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Editorial

From sequence to function: the impact of the genome sequence on *Drosophila* biology

It was a little over a decade ago that first draft of the *Drosophila melanogaster* genome sequence was published [1] followed by the genomes of a further 11 species of related *Drosophilias* [2]: it is fair to say that these landmarks in fly biology have driven tremendous advances in our ability to manipulate and decipher the genome, bringing about a much richer understanding of eukaryotic biology. This special issue of *Briefings in Functional Genomics* presents a series of up-to-date reviews reflecting the impact of the genome sequences, and of the genomic technologies that have sprung from the sequences, on a various facets of fly biology. The reviews have been chosen to reflect the range of studies that utilise *Drosophila* as a model, ranging from the basic circuitry of transcriptional regulatory networks, through the emerging field of post-transcriptional regulation by small RNAs, detailed analysis of tissue morphogenesis to more complex whole organism phenotypes such as behaviour and immunity. We emphasise that these reviews provide just a glimpse into the world of the fly, but exemplify how genomics is driving our understanding of complex regulatory pathways and the sophisticated organisation of the eukaryotic genome.

In 1910, Thomas Hunt Morgan serendipitously discovered the first *Drosophila* mutant (*white*, a mutation resulting in the loss of the red eye pigment) setting the scene for over a century of genetic research that established the fly as an exquisitely tractable system for investigating how metazoans are built and function. The discovery of giant polytene chromosomes in the nuclei of larval salivary glands [3, 4] had a profound impact on the use of the fly as system for understanding heredity since they provided a detailed physical map of the genome long before the chemical nature of the gene was known. The molecular biology revolution sparked by Watson and Crick's model of DNA structure [5] impacted on all of biology and the fly genome provided the foundation for the first large-scale cloning effort when the Hogness group [6] generated a contiguous chromosome walk across the Bithorax Complex, a region containing a set of Hox regulators intensively characterised at the genetic level by Ed Lewis [7]. Many of us will still remember their early careers as fly biologists, cloning tiny fragments of the genome in the hope of gaining some insights into the underlying molecular basis of particular mutations, most often those generating developmental phenotypes. The combination of superb genetic tools, a map of the genome laid out in polytene chromosomes and the tools of molecular biology, established *Drosophila* at the vanguard of the genetic revolution as we sought to understand the molecular logic of life. Virtually every aspect of fly biology, from the basic biochemistry of metabolism, through the pathways mediating cell–cell signalling, control of gene expression by transcription factors, to complex whole organism phenotypes such as sexual dimorphism or behaviour, were attacked by fly biologists. The work from the fly was quickly shown to be relevant to our understanding of much more complex organisms such as man, since many of the molecular pathways have been conserved over the course of evolution.

While the gene-by-gene approach was undoubtedly successful, in reality it was painfully slow and did not, for the most part, easily allow the identification and analysis of entire pathways. The genomics revolution changed this and facilitated experimental approaches that have led to a much more comprehensive understanding of how the information encoded in genome sequence is translated into the incredible sophistication that is the hallmark of a multicellular organism. We collect here a series of reviews from leaders in the field of fly functional genomics, starting with a view from the nucleus,

through to the cytoplasm and out to the tissues and systems that build the animal. We begin with a discussion of the regulatory genome by Matthew Slattery, Nicolas Nègre and Kevin White: the White lab have been one of the major contributors to the modENCODE (Model Organism ENCyclopedia Of DNA Elements) project [8], an international effort aimed at uncovering and cataloguing functional elements across the entire genomes of both *Drosophila* and *Caenorhabditis elegans*. Their paper discusses how *in vivo* mapping of DNA-binding proteins using Chromatin Immunopurification (ChIP) technology has dramatically changed our view of transcription factor biology, uncovering considerably more *in vivo* binding locations than previously suspected. They discuss how data from a number of genome-wide studies are being coordinated to drive a better understanding of gene regulatory networks and lay out the considerable challenges that remain in our efforts to decipher the regulatory code of the genome. A critical feature of the eukaryotic nucleus, and one important for furthering our understanding of gene regulation, is deciphering how the genome is organised as chromatin in the nucleus. Rob White reviews how genomic technologies, particularly the recent development of methods for capturing the 3D architecture of the genome, provide a much richer understanding of the link between the structure of the genome and how it is transcribed. Of course, gene transcription is only the first step in gene regulation and it has long been suspected that considerable post-transcriptional regulation may be used by eukaryotes. The discovery of small regulatory RNAs in *C. elegans* [9, 10] sparked an increased interest in posttranscriptional control, but it really needed genome sequence to begin to uncover the true complexity of this process. Antonio Marco reviews the biology of regulatory RNAs in the fly as a prelude to discussing how multiple *Drosophila* genome sequences are contributing to our understanding of the evolutionary biology of these intriguing molecules.

Having considered the molecular biology of some of the key basic functions in the fly, we go on to consider how genomics and genome sequence have contributed to our understanding of defined processes. We begin with a discussion of the regulatory networks underpinning the development of an organ system in the fly, the heart. The *Drosophila* heart is a relatively simple organ yet it appears that much of its development and function is relevant to understanding the much more complex mammalian heart. Denis Seyres, Laurence Röder and Laurent Perrin review how genomics approaches, including the use of functional tools such as targeted RNAi constructs built with the help of genome sequence, have facilitated a much more comprehensive view of the regulatory networks governing heart development. It is important to realise that the approaches used in studying the heart are being applied to many other organ systems in the fly. Another central aspect of animal biology is the way that individuals respond to the environment, particularly to life threatening challenges such as infection. Since the pioneering work of Lemaitre [11] began to uncover the incredible similarly between the fly and human humoral immune responses, *Drosophila* has been a focus for the study of host–pathogen interactions. Luis Teixeira reviews how genomics is helping to uncover the way complex immunity pathways are coordinated in the fly and how invading organisms in turn control the fly genome to evade detection or elimination.

Sex has always fascinated biologists! In particular, the study of sexual dimorphism, the phenotypic differences between males and females that characterises all sexually reproducing organisms, offers an almost unique opportunity to study how two often dramatically different whole organism phenotypes can be generated from the same genome sequence. Sexual dimorphism in the fly has been very well tackled at the genetic level and we have a fairly good conceptual understanding of how the process is regulated. Emily Clough and Brian Oliver review how genomics approaches are being used to bridge the gap between the genetic control circuitry and the whole organism phenotype, in effect we need to understand how transcriptional regulators are being deployed in every cell to, sometimes subtly, change the expression of many genes in the genome. The fly is a complex organism with a well-developed nervous system exhibiting a range of sophisticated behaviours. Among these are sexually dimorphic behaviours necessary for successful mating and thought to be important in evolving new species through reproductive isolation. Complex behaviours also include the circadian rhythms that overlay much of the basic physiology of the fly and the memory circuits that help the fly make sense of the world. Megan Neville and Stephen Goodwin review how genomics have impacted on our attempts to decipher the pathways

governing such complex phenotypes and highlight some of the shortcomings of such approaches, indicating where we need to do better if we are to get to grips with that most mysterious of biological systems: the brain. We finish with an important contribution from Ko-Fan Chen and Damian Crowther that emphasises how the fly is being used as a model system for understanding the complexity of human diseases. Fascinating as *Drosophila* is to study in its own right, in many situations it is used as a useful model for exploring more complicated, and considerably less experimentally tractable, human traits and conditions. They exemplify how genomics, high-throughput genetic screens and computational biology can be used to uncover molecular components of disease pathways or identify potential therapeutic targets. A few years ago, the fly was rarely considered as a viable system for exploring facets of human disease, the genome sequence changed that view and the final contribution of this special issue provides a timely reminder of how powerful *Drosophila* is as a model system for investigating even the most sophisticated aspects of biology. We hope that these few reviews provide a window into the world of the fly and how the powerful new approaches developed in the post-genome era are beginning to shed light on the complexities of life.

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