Express yourself: How zygotes sort out imprinted genes

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Writing in the February 17, 2012 issue of the journal *Cell*, researchers at the Ludwig Institute for Cancer Research, the University of California, San Diego School of Medicine and the Toronto Western Research Institute peel away some of the enduring mystery of how zygotes or fertilized eggs determine which copies of parental genes will be used or ignored.

In developing humans and other mammals, not all genes are created equal – or equally used. The expression of certain genes, known as imprinted genes, is determined by just one copy of the parents' genetic contribution. In humans, there are at least 80 known imprinted genes. If a copy of an imprinted gene fails to function correctly – or if both copies are expressed – the result can be a variety of heritable conditions, such as Prader-Willi and Angelman syndromes, or diseases like cancer.

In the *Cell* paper, a team of scientists, led by Bing Ren, PhD, head of the Laboratory of Gene Regulation at the Ludwig Institute for Cancer Research at UC San Diego, describe in greater detail how differential DNA methylation in the two parental genomes set the stage for selective expression of imprinted genes in the mouse. Differential DNA methylation is essential to normal development in humans and other higher organisms. It involves the addition of hydrocarbon compounds called methyls to cytosine, one of the four bases or building blocks of DNA. Such addition alters the expression of different genes, boosting or suppressing them to help direct embryonic growth and development.

The process is sometimes called epigenetic regulation. Epigenetics is the study of factors influencing inheritance beyond the genes themselves. "DNA is just half the story," said Ren, who also heads the San Diego Epigenome Center, one of four centers established by the National Institutes of Health to focus on epigenetics research.

"Understanding how these limited imprinted regions control regulation can help us better understand how certain diseases happen," said Ren, a professor of cellular and molecular medicine in the UC San Diego School of Medicine. "That can help us develop better diagnostic tools for detecting genetic abnormalities and perhaps learn how to predict whether something bad will happen."

Using a deep sequencing, high-throughput screening technology developed by Joseph Ecker at the Salk Institute for Biological Studies, Ren and colleagues found parent-of-origin specific DNA methylation imprints at 1,952 dinucleotide sequences in the mouse genome. The imprinted sequences formed 55 discrete clusters that included virtually all of the known germline differentially methylated regions and 23 previously unknown regions.

"That suggests it's a very accurate tool," said Wei Xie, first author of the paper and a postdoctoral researcher in Ren's laboratory.

The researchers also found a unique type of methylation in the brain that was previously only seen in embryonic cells. "At this point we do not know what the significance of this modification is in the brain, but it is very specific, suggesting that it correlates to an important biological function" said Cathy L. Barr, PhD, a senior scientist at the Toronto Western Research Institute, the Hospital for Sick Children and co-author of the paper.