Diabetes Center researchers contribute to ?most comprehensive? human epigenome roadmap

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Michael McManus, Alex Marson participate to novel study

By Kathleen Jay

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SAN FRANCISCO (March 11, 2015) ? Two researchers from the Diabetes Center at UCSF [1] ? Michael McManus [2], PhD, and Alex Marson [3], MD, PhD ? recently contributed to what is being deemed the most complete mapping of the human epigenome to date.

Epigenomes are patterns of chemical annotations to the genome that determine whether, how, and when genes are activated.

Using massive data analysis to understand how and why certain genes turn off and on in human cells, McManus? and Marson?s results ? which were among two dozen papers simultaneously published online last month in the journal Nature [4] ? could lead to new treatments for many conditions, such as diabetes and other autoimmune diseases.


McManus analyzes ?epigenome fingerprint?:

?Your genome DNA is pretty much the same in all cells of your body,? Michael McManus [6],
an associate professor of microbiology and immunology and the holder of the Vincent and Stella Coates Endowed Chair in Diabetes Research, said.

?However, there is something called the epigenome which varies among the hundreds of cell types in your body. For example, insulin-producing pancreatic beta cells have a very different epigenome signature than T-cells,? McManus, a co-author of the Epigenome Roadmap study, said. Integrative analysis of 111 reference human epigenomes [7].

To understand why certain genes turn off and on in human cells, McManus teamed up with several teams of national and international researchers to generate 2,805 genome-wide datasets, which encompassed a total of 150 billion sequencing reads, corresponding to 3,174-fold coverage of the human genome.

Applying machine-learning algorithms that could translate the datasets into a reference map, they processed this massive data set to look for epigenomic changes in 111 cell types and tissues.

?This roadmap project is significant in that we identified a fingerprint signature for 111 cell types in the human body,? McManus said. ?Knowing what the healthy epigenome fingerprint looks like, we now have a reference set for comparing disease tissue fingerprints.?

Assisting McManus on his contribution to the study include members of his lab Matthew J. Hangauer, Hunter Richards and Ian Vaughn. The study included several other members of the UCSF community, with the UCSF teams led by Cancer Center member Joe Costello, PhD (Karen Osney Brownstein Endowed Chair in Neuro-Oncology in the UCSF Department of Neurological Surgery).

?As a result of this study, we may have a better understanding of diseases, such as diabetes and cancer. This work also provides telltale biomarkers that reveal early onset of disease, and may help define a course of effective treatment.?

Marson focuses on mapping switches throughout the genome

?The Epigenome Roadmap Project is more than just a sequel to the Human Genome Project,? UCSF Sandler Faculty Fellow Alex Marson said. ?Sequencing the human genome showed us where genes lie in our chromosomes. The Epigenome Roadmap is now revealing the locations of the switches that control when and how genes are turned on and off in specialized cell types.?

In work published online last October in Nature entitled Genetic and epigenetic fine mapping of causal autoimmune disease variants [8] and that also appears in print as part of the REP collection, Marson and colleagues at the Broad Institute of MIT and Harvard and at the Yale School of Medicine showed that epigenomic effects on immune cells can contribute to autoimmune disease.

?Our work demonstrates that the map of switches throughout the genome is a powerful framework to interpret the genetics of autoimmune diseases, such as type 1 diabetes,? Marson added. ?The roadmap has allowed us to extract biological insight from the vast majority of DNA variants that contribute to risk of autoimmune diseases. Most of these DNA variants do not appear in genes themselves, but largely occur in the switches that control gene activity in the immune system.?
By integrating human genetics with epigenomic maps of immune cells, Marson and his colleagues have begun to parse human autoimmune diseases by regulatory elements, target genes and cell types affected by the DNA variants that contribute to risk of type 1 diabetes and other autoimmune diseases.

This large-scale effort is culminating at a moment of unprecedented tools to perturb non-coding sequence. Functional studies are essential to advance our understanding of disease genetics and CRISPR genome editing will allow us to perform these studies. We hope that targeted genome editing of disease variants will also create powerful in vitro and in vivo models to test candidate drugs to correct disease-specific pathology.

I am pleased that Alex’s and Michael’s research provides novel insights into these powerful regulators of gene function,? Matthias Hebrok [11], PhD, director of the Diabetes Center at UCSF and holder of the Hurlbut-Johnson Distinguished Professorship in Diabetes Research, said. ?Their work is vital to increasing our understanding of the mechanisms that contribute to beta and immune cell function. As our team continues in our pursuit of our ultimate mission ? to prevent and cure diabetes ? Alex’s and Michael’s investigations shed important new light on the overall picture of disease progression.?

For more information, please visit http://diabetes.ucsf.edu [1].

Caption: Michael McManus, at left, and Alex Marson, contributed to the most-complete mapping of the human epigenome to date. (PHOTO: Kathleen Jay/UCSF)

Integrative analysis of 111 reference human epigenomes. [7]


Genetic and epigenetic fine mapping of causal autoimmune disease variants. [8]
