Scientists emphasize metabolites' role in understanding disease

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Overreliance on genetic-centered approaches in predicting, diagnosing and treating disease will lead to few future scientific breakthroughs, cautioned a University of Alabama researcher who co-authored an article in an early online issue of *Genetics* that advocates for a greater emphasis on the body's metabolites in understanding illnesses.

"To augment the value of genetic data, the scientific community needs to add additional information from things like metabolomics – the analysis of metabolites within an organism," said Dr. Laura Reed, a University of Alabama geneticist and the March 25 paper's lead author.

"The Human Genome Project has been sold as something that is going to revolutionize medicine – that soon we will get our genomes sequenced, and we will be able to figure out exactly what diseases we are at risk for and, maybe, the best way to treat them," said Reed. "While it's true there are important innovations to come from that kind of information, it is much more limited than some may have hoped."

Using fruit flies as animal models in the research publishing in *Genetics*, the multi-institution team demonstrated how genetics, in combination with metabolomics and gene expression—how genes are turned on—can be used to predict heart disease and the organism's response to environmental change, said Reed.

The paper's additional co-authors include representatives from Georgia Tech, Sanford-Burnham Medical Research Institute, La Jolla, Calif.;

North Carolina State University; Huck Institutes of the Life Sciences, University Park, Pa.; and Bayer CropScience, Monheim, Germany.

Metabolites are naturally occurring chemicals in the body. While a few, like cholesterol and blood glucose are routinely monitored for the insights they can provide into health conditions, additional metabolites merit closer inspection, the researchers said. Glycine, a metabolite which serves as both an essential amino acid and a neurotransmitter, has previously been shown as a predictor of heart disease and certain cancers.

"We identified another nine metabolites that are also good predictors that have not yet been previously described as associated with these traits," Reed said. "They are good candidates for exploring further. They may not be causal, but they may be correlated."

One day, Reed said, in addition to doctors measuring blood glucose and cholesterol levels, perhaps they will routinely measure other metabolites as way of improving predictions of disease risks.

In one of the project's aspects, headed by UA, 187 metabolites were measured in flies to determine which ones' levels changed in correlation with weight changes in the flies.

As with mice and other widely accepted animal models used in studying human conditions, many of the biological systems within fruit flies share enough similarities with humans to potentially draw effective insight into human conditions, Reed said.

For example, flies can contract diabetes and, as they age, heart disease. Their insulin-signaling pathways, key in diabetes, share similarities with those of humans, as do their kidneys, liver and the adipose tissue – the types of tissue where fat is stored.

Hundreds of genetically identical flies, grouped by 20 distinct genetic lines, were tested across four different diets. In this way, the researchers are able to determine which aspect of their disease is because of their genes and which aspect is because of their environment or diet.

"One of the important things we found is that the effects of diet are relatively small for gene expression, but much more significant for all the metabolites."

In another aspect of the research, led by Georgia Tech, the scientists tracked how the frequency of genes in wild flies changed through time (over multiple generations) in response to diet. Rather than seeing changes in one particular gene or a small group of genes, the researchers saw changes across the entire genome.

"We can't expect to find a gene or just a few genes that explain any phenotype, including disease," Reed said. Disease is a holistic problem, she said, and it's unlikely that additional "miracle drugs" await discovery.

"It's going to be a holistic solution," Reed said.

Reed said she realizes the paper may not be warmly embraced by all her fellow geneticists.

"The overall point of the paper is not a very popular idea," Reed admitted, "because it basically means things are much more complicated than we want them to be. But, that's reality.

"This does not mean that we can't incrementally improve things by understanding the genes that are involved, but, perhaps, a more expedient approach would be analyzing higher level traits, like metabolites, that might summarize what's occurring in the genome in ways more useful for diagnostic or treatment purposes."

Provided by University of Alabama in Tuscaloosa