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Personalized gene networks enhance study of disease

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Researchers at Penn State College of Medicine have developed a new method to model how genes interact with each other—and it may someday contribute to the development of personalized treatments for patients.

According to the researchers, the new model is able to construct personalized networks for an individual patient that can show complex gene interactions in multiple directions and predict how those interactions may change over time.

Genes encoded in human DNA determine physical characteristics like hair color or body shape. Historically, it was believed that a single gene influenced a single trait. Modern scientists understand that genes influence each other in a complex web of connections called gene regulatory networks.

Rongling Wu, distinguished professor of public health sciences and statistics, led a team of researchers at Penn State and several other universities in developing a model that can construct gene regulatory networks for individual patients. He said that the model could help enhance the field of personalized medicine.

"This model may allow us to study why patients receiving the same treatment may have different results," said Wu, who is also a member of the Penn State Cancer Institute. "If we can identify the unique genetic processes underlying the different physical outcomes, we may be able to

develop personalized treatments."

Wu described the creation and characteristics of the new model—called an idopNetwork (informative, dynamic, omnidirectional and personalized networks)—in the Oct. 11 issue of Nature Partner Journals' *Systems Biology and Applications*.

idopNetworks are constructed using data obtained from genetic experiments and tests. When the genetic data are processed using differential equations, the result is a model that informs how genes relate to each other. According to the researchers, these gene relationships may differ from person to person.

"There are tens of thousands of genes in human beings," said Wu. "idopNetworks give us the ability to reconstruct a network that paints a personal, intricate picture of the relationship between all these genes for each person."

According to Wu, groups of genes that influence each other can be organized into clusters called modules. For example, a module may show how gene A can influence gene B—whether one promotes or prevents the activity of another. It might also show how genes C, D and E influence the activity of A while genes F and G may affect the activity of gene B. Relationships between genes organized into modules can also be illustrated to show a bigger picture of gene activity in a cell, tissue or organism.

"In one patient, one gene's activity may influence a second gene's activity," Wu said. "It is possible that in a second patient the second gene's activity actually influences the first gene's activity. It is essential that we identify and understand these differences when developing personalized medicine approaches."

Wu said previous mathematical methods for constructing dynamic gene regulatory networks are limited by their necessity to collect genetic data at multiple time points. By integrating the strengths of other disciplines, such as ecology and game theory, into mathematical equations, idopNetworks do not need to rely on data from multiple time points. They can monitor the snapshots of biological processes and dynamically predict how gene networks vary in response to changes in time and environment.

"Traditional approaches involved reconstructing networks at one time point from data collected at multiple time points," said Ming Wang, co-author and professor of public health sciences at the College of Medicine. "Our approach is statistically innovative in that it allows us to use data from one time point to reconstruct a network that is dynamic and can predict changes based on time and environment."

Wu and collaborators studied genetic data collected at the University of Florida from patients who had undergone a surgical intervention for a circulatory disease in a separate study. Of the 48 participants, 35 had successful outcomes. They used the data to construct idopNetworks of 1,870 genes for each individual—and found that the people with successful outcomes had more connections within their networks. They also found that one gene played a critical role in regulating many of the genes within each person's network.

According to the researchers, once a critical gene within a network is identified, further studies can be initiated to find out how many other genes it regulates and through what methods. This data may help in designing therapeutic interventions for patients with certain conditions. It may also help scientists investigate how changes in genes contribute to human disease.

"idopNetworks are flexible and may help us build tissue-specific gene

regulatory networks using Genotype-Tissue Expression Project data," said Chixiang Chen, first author and Ph.D. candidate at the College of Medicine. "That data comes from a long-term project supported by the National Institutes of Health that aims to build a comprehensive public resource containing information on gene expression in specific tissues."

Chen says idopNetworks constructed from this data set may help investigators determine what normal activity looks like in healthy tissues. It may also help them identify differences between the gene regulatory networks of healthy tissues and diseased tissues—which may help lead to the development therapeutic interventions for diseases like cancer.

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