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Deconstructing the dynamic genome

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Two international teams of researchers led by Ludwig San Diego's Bing Ren have published in the current issue of *Nature* two papers that analyze in unprecedented detail the variability and regulation of gene expression across the entire human genome, and their correspondence with the physical structure of chromosomes.

"We expect that our findings, which describe the interplay of chromosomal structure, regulation and gene expression across a broad array of tissues, will inform research in every branch of mammalian biology and provide information of great value to the study of most human diseases, not least cancer," said Ren.

If the human genome is a recipe book, its chapters are 23 distinct chromosomes—each of which is stuffed, in rough duplicate, into the nucleus of almost all the cells of the human body. But how exactly is that single recipe book read appropriately to build the body's diverse constituency of cells? Or, for that matter, to generate a community of humans so variegated in their appearance, internal biochemistry and susceptibility to disease?

The two papers address key elements of these riddles. One captures the extent to which the same genes—known as alleles—inherited from each parent are expressed at different levels across the genome, so that each version of the gene generates different amounts of the protein it encodes. It links that difference in expression to the distribution and sequence of "enhancers" on each copy of each chromosome. Enhancers are stretches of DNA that do not encode proteins but can boost gene

expression from great distances along the linear strand of DNA.

"This is the first time that anyone has looked globally at how gene expression differs between each matching pair of chromosomes across a diverse set of cell types, and our findings are striking," said Ren. "Some 30 percent of the gene set we carry is expressed variably across some 20 types of tissues, depending on which parent the alleles came from. Much of that variation appears to come from differences in sequences that regulate the transcription—or reading—of genes."

The other study examines how the three dimensional structure of chromosomes and the distribution of biochemical (or epigenetic) tags that regulate gene expression differ between different types of cells. It also integrates data from the former paper into this analysis to reveal how all of these phenomena interact to control the appropriate expression of the genome. Taken together, these findings add dimension and depth to our understanding of the physical and functional dynamics of the genome, and how its expression is globally regulated to generate the sublime complexity of the human body.

Both studies are invaluable to a deeper understanding of normal biology as well as disease. The data will, for example, help explain precisely why particular parental traits are often so unevenly expressed and why specific deleterious mutations vary in their effects from person to person. They will also serve as a reference that researchers can use to develop a more sophisticated understanding of how gene regulation and chromosomal structure are altered in diseases such as cancer.

Stemming from five years of research, the papers are two of six published this week in *Nature* that capture the key discoveries of the $300 million Roadmap Epigenomics Program of the US National Institutes of Health. Ren led one of four reference epigenome mapping centers for the program, and his center focused primarily on how DNA

and chromatin—the complex of DNA and its protein packaging that makes chromosomes—are chemically tagged at specific places to control the expression of genes across the human genome.

More information: The research will be freely available to all: www.nature.com/epigenomeroadmap

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