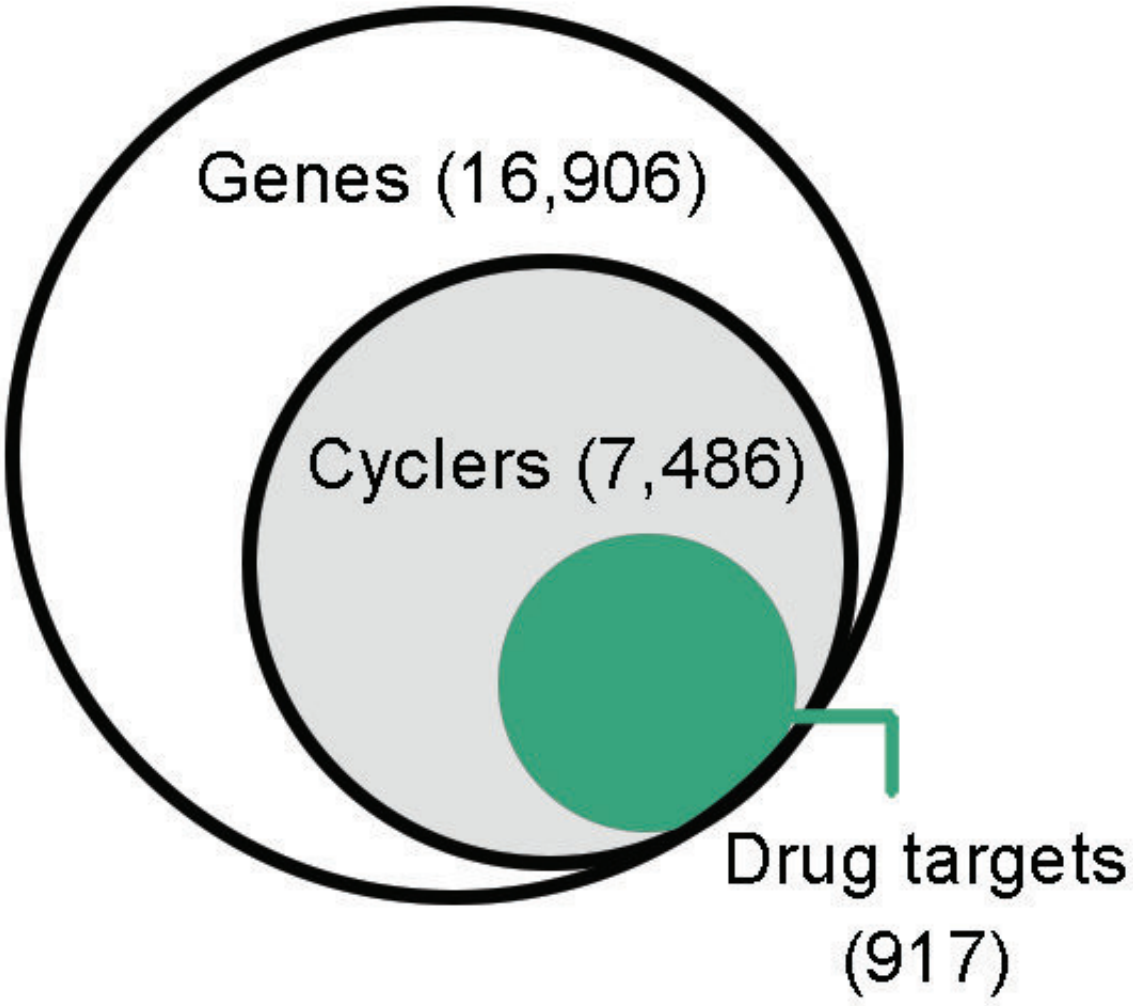
Timing may be everything when taking meds

September 12 2018



Of a total of 16,906 genes analyzed in 13 human tissues, almost 7,500 were cyclers. 917 of these genes encode for at least one drug target, transporter, or

metabolizing enzyme. Credit: M.D. Ruben et al., *Science Translational Medicine* (2018)

Using new bioinformatics tools to analyze thousands of human tissue samples, researchers at Cincinnati Children's Hospital Medical Center created a new database of daily rhythms in human gene activity—including many genes that regulate how drugs work.

Reporting in *Science Translational Medicine*, researchers say their results could have significant implications for a growing field of study called circadian medicine—timing the administration of drugs or other therapies to coincide with the body's internal clock.

"We identified rhythms in gene expression across the body in a large and diverse group of people," says John Hogenesch, Ph.D., senior investigator and a circadian biologist in the divisions of Human Genetics and Immunobiology. "It doesn't matter if you're male, female, young or old, or what your ethnicity is, your body's internal clock regulates half your genome. This includes drug metabolizing enzymes, transporters, and targets. Now we are learning which drugs hit clock-regulated products and may benefit from optimizing administration time in people."

The authors stress additional studies are needed before these findings are translated into clinical practice. This includes studies in pre-clinical models, which could support future time-of-day drug administration studies in people.

"As most of these drugs are safe and approved, this process should go much faster than traditional drug discovery, which can take a decade or more," Hogenesch said.

Applying CYCLOPS

One challenge to applying biological time in clinical practice is the lack of knowledge about how the circadian clock controls rhythms in humans. To fill that gap, the researchers used their recently developed computer algorithm called cycling ordering by periodic structure, or CYCLOPS.

The algorithm is a new approach to study how the body's internal clock regulates round-the-clock changes in gene activity in people.

Hogenesch and his team used CYCLOPS to analyze the timing of gene-to-tissue interactions in the 13 tissue types, which came from 632 human donors. Raw data about the samples came from the Genotype-Tissue Expression (GTEx) Consortium. Funded by the National Institutes of Health, GTEx catalogues genetic variation and its influence on gene expression in and between major tissues in the human body.

Of the thousands of genes that cycled rhythmically in the different human tissues, core clock genes were among the most robust. This finding also aligned with earlier studies in other vertebrates. Of these, 917 genes code for proteins that help transport or metabolize drugs or are themselves drug targets.

"Overall this connects thousands of different drugs, both approved and experimental, to nearly 1,000 cycling genes," explains Marc Ruben, Ph.D., the study's first author and a research fellow. "We found that genes that cycle in the human cardiovascular system are targeted by many of these drugs."

Heart of the Matter

The researchers report 136 drug targets rhythmically cycling in at least

one of four cardiac tissues, the atrial chamber, aorta, coronary artery, and the tibial artery. Many of these are "standard-of-care" targets for drugs used to treat heart disease, e.g. a family of drugs called calcium channel blockers. These drugs inhibit the influx of calcium into heart and blood vessels cells to promote smooth muscle relaxation and are used to treat hypertension and angina.

The researchers also discussed other challenges in putting these ideas in practice. One of these challenges is measuring body time.

"It's not as simple as taking your medication in the morning," explained Ruben. "One in six US workers are now shift workers, so while it may be morning for most, it is bedtime for some. We need a robust way to measure body time to account for this."

More information: M.D. Ruben el al., "A database of tissue-specific rhythmically expressed human genes has potential applications in circadian medicine," *Science Translational Medicine* (2018). stm.sciencemag.org/lookup/doi/ … scitranslmed.aat8806

Provided by Cincinnati Children's Hospital Medical Center