Researchers develop C. elegans as a model for investigating metabolism variations between individuals

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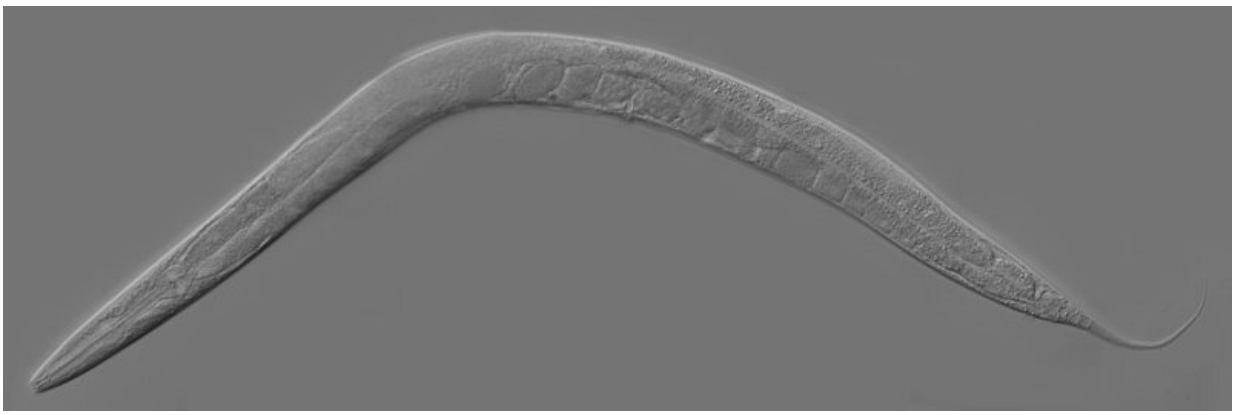

Caenorhabditis elegans. Credit: Kbradnam at English Wikipedia/Wikimedia Commons, CC BY-SA 2.5

Using four unrelated strains of the microscopic nematode C. elegans originating from different parts of the world, a group of worm biologists have developed a model system to study individual differences in metabolism. The use of C. elegans, a widely studied model organism, allowed the team to study the unique and complex interplay between genetics, diet, microbiota and other environmental factors that can affect fundamental metabolic processes in different individuals. This advancement represents a potentially important step toward "personalized" or "precision" medicine, a relatively new discipline that

tailors dietary advice and disease treatment to an individual's own genome sequence.

The research, by Marian Walhout, Ph.D., the Maroun Semaan Chair in Biomedical Research and chair and professor of systems biology at UMass Chan Medical School and collaborators Erik Andersen, Ph.D., from Northwestern University and Frank Schroeder, Ph.D., from Cornell University, published in *Nature*, identifies a novel metabolic condition linked to variation in the hphd-1 gene of a strain of C. elegans found on the Big Island in Hawaii. The strain, known as DL238, has an abnormal accumulation and secretion of the metabolite 3-hydroxypropionate (3HP). Moreover, this strain was found to generate a set of novel metabolites that have 3HP conjugated to several amino acids. These novel metabolites are not found in the laboratory strain that has been used for decades to make seminal biological discoveries. By conjugating 3HP to amino acids, DL238 is removing 3HP, which is toxic at high concentrations.

"This work provides an important step toward the development of metabolic network models that capture individual-specific differences of metabolism and more closely represent the diversity that is found over entire species," said Walhout. "Employing this system, we can begin studying interindividual metabolism and the unique interplay of metabolites, diets and environments on an individual level."

When the human genome was sequenced, clinical researchers envisioned an era when our personal genomic information could be used to tailor medical treatments to fit the needs of each individual, explained Walhout. Despite the completion of the Human Genome Project in 2003, and advancements in genomics and deep sequencing technologies, personalized medicine remains more promise than reality.

Part of the challenge in developing personalized medicine is that our

DNA makes up only a portion of human health; an individual's diet and environment both profoundly impact metabolic processes. And because no two individuals have the same exact diet, unraveling the complex interplay of genetics, diet and environment and connecting these to variations in metabolism is cumbersome. In addition to sequencing individual genomes, scientists would need to replicate metabolic measurements in people of the same age and gender, who ideally would also consume the same exact diet and experience identical environments.

To address this challenge, Walhout, a leader in metabolism and gene expression research, teamed up with Dr. Andersen, an expert in quantitative genetics, and Dr. Schroeder, a chemist, to develop a comparative system for studying interindividual variations in metabolism.

The group designed a system where environmental conditions and diet were constant among "individuals" with variable genomes, much like our genomes vary from person-to-person. To do this, the four separate strains of C. elegans with completely sequenced genomes—including the standard laboratory strain, two from Hawaii and another from Taiwan—were grown under identical conditions: each strain was grown at the same time in the same incubator and were fed the same diet.

"Each strain represents an individual," said Olga Ponomarova, Ph.D., a postdoctoral researcher in the Walhout lab and co-author of the study. "We collected about 100,000 animals from each strain and because they are all grown in the same conditions, given the same diet and have the same genome, it's possible to explore how genetic differences among the four strains impact metabolism. It's like comparing four different people."

At its core, metabolism is the set of life-sustaining chemical reactions in organisms. The three main purposes of metabolism are: the conversion

of food into energy for cellular processes; the conversion of food to building blocks for proteins, such as lipids, nucleic acids and some carbohydrates; and the elimination of wastes generated by these two processes.

A series of experiments including gas chromatography–mass spectrometry, high performance liquid chromatography-mass spectrometry, and metabolic network analysis were performed and analyzed to identify possible differences and variations in metabolites between the four strains. As a result, more than 20,000 likely metabolites, the small molecules that collectively carry out metabolism, were detected, most of which remain unknown.

When researchers compared the presence of metabolites between the four strains, they found more than 200 metabolites that were highly specific to one of the strains. One metabolite, 3HP, was found in exceptionally high abundance in the DL238 strain from Hawaii. Past studies by the Walhout lab have shown that high 3HP levels are found in nematodes whose diet are low in vitamin B12. These studies showed that 3HP is formed during propionate breakdown via a B12-independent metabolic route, or shunt. 3-HP is then metabolized by the HPHD-1 enzyme and ultimately converted into acetyl-CoA.

In the current study, researchers were able to trace the abundance of 3HP molecules in the DL238 strain to a variation in the hphd-1 gene, which allows 3HP to accumulate. To compensate for the excess 3HP, the DL238 C. elegans developed a mechanism for "shunting" the excess molecule out of the animal cells by cojoining 3HP with amino acids. This keeps the 3HP molecule from building to toxic levels and may be an adaptation to changing nutrient conditions, according to Walhout, who referred to the system as "a shunt within a shunt."

The study shows the power of moving toward a pan-species metabolic

network model for deep biological investigations. "We're just starting to scratch the surface," said Walhout. "Our study only uses four strains, but the next step is to see what we find when we look at 100 different strains. Or what happens when we use the same strain but vary the diets.

"We've put together a really robust model for measuring metabolic variation between individuals," said Walhout. "What made this possible, more than anything, is our unique, multidisciplinary collaboration. It's the expertise that each lab brought to this project that enabled this discovery."

More information: Bennett W. Fox et al, C. elegans as a model for inter-individual variation in metabolism, *Nature* (2022). DOI: 10.1038/s41586-022-04951-3

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