

An Unexpected BMP in the Road



How the Human Genome Project May Help Diabetes

Evan David Rosen, M.D., Ph.D.

Assistant Professor of Medicine, Harvard Medical School

When the decision was made more than a decade ago to sequence the human genome, there was a tremendous amount of debate within the scientific community about whether the project would be worth the effort and expense. Proponents claimed that numerous health benefits would result, such as the identification of disease-causing genes and the development of new treatments. Ultimately, these arguments carried the day.

We've now had the human genome sequence in hand for more than a year. The mouse genome was mapped recently, and several more genomes are likely in the near future. Has the promise of genomics been fulfilled? Well, the answer is yes and no. Clearly, the hunt for disease-causing genes has been aided by the complete sequence, especially for diseases caused by a single aberrant gene. For more common diseases (like diabetes and obesity) that involve multiple genes, progress has been a bit slower, although most people in the field feel that with enough time and elbow grease, we will eventually find these genes as well.

Where the promise of genomics has been least fulfilled, however, is in the area of treatment. Simply put, the vast amount of information that we have accumulated through DNA sequencing of the human genome has not yet been translated into useful drugs for people in need of them.

A new report in the journal *Nature Biotechnology*, however, introduced a potentially exciting new anti-diabetes drug that was discovered through genomic approaches—exactly the sort of discovery that genome groupies have been promising for years.

Here's how it happened. Researchers at a biotechnology company called Human Genome Sciences searched computer databases filled with DNA sequences, looking for genes encoding proteins that are secreted from cells. The idea was that these "secreted" proteins might be important hormones or other messengers involved in the regulation of blood sugar levels. This task would have been impossible except for the fact that secreted proteins usually have a small identifying tag on them, a so-called "signal sequence" that tells the cell, "Hey, I'm supposed to be secreted." The scientists looked at a staggeringly large number of protein sequences (roughly 3 million) in tissues throughout the body, and unearthed 8,000 that contained a signal sequence.

The next step was equally daunting. Each of these 8,000 genes was studied individually. First they were inserted into cells grown in the laboratory. Next the "media"—the secretions of these cells—was collected. Each batch of medium, which should contain one of the 8,000 secreted proteins, was then injected onto several different types of cells relevant to diabetes. For example, a sample from each of the 8,000 different media was injected onto pancreatic beta cells, to see if they triggered the secretion of insulin. Similarly, tests on liver cells were performed to see if the samples could shut down the liver's sugar production. Other types of cells were also studied, such as muscle and fat cells, to see if they could be stimulated to absorb glucose. This "high-throughput screen" yielded a few candidate proteins with anti-diabetic potential. The most promising one turned out to be a hormone called bone morphogenic protein-9 (BMP-9).

The authors then collected purified BMP-9, and repeated their assays. They found that BMP-9 could suppress the ability of liver cells to make sugar nearly as well as insulin. BMP-9 could also regulate key enzymes in muscle cells known to be involved in glucose uptake. The next step was to test the effects of BMP-9 in mice. In normal, non-diabetic mice, BMP-9 caused a reduction in glucose levels comparable to that seen with an injection of insulin. Insulin, however, had its peak effect within thirty minutes, while BMP-9 didn't kick in until 24-48 hours had passed. The reason for this delay isn't clear, but it raises exciting questions about the possible use of BMP-9 as a long-acting drug for diabetes. When BMP-9 was given to obese mice with type 2 diabetes, it also reduced blood sugar levels effectively for close to 50 hours after the injection. In addition to mimicking insulin's action in liver and muscle, BMP-9 had other beneficial effects in the mice, such as reducing food intake and stimulating insulin secretion.

Despite its name, BMP-9 is made by liver cells, not bone. While these studies were designed to look at the effects of BMP-9 at high doses, it may yet turn out that BMP-9 is an important player in normal glucose regulation. If so, it would be the first such factor produced by the liver to be identified, although the existence of such a protein has long been speculated.

BMP-9 is one of a family of secreted proteins made by different tissues. Members of this family are known to be involved in such processes as cellular growth and organ development. Amazingly, over 4,000 papers have been published on BMP proteins, with nary a clue that BMP-9 might be involved in regulating glucose levels. While it remains to be seen if BMP-9 will turn out to be a safe and effective diabetes therapy, it is clear that we would never had any reason to study it in diabetes without this sort of high-tech screen. And this screen could not have been done without the knowledge created by the sequencing of the complete genome.

References:

Cecil Chen, Krzysztof J. Grzegorzewski, Steve Barash, Qinghai Zhao, Helmut Schneider, Qi Wang, Mallika Singh, Laurie Pukac, Adam C. Bell, Roxanne Duan,

Tim Coleman, Alokesh Duttaroy, Susan Cheng, Jon Hirsch, Linyi Zhang, Yanick Lazard, Carrie Fischer, Melisa Carey Barber, Zhi-Dong Ma, Ya-Qin Zhang, Peter Reavey, Lilin Zhong, Baiqin Teng, Indra Sanyal, Steve M. Ruben, Olivier Blondel, Charles E. Birse. An integrated functional genomics screening program reveals a role for BMP-9 in glucose homeostasis. *Nature Biotechnology* 21, 294 - 301 Mar 2003