



# Regulatory Systems Biology

[www.cambridgecancer.org.uk/duncanodom](http://www.cambridgecancer.org.uk/duncanodom)

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How the functional elements that control gene expression are used to create a diversity of tissues remains poorly understood. The ultimate aim of classical genetics and modern genomics is to understand on a molecular basis how the genome is deployed to create a diversity of tissues and species. Understanding this process has profound implications for understanding cancer because one of the major hallmarks of tumour progression is the perturbation of gene expression programs. We are interested in two critical control points in transcriptional regulation: namely transcription factor binding and the use of small RNAs, including siRNA and microRNA, to modulate gene expression.

### Tissue-specific transcription factors and the control of cellular gene expression

Transcriptional regulatory control is known to be combinatorial in yeast and bacteria, but until recently, it was unknown whether this combinatorial nature extended *in vivo* to mammalian tissues. Master regulators in primary human hepatocytes form a highly interconnected core circuitry that frequently bind the genome combinatorially (Figure 1) (Odom et al. *Mol. Syst. Biol.* 2006; 2:2006.0017). Remarkably, though, transcriptional regulation can vary much more rapidly and widely than previously appreciated between mouse and human tissues that are conserved (Odom et al. *Nat. Genet.* 2007; 39:730).

In asking what controls this, we realized that a number of factors could contribute to causing the variability in transcription and transcriptional regulation between mouse and human. These possible causes could include the variability of genetic sequences, the kinds of marks left in the histone proteins that DNA wrap around (commonly thought of as 'epigenetics'), or even diet or environmental differences between different species. In order to isolate a single one of these variables, we used a mouse model of Down's syndrome with our collaborators Elizabeth Fisher (University College London) and Victor Tybulewyc (National Institute for Medical Research, London) that carries a virtually complete copy of a human chromosome (O'Doherty et al. *Science* 2005; 309:2033).

We were able to demonstrate that genetic sequence dominates all other factors in directing transcription (Wilson et al., *Science* 2008; 322:434) (Figure 2). This result

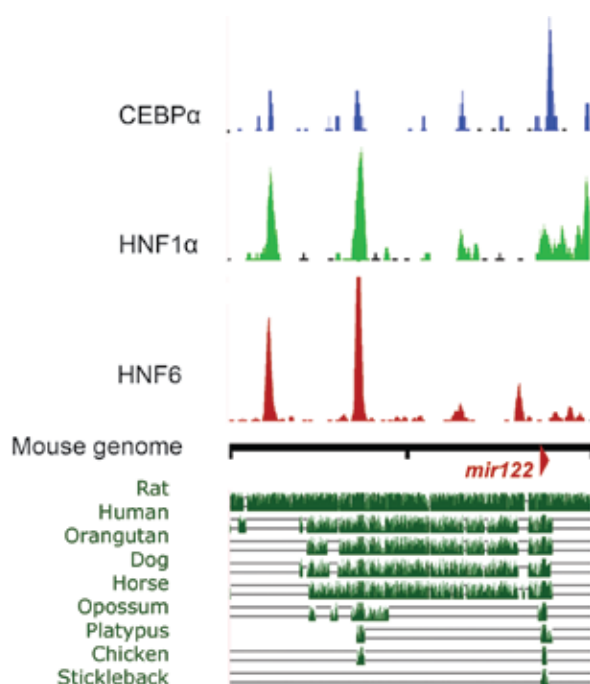


Figure 1. microRNA loci are regulated by tissue-specific transcription factors

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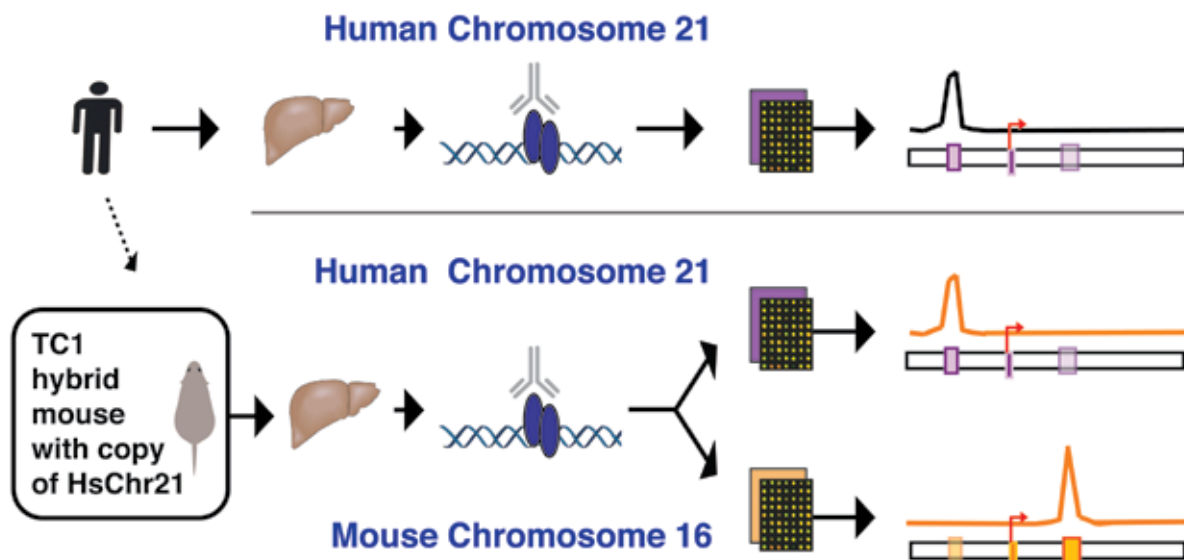


Figure 2. Human genetic sequence is handled in mouse precisely as if it were handled in human. In cases where a transcription factor binding event, for instance, has moved between human and mouse, that binding event aligns with events found in normal human hepatocytes, not those found in mouse hepatocytes. This demonstrates the primacy of genetic sequences in determining tissue-specific and species-specific transcription.

has serious implications for a number of scientific approaches. It shows that attempts to sequence cancer genomes, as is being pursued by the Sanger Institute and others world-wide, are in a sense asking the correct questions, as our data suggests that the genetic alterations are truly crucial events for carcinogenesis and cancer gene expression.

#### Understanding the role that transcriptional regulatory networks play in controlling small RNAs

A recent topic of substantial investigation is the role that microRNAs play in regulating transcription, but little attention has been paid to date in understanding how microRNAs themselves are regulated. We performed an integrated set of experiments that use conservation of microRNA

expression, genome-wide maps of transcription factor binding in seven species, and molecular biological techniques to remove key microRNAs from cells *in vivo* to deconstruct how microRNAs are themselves regulated. Our preliminary experiments indicate the lineage-specific transcription factors bind to and potentially regulate the expression of many of the microRNAs and other small RNAs that are involved in tissue-specific transcription (Figure 1). Most importantly, we are able to begin investigating how small RNAs as a complete module are integrated in the transcriptional networks that control gene expression in particular tissues.

[Publications listed on page 60](#)