per kb, respectively) spread across the entire 3′UTR. Importantly, the vast majority of the cis-elements function independently of neighboring elements. Additionally, despite the overall repressive effect of the 3′ UTRs, I found that many regulatory cis-elements enhance gene expression, rather than repressing it. I hypothesize that the enhancing cis-elements counteract a repressive effect of 3′ UTR length. In a second study, I explored the effect of 3′ UTR length on gene expression using, as 3′UTR mimics, randomly-generated, nucleotide-composition matched, sequences of varying lengths. Long 3′ UTRs have previously been identified as targets of an mRNA surveillance mechanism called nonsense-mediated decay (NMD). In this study, I discovered a novel role for 3′ UTR length in triggering an NMD-independent decay pathway in human cell lines. Reporter transcripts with random 3′ UTR mimics as short as 400 nucleotides were repressed by this pathway, with the repression growing stronger with increasing length. While the mechanism of this novel pathway remains to be elucidated, I have determined that it affects the decay rate of mature mRNAs in a deadenylation-independent manner. Overall, by determining the density and extent of interactions of cis-element within example mammalian 3′ UTRs and by identifying a novel role for 3′ UTR length in regulating gene expression, this work furthers our understanding of fundamental aspects of 3′ UTR-mediated gene regulation. ... The zinc-finger transcription

factor AJ18 is expressed during osteogenic differentiation. In a previous study the minimal AJ18 promoter was mapped to a 258 bp region, which encompasses 76 bp upstream of the transcription start site. In this study, the 76 bp region was analyzed in further detail to show that a 10 bp region (-76 to -67, CAGCAGCAGT) is responsible for the majority of the transcriptional activity. This 10 bp region may represent a novel regulatory element as no known transcription factors are predicted to bind to this motif. Preliminary EMSA analyses suggest the presence of at least one nuclear protein binding to this motif, and positions C1, A2 and T10 in this sequence appear to be critical for this protein binding activity. Further studies are required to determine the relative importance of the other nucleotides in this consensus sequence for the binding of presumable regulatory protein(s). In Gene Regulatory Sequences and Human Disease, the Editor will introduce the different technological advances that led to this breakthrough. In addition, several examples will be provided of nucleotide variants in noncoding sequences that have been shown to be associated with various human diseases. Ovine progressive pneumonia is an incurable, slowly fatal infection that affects up to half of all flocks in the United States, caused by ovine lentivirus. Sheep suffer debilitating pneumonia, arthritis, encephalitis, and mastitis. Infection causes significant losses to all aspects of sheep production endangering supply of meat, milk, and wool products for human consumption. Identification of host factors that decrease susceptibility to infectious disease is a key step in combating ovine lentivirus and other retroviruses such as human immunodeficiency virus. We built upon previous work that detected a genomic region at four zinc finger genes ZNF389, ZNF192, ZSCAN16, and ZNF165 as strongly

associated with 50% reduction in proviral load. Since proviral load is correlated with severity of disease and lifespan in production flocks, the aim was to find genetic variants to predict this resilient phenotype and that may be causal mutations. DNA regulatory elements in sheep macrophages were annotated because most mutations responsible for phenotypic consequences are found within these elements. Alveolar macrophages function in innate and adaptive immunity as well as wound healing in the lungs dependent on tissue-specific gene expression under epigenetic regulation. The functional diversity of tissue-resident macrophages highlights the need to study tissue-specific regulatory elements that control gene expression. This study reported the first genome-wide survey of regulatory elements in any sheep immune cell, specifically those enriched for H3K4me3 (active promoters), H3K27ac (active enhancers), H3K4me1 (enhancers), CTCF (domain anchors), and H3K27me3 (silencers) which allowed assignment of putative biological function to 12% of the sheep genome. This annotation of transcriptional regulatory elements in target tissues will aid researchers in identifying genetic mutations of immunological consequence for many infectious diseases. A haplotype cluster of at least ten small DNA polymorphisms within the active cis-regulatory elements for ZNF389 were significantly associated with the resilient phenotype to ovine lentivirus in multiple sheep populations. Other zinc finger transcription factors, like ZAP, have been implicated in restriction of retroviral replication from several host species. These data will empower research into functional mutations at sheep regulatory elements and development of marker-assisted selection schemes to develop disease-resilient production flocks. Gene expression in plants is partly regulated through an interaction of trans-acting

factors with the promoter regions of the gene. Trans-acting factor binding sites consist of short nucleotide sequences most often present in the upstream promoter region. These binding sites, the cis-regulatory elements (CREs), vary in structure, complexity and function. In binding to trans-acting factors, CREs connect genes to signalling and regulatory pathways that affect plant growth, development, and response to the environment. As words in a language, CREs and thus promoters can be analyzed by looking for spelling (patterns of nucleotides) associated with meaning (functions). Considering CREs as words in a language, this kind of analysis provides a great opportunity for comprehensive understanding of promoter language. Identification and characterization of CREs are challenging either experimentally or bioinformatically, and has previously been accomplished by discovering degenerate words, with ambiguous nucleotides. This kind of result implicitly makes a hypothesis that binding of a specific trans-acting factor is somewhat promiscuous (or sloppy) and that all words represented by a degenerate pattern are equally good at binding. In this study, we unpack the "degeneracy hypothesis" by systematically considering each combination of letters independently for CRE function. Our results demonstrate that not all degenerate combinations of published CREs have the same effect on gene expression. A systematic search and comparison of all 65,536 possible 8 bp CRE words were searched in the 500 bp and 1000 bp upstream promoters of all genes in Arabidopsis thaliana and Oryza sativa, respectively. The function of each CRE was evaluated by statistically comparing the presence or absence of the element in the promoter with that genes response (induction or suppression) to stimuli in 1691 public availability transcriptomes of differential gene expression data.

Arabidopsis, a model dicot plant had a much larger number of such data sets, than rice, however rice was chosen as a comparison as it had the largest number of datasets for a monocot, the most distantly related plant group with sufficient data available. A comprehensive list of 8 bp words associated with differential gene expression, linguistically known as lexicon, was retrieved for both species by establishing that the presence of a CRE significantly increased the likelihood for differential expression by at least one stimulus. The lexicons were composed of 641 and 856 CREs respectively in Arabidopsis and rice, and there were only 78 shared CREs between the two lexicons. The CRE lexicon was then characterized for their strength and breadth of response, occurrence frequency, sequence complexity, and sequence conservation between two species. In Arabidopsis, evening element (EE) showed the strongest response to a cold stress transcriptome (p-value 10-99). In rice, the element AAACCCTA showed strongest response to a tissue specific transcriptome (p-value 10-79). The breadth of response varied between the two species due to number of transcriptomes used in the study. The element AAACCCTA and GCGGCGGA significantly correlated to 197 and 58 transcriptomes in both Arabidopsis and rice, respectively. On the other side of the breadth scale there were also many CREs with very restricted response. There were 291 and 258 CREs in Arabidopsis and rice, respectively, significantly correlated to a single stimulus. Occurrence frequency revealed that the most abundant CREs in Arabidopsis and rice genes were TATA box and TATA box like CREs. The structure of the CREs in the lexicon was also varied. CREs were distributed on seven levels of complexity. Level one comprised CREs having 8 copies of the same nucleotide, level seven comprised CREs having two copies of the same nucleotide.

In Arabidopsis, out of 641 CREs, 314 were of level 6 complexity, which means having 3 copies of the same nucleotide. In rice, the majority of the lexicon, 263 CREs were of level 5 complexity, which means having 4 copies of the same nucleotide. Each CRE of the lexicon was correlated to at least one experimental condition in the differential gene expression data, but many were correlated to multiple and often related conditions such as drought, temperature and salinity. Therefore, each CRE was assigned a "meaning", i.e. the associated stimuli, thus providing a sort of CRE function dictionary in addition to the lexicon itself. Many CREs possessed different meanings (termed homographs in language), and in many cases the meanings of different CREs overlapped like language synonyms. Sharing meanings (synonyms) was often among CREs with strong sequence similarity (homonyms or homophones), however, not in all cases. Analyzed as a linguistic aspect, CRE homonymity and synonymity was applied to explore the hypothesis "all CRE synonyms are also homonyms and all CRE homonyms are also synonyms." (Abstract shortened by ProQuest.) For closely-related species, development begins at a very similar state yet the adult organisms display an array of distinguishing morphological traits. A major focus in evolutionary developmental biology is to understand what genetic steps were taken on evolutionary paths towards this array of traits. Historically, early studies into morphological diversity emphasized differences through new genes and changes to their protein-coding sequence. In the genome-era of genetics research, it has become clear that many species protein-coding sequence identities are very similar and changes in gene numbers have been somewhat modest. Thus, another type of genetic change must have contributed largely to diversity. In recent years, a

plethora of case studies have been reported in which genetic alterations responsible for morphological evolution were found that modify how genes are expressed. These alterations occur in non-protein coding sequences called cis-regulatory elements (CREs), which control gene expression through their interactions with transcription factor proteins. Moreover, the transcription factor to CRE interactions connects genes into a regulatory network. At the onset of my dissertation research, little was known about the paths of CRE evolution, and how gene regulatory networks evolve to alter morphology. Moreover, tools were inadequate to study both CREs and gene regulatory networks. My dissertation research focused on gaining insights on the mechanistic underpinnings of the evolution of a CRE known as the dimorphic element (Chapter 3), which functions in an evolved gene regulatory network for patterning Drosophila (D.) melanogaster fruit flies abdomen pigmentation (Chapter 4). These studies required the establishment of a quantitative method for comparing the gene regulatory capabilities of CREs (Chapter 2). In Chapter 2, a protocol, utilized throughout my dissertation, was developed that enables the quantification of CRE activity by measuring the level of Green Fluorescent Protein (GFP) production within D. melanogaster. In Chapter 3, this method showed that evolved differences in abdomen pigmentation recurrently involved function-altering mutations in the dimorphic element for D. melanogaster populations and closely-related species. Many of these key mutations did not overlap known transcription factor binding sites. This outcome may be due to pleiotropic constraints on these conserved binding sites while other transcription factors binding sites were perhaps gained or loss. In order to find potential transcription factors for these evolved binding sites, I led a genetic screen to find

pigmentation network transcription factors by RNA interference. We found twenty-four novel transcription factors controlling abdomen pigmentation (Chapter 4). These results show that the abdominal pigmentation network is quite complex and future studies are needed to connect these factors to the CREs they regulate. A remaining obstacle to understand CRE function and evolution is to understand the in vivo effects of mutations. In Chapter 5, a protocol CRISPR CREam is presented which I have been developing to remove a CRE from its endogenous gene context and replace it with a variant CRE. Collectively, my dissertation has furthered the understanding of CREs and a model gene regulatory network. With the development of new genetic tools, CRE and network biology should be poised for drastic progress.

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available exclusively from us. You now have a source you can cite with authority, confidence, and credibility. More information is available at http://www.ScholarlyEditions.com/. Matrix metalloproteinases (MMPs) are major players in various pathological conditions including arthritis. Among numerous MMPs implicated in arthritis, MMP-13 (collagenase-3) is of particular interest. In chondrocytes, MMP-13 is involved in normal tissue turnover, although increased enzyme activity plays a pivotal role in cartilage destruction during the pathogenesis of arthritis. The pattern of MMP-13 gene expression is highly tissue-specific. In general, normal adult human tissues lack MMP-13 expression, with the exception of chondrocytes although at very low levels. In contrast, abnormal expression and activity of MMP-13 have been reported in various degenerative diseases such as rheumatoid arthritis, osteoarthritis and cancer. The mechanisms leading to the activation of MMP-13 gene expression in pathological processes have, however, been elusive. To better understand the tissue-specific regulatory mechanisms for MMP-13 gene expression, a search for unknown cis-acting regulatory elements (cis-elements) in the proximal promoter of human MMP-13 gene was undertaken. Short DNA sequences that potentially function as cis-elements were extracted from the human MMP-13 promoter based on their under-representation in other human MMP promoters using a novel computational approach. Using electrophoretic mobility shift assays, two potential cis-elements (S2 and S4) were identified that may function in the regulation of MMP-13 promoter in a cell type-specific manner. Bioinformatics analyses showed that the putative cis-element sequences had homology to several known transcription factor binding site sequences; however, the molecular weights of the candidate transcription factors were substantially different

from the approximated molecular weights (50 & sim;55kDa) of the S2- and S4-binding proteins. Transient transfection experiments with MMP-13 promoter-luciferase reporter constructs containing mutations at S2 or S4 sequences as well as with S2 and S4 decoy oligonucleotides have demonstrated that the novel cis-elements play a role in the regulation of MMP-13 gene expression in chondrocytes. The findings in this study may present a valuable therapeutic opportunity to selectively inhibit the expression of MMP-13 in a variety of human disorders where uncontrolled degradation of the extracelluar matrix is implicated. Cilia are highly-conserved organelles ubiquitously present in metazoans and some unicellular eukaryotes. In humans, ciliary defects result in a plethora of serious genetic diseases termed ciliopathies. Despite their diverse morphology and function, cilia are comprised of a core set of proteins, and many ciliary genes share similar but likely not identical regulation mechanisms. Our research aims to understand the variations in cis-regulatory elements in ciliary genes and the impact of such variations on transcriptional regulation. We hypothesize that cis-regulatory elements in different ciliary promoters are unique and that this uniqueness impacts the expression and function of ciliary genes. We focus on a particular cis-regulatory element, the X-box motif, which functions as the binding motif for RFX/DAF-19, a transcription factor that regulates ciliary gene expression. We identify and analyze X-box motifs for a set of 32 well-studied ciliary genes in C. elegans and their orthologs in 25 additional nematodes, including both free-living and parasitic species. My research consists of three modules. First, we curate ciliary gene orthologs using a combined approach, including homology-based gene finding and RNA-seq-based

improvement. The primary goal of this step is to ensure that the 5' ends of the genes are accurately defined in order to properly locate ciliary promoters. Second, we search for putative X-box motifs in these promoters using computational tools to identify motifs that resemble the consensus. For the promoters from which consensus X-box motifs are not found, we will search for X-box motifs that may show more differences from the consensus using frequency matrix-based search and regular expressions, which we call "atypical" X-box motifs. Third, we analyze the putative atypical X-box motifs, focusing on their sequence similarities, positions in promoter sequences, and flanking sequences, and compare them against the consensus X-box motifs. In this study, I will highlight progress made and challenges encountered for defining X-box motifs in ciliary genes. Long-Range Control of Gene Expression covers the current progress in understanding the mechanisms for genomic control of gene expression, which has grown considerably in the last few years as insight into genome organization and chromatin regulation has advanced. Discusses the evolution of cis-regulatory sequences in drosophila Includes information on genomic imprinting and imprinting defects in humans Includes a chapter on epigenetic gene regulation in cancer Cis-Regulatory element evolution is a key mechanism of biological diversification. Surprisingly little is known, however, about patterns of gene regulatory evolution across a range of divergence times, and the extent to which such variation drives local genomic adaptation. In chapter 1, we introduce the functional genomic methods used in this dissertation, and briefly discuss the current state and future prospects for the study of gene regulatory evolution. In chapter 2, we characterize the evolution of regulatory loci in butterflies and moths using ChIP-seq annotation of

regulatory elements across three stages of Heliconius head development. In the process we provide a high quality, functionally annotated genome assembly for the butterfly Heliconius erato. Comparing cis-regulatory element conservation across six lepidopteran genomes, we find that regulatory sequences evolve at a pace similar to that of protein-coding regions. we also observe that elements active at multiple developmental stages are markedly more conserved than elements with stage-specific activity. Surprisingly, we also find that stage-specific proximal and distal regulatory elements evolve at nearly identical rates. This study provides a benchmark for genome-wide patterns of regulatory element evolution in insects, and shows that developmental timing of activity strongly predicts patterns of regulatory sequence evolution. In chapter 3, we use functional assays for chromatin accessibility and histone modifications to test the hypothesis that intraspecific genomic divergence is linked to regulatory variation between distinct populations of Heliconius butterflies. We show that population-level variability in both chromatin accessibility and regulatory activity are abundant within the Heliconius genome. We further show that differences in regulatory activity between populations do not require associated differences in chromatin accessibility, illustrating that different modes of regulatory variation can be evolutionarily decoupled. Importantly, patterns of regulatory variation depart from neutral expectations, suggesting that selection underlies much of the observed regulatory divergence. Supporting this, genomic regions with high Fst are highly enriched for variable regulatory elements, and half of all differentially expressed genes have variable promoter-associated regulatory elements. Our work shows that regulatory elements vary between populations at

different functional levels, and that selection on variable elements is a major force underlying genomic divergence within species. ... LHX3 is a transcription factor important in pituitary and nervous system development. Patients with mutations in coding regions of the gene have combined pituitary hormone deficiency (CPHD) that causes growth, fertility, and metabolic problems. Promoter and intronic elements of LHX3 important for basal gene expression in vitro have been identified, but the key regulatory elements necessary for in vivo expression were unknown. With these studies, I sought to elucidate how LHX3 gene expression is regulated in vivo. Based on sequence conservation between species in non-coding regions, I identified a 7.9 kilobase (kb) region 3' of the human LHX3 gene as a potential regulatory element. In a beta galactosidase transgenic mouse model, this region directed spatial and temporal expression to the developing pituitary gland and spinal cord in a pattern consistent with endogenous LHX3 expression. Using a systematic series of deletions, I found that the conserved region contains multiple nervous system enhancers and a minimal 180 base pair (bp) enhancer that direct expression to both the pituitary and spinal cord in transgenic mice. Within this minimal enhancer, TAAT/ATTA sequences that are characteristic of homeodomain protein binding sites are required to direct expression. I performed DNA binding experiments and chromatin immunoprecipitation assays to reveal that the ISL1 and PITX1 proteins specifically recognize these elements in vitro and in vivo. Based on in vivo mutational analyses, two tandem ISL1 binding sites are required for enhancer activity in the pituitary and spine and a PITX1 binding site is required for spatial patterning of gene expression in the pituitary. Additional experiments demonstrated that these three elements cannot alone direct

gene expression, suggesting a combination of factors is required for enhancer activity. This study reveals that the key regulatory elements guiding developmental regulation of the human LHX3 gene lie in this conserved downstream region. Further, this work implicates ISL1 as a new transcriptional regulator of LHX3 and describes a possible mechanism for the regulation of LHX3 by a known upstream factor, PITX1. Identification of important regulatory regions will also enable genetic screening in candidate CPHD patients and will thereby facilitate patient treatment and genetic counseling. The advance of experimental technologies in biology, including complete genome sequencing and high density microarray, has enabled biologists to collect molecular biology data at an unprecedented pace and scale. However, due to the diverse types and enormous amount of data from these high-throughput experiments, more sophisticated computational methods are urgently needed to analyze them in order to reveal useful biological insight. In this dissertation work, we identified several critical challenges in modeling gene transcriptional regulatory networks, and developed machine learning based algorithms to address these challenges. First, we proposed a genome-wide cis-regulatory motif discovery approach by combining promoter sequences and gene co-expression networks to predict the cis-regulatory motif of each individual gene, thereby overcoming the disadvantages of current clustering based methods that often fail to provide gene- specific or species-specific predictions. Second, we developed a multi-instance-learning based method to model the physical interactions between transcription factors (TF) and DNA, which, by better handling of DNA sequence regional information, significantly outperformed traditional single-instance-learning based methods in predicting both in

vivo and in vitro TF-DNA interactions. Finally, we proposed a novel TF-DNA interaction model by utilizing structural features with multi-instance learning, which further improved the accuracy of modeling in vitro TF-DNA interactions. This research clearly demonstrated the advantage of machine learning methods in modeling transcriptional regulatory networks, and revealed several promising new directions for future development of computational methods in this area. RNA Motifs and Regulatory Elements is the new edition of the successful book, "Regulatory RNA". It alerts the reader to the importance of regulatory RNA elements for the many different areas of cellular life. The computational and experimental methods and tools to search for new interesting regulatory RNA structures are explained and compared. The knowledge on regulatory RNA structures and elements already available is concisely summarized as well as catalogued. In addition, interesting RNA elements are analyzed in detail regarding their dynamics, regulation, and as a dominant topic of current resarch in molecular biology, including areas such as RNA mediated regulation of gene-expression, DNA/RNA chip data, and ribozymes, splicing, or telomerases in aging. Medical implications are also covered. Future progress and research are finally outlined. This dissertation, "Identification of Novel Distal Regulatory Elements of the Human Neuroglobin Gene" by Kin-tung, Tam, □□□, was obtained from The University of Hong Kong (Pokfulam, Hong Kong) and is being sold pursuant to Creative Commons: Attribution 3.0 Hong Kong License. The content of this dissertation has not been altered in any way. We have altered the formatting in order to facilitate the ease of printing and reading of the dissertation. All rights not granted by the above license are retained by the author. Abstract: Neuroglobin (Ngb), a new member of the vertebrate

globin family, is localized predominantly in the neurons, retina and a number of endocrine tissues. Although the physiological function is still unclear, accumulating evidence demonstrated that Ngb is involved in cellular oxygen homeostasis and functions as a neuroprotectant. Ngb is found to protect cells and tissues from hypoxic and ischemic damage and has the ability to alleviate the symptoms of stroke and Alzheimer's disease in rodent's brain. In the present study, we hypothesize that distal regulatory elements are involved in the optimal expression of the Ngb gene. The objective of this project is to search for distal regulatory elements of the human Ngb gene and to characterize the underlying mechanism for Ngb gene tissue-specific expression. By chromosome conformation capture (3C) technique we identified two novel distal regulatory elements located -70kb upstream and +100kb downstream from the Ngb gene. ENCODE database showed the presence of DNaseI hypersensitive and multiple transcription factor binding sites in these regions. Further analyses using luciferase reporter assay and electrophoretic mobility shift assays (EMSA) suggested that the -70kb region upstream of the Ngb gene contained a neuronal-specific enhancer and the presence of GATA transcription factor binding sites. In vivo studies by chromatin immunoprecipitation (ChIP) analysis further confirmed the specific binding of GATA-2 and histone hyperacetylation at the -70kb element. Knockdown of GATA-2 caused Ngb expression level to drop dramatically, indicating GATA-2 as an essential transcription factor for the activation of Ngb expression. Taken together, I show that the Ngb gene is regulated by cell type-specific loop formation between its promoter and a newly identified GATA-2 bound distal regulatory element. This element is a bona fide distal regulatory element for Ngb gene and may be a key regulator for the spatial and

temporal expression of the Ngb gene. Subjects: Globin - Synthesis - Regulation Globin genes - Expression Computational Genomics with R provides a starting point for beginners in genomic data analysis and also guides more advanced practitioners to sophisticated data analysis techniques in genomics. The book covers topics from R programming, to machine learning and statistics, to the latest genomic data analysis techniques. The text provides accessible information and explanations, always with the genomics context in the background. This also contains practical and well-documented examples in R so readers can analyze their data by simply reusing the code presented. As the field of computational genomics is interdisciplinary, it requires different starting points for people with different backgrounds. For example, a biologist might skip sections on basic genome biology and start with R programming, whereas a computer scientist might want to start with genome biology. After reading: You will have the basics of R and be able to dive right into specialized uses of R for computational genomics such as using Bioconductor packages. You will be familiar with statistics, supervised and unsupervised learning techniques that are important in data modeling, and exploratory analysis of high-dimensional data. You will understand genomic intervals and operations on them that are used for tasks such as aligned read counting and genomic feature annotation. You will know the basics of processing and quality checking high-throughput sequencing data. You will be able to do sequence analysis, such as calculating GC content for parts of a genome or finding transcription factor binding sites. You will know about visualization techniques used in genomics, such as heatmaps, meta-gene plots, and genomic track visualization. You will be familiar with analysis of different high-throughput

sequencing data sets, such as RNA-seq, ChIP-seq, and BS-seq. You will know basic techniques for integrating and interpreting multi-omics datasets. Altuna Akalin is a group leader and head of the Bioinformatics and Omics Data Science Platform at the Berlin Institute of Medical Systems Biology, Max Delbrück Center, Berlin. He has been developing computational methods for analyzing and integrating large-scale genomics data sets since 2002. He has published an extensive body of work in this area. The framework for this book grew out of the yearly computational genomics courses he has been organizing and teaching since 2015. "This is a Ph.D. dissertation. Androgens are male sex hormones, produced by the tests and to a lesser extent by the adrenals. Apart from their essential role in the development of the male phenotype, androgens are absolutely required for the maintenance of"

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- Gene Transfer To Plants
- Genome wide Analysis Of Regulatory Element Sequence Evolution In Cichlid Fishes
- Functional Analysis Of A Regulatory Element Controlling Spatial And Temporal Expression Of Hoxc8 In Mouse Development
- Identification And Analysis Of The Cis

regulatory Element For The AID mediated Somatic Hypermutation And Application Of This Process For The Artificial Protein Evolution In Chicken B cell Line DT4
- Cis regulatory Evolution In Heliconius Butterflies
- Androgen Induced Activation Of Sterol Regulatory Element Binding Proteins Srebps Enhanced Lipogenesis In Tumor Cells
- 3 UTR Sequences And Syntax
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- Analysis Of The Cell Cycle Regulatory Element Of A Hamster Histone H32 Promoter And Its Interaction With Nuclear Factors
- Plant Systems Biology
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- Preparing For Future Products Of Biotechnology
- In Vivo Analysis Of Human LHX3 Gene Regulation
- Identification Of A Novel Regulatory Element In The Promoter Of AJ18
- Comparative Analysis Of Ciliary Gene Regulation In Nematodes
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- RNA Motifs And Regulatory Elements