MedicalXpress

Combining genomics and metabolism identifies long-sought mitochondrial choline transporter

July 8 2024

Credit: Unsplash/CC0 Public Domain

A multidisciplinary research team has developed a discovery platform to probe the function of genes involved in metabolism—the sum of all life-sustaining chemical reactions.

The investigators used the new platform, called GeneMAP (Gene-Metabolite Association Prediction), to identify a gene necessary for mitochondrial choline transport. The resource and derived findings were published July 8 in the journal Nature Genetics.

"We sought to gain insight into a fundamental question: "How does genetic variation determine our "chemical individuality"—the inherited differences that make us biochemically unique?" said Eric Gamazon, Ph.D., associate professor of Medicine in the Division of Genetic Medicine at Vanderbilt University Medical Center. Gamazon is the senior and co-corresponding author of the study with Kivanç Birsoy, Ph.D., of The Rockefeller University.

Metabolic reactions play critical roles in nutrient absorption, energy production, waste disposal, and synthesis of cellular building blocks including proteins, lipids and nucleic acids. About 20% of protein-coding genes are dedicated to metabolism, including genes that code for small-molecule transporters and enzymes, Gamazon said.

Abnormalities in metabolic functions are associated with a range of disorders including neurodegenerative diseases and cancers.

"Despite decades of research, many metabolic genes still lack known molecular substrates. The challenge is in part due to the enormous structural and functional diversity of the proteins," Gamazon said.

To discover functions for "orphan" transporters and enzymes—proteins with unknown substrates—the researchers developed the GeneMAP discovery platform. They used datasets from two independent large-scale human metabolome genome-wide/transcriptome-wide association studies and demonstrated with in silico validation that GeneMAP can identify known gene-metabolite associations and discover new ones.

In addition, they showed that GeneMAP-derived metabolic networks can be used to infer the biochemical identity of uncharacterized metabolites.

To experimentally validate new gene-metabolite associations, the researchers selected their top finding (SLC25A48-choline) and performed in vitro biochemical studies. SLC25A48 is a mitochondrial transporter that did not have a defined substrate for transport. Choline is an essential nutrient used in multiple metabolic reactions and in the synthesis of cell membrane lipids.

The researchers showed that SLC25A48 is a genetic determinant of plasma choline levels. They further conducted radioactive mitochondrial choline uptake assays and isotope tracing experiments to demonstrate that loss of SLC25A48 impairs mitochondrial choline transport and synthesis of the choline downstream metabolite betaine.

They also investigated the consequences of the relationship between SLC25A48 and choline on the human medical phenome (symptoms, traits and diseases listed in electronic health records) using large-scale biobanks (UK Biobank and BioVU). They identified eight disease associations.

"What's exciting about this study is its interdisciplinarity—the combination of genomics and metabolism to identify a long-sought mitochondrial choline transporter," Gamazon said.

"We think, given the extensive in silico validation studies in independent datasets and the proof-of-principle experimental studies, our approach can help identify the substrates of a wide range of enzymes and transporters, and 'deorphanize' these metabolic proteins."

Birsoy is Chapman-Perelman Associate Professor, Head of the Laboratory of Metabolic Regulation and Genetics at The Rockefeller

University, and a Searle and Pew-Stewart Scholar.

More information: Metabolic gene function discovery platform GeneMAP identifies SLC25A48 as necessary for mitochondrial choline import, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01827-2

Provided by Vanderbilt University Medical Center