In quest for new therapies, team unlocks hidden information in human genome

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The work of molecular biologist Joseph M. Miano, Ph.D., and clinician Craig Benson, M.D., seems worlds apart: Miano helps head the Aab Cardiovascular Research Institute and Benson is chief resident of the combined Internal Medicine and Pediatrics program at the University of Rochester Medical Center. Though the chance of their professional paths crossing was highly unlikely, shared enthusiasm, intense curiosity and a little detective work led to a unique collaboration and important new insights on the inner workings of the human genome.

Together, Miano and Benson created a model resource that not only identifies but also outlines the function of some of the most common mutations in the human genome. At a time when research linking genetic mutations to disease risk is booming – a result of the sequencing of the human genome in the early 2000's – the clinician-scientist team is pursuing what they think is an even more significant path: They are zeroing in on how certain mutations actually work, information they believe will help guide the development of new prevention and treatment options.

"It is valuable to know when someone is at greater risk for disease, but that information doesn't explain the mechanism of disease or give any insight into what we might be able to do therapeutically for patients," said Benson, lead author of the new study published in *Physiological Genomics*. "Our goal is to help scientists figure out what's happening at the molecular level so they can determine the best way to potentially treat disease. As a clinician, that is what is most important for me,

understanding how we can improve patient care."

Benson, who came to Rochester for medical school in 2003, stayed for a medicine-pediatrics residency and participated in the program's research track, which allowed him some time to conduct research. With an undergraduate degree in business and computer information systems and a master's degree in health informatics, he was eager to study bioinformatics and genomics. Not sure where to start, given the Medical Center's vast research enterprise, he launched a broad internal search to find a program or person to pursue.

Miano, a self-described "gene jock" whose lab focuses on finding and describing hidden information within the human genome, popped up in the search. Opportunely, he was in great need of someone with a computer background to scour databases full of information on the genome to help him advance his research. For years Miano wanted to create the database the pair recently unveiled, but it wasn't until Benson approached him that the idea really got off the ground.

"To have Craig, a young resident, reach out to me and say, 'I'm interested and have the skills you need,' was a huge blessing," said Miano, a faculty member in the School of Medicine and Dentistry for the past 11 years. "While we don't see partnerships like this every day, it is a really beautiful collaboration that I hope the University can replicate more in the future."

Once connected, the pair honed in on mutations in the human genome that affect a critical "lock and key" combination that scientists believe is responsible for turning on or off a wide range of genes that create many of the proteins we are made of. When the "lock" – a segment of DNA known as the CArG box – and the "key" – a protein known as SRF – come together or bind, they unlock the ability of a cell to turn on a gene.

While there are thousands of genetic lock and key combinations that turn genes on or off, the authors chose to study this particular one because, according to Miano, it is absolutely vital for life. "It is found in every organ system, from the heart and eyes, to the skin and bones. Studies suggest it may regulate up to 20 percent of our protein-creating genes, which is a very large collection of genes."

Benson spearheaded the first segment of the study, identifying where the lock and key are located within the vast section of the genome that scientists know the least about – the 98.5 percent that does not create proteins. He developed a computer program and, using a publicly available database derived from the Human Genome Project, scanned about five percent of the genome for the locks. Once he identified these sites – more than 8,000 – he created a similar program to look for mutations within these locks. Ultimately, he found 115 sites containing mutations.

Next, Miano stepped in to analyze how these mutations affect the lock and key. Experiments in his laboratory using human cells revealed that when a mutation is present, the lock and key is weaker; it doesn't fit together or bind as well as when it is free of any mutations. Though they didn't study gene expression, the authors infer that an altered lock and key likely changes how strongly a gene is turned on or suppressed, which could influence disease.

"Our findings are important because if a scientist discovers that one of the mutations we identified and tested is linked to a particular disease, our database will immediately provide a deeper understanding of the mutation and consequently a window into why the disease may be happening," noted Miano.

Miano and Benson don't know of any diseases caused by the mutations they identified yet, but Benson did discover that some of the mutations

are linked to conditions such as type 2 diabetes, coronary artery disease and ischemic stroke. Further study is needed to see if and how the mutations play a role.

The two plan to continue their work together, even when Benson starts a cardiology fellowship program at Harvard next year. They credit their successful collaboration to a mutual passion for the research, flexibility and understanding.

"Joe recognized and appreciated the limitations I had in taking on this research, because my primary responsibility was as a clinician. He understood that I couldn't be in the lab every day, but at the same time he knew I was committed," said Benson, who has spent the past four years practicing at the Culver Medical Center, part of the University's Center for Primary Care. "The attending physicians in my program were also very encouraging when it came to my research; I couldn't imagine trying to do this without their support."

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