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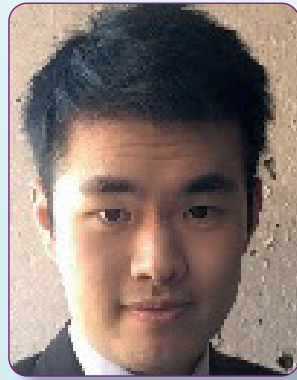
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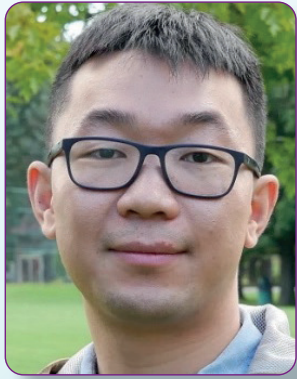
Yiheng Chen, MSc
Doctoral student, Richards Laboratory, Lady Davis Institute
Department of Human Genetics, McGill University

Tianyuan Lu, PhD
Senior Bioinformatics Scientist
5 Prime Sciences

Brent Richards, MD, MSc
Senior Investigator, Lady Davis Institute

Professor, Departments of Medicine,
Human Genetics, Epidemiology and Biostatistics,
McGill University

nature genetics

Genomic atlas of the plasma metabolome prioritizes metabolites implicated in human diseases

Yiheng Chen, Tianyuan Lu, Ulrika Pettersson-Kymmer, Isobel D. Stewart, Guillaume Butler-Laporte, Tomoko Nakanishi, Agustin Cerani, Kevin Y. H. Liang, Satoshi Yoshiji, Julian Daniel Sunday Willett, Chen-Yang Su, Parminder Raina, Celia M. T. Greenwood, Yossi Farjoun, Vincenzo Forgetta, Claudia Langenberg, Sirui Zhou, Claes Ohlsson and J. Brent Richards.

Metabolic processes can influence disease risk and provide therapeutic targets.

By conducting genome-wide association studies of 1,091 blood metabolites and 309 metabolite ratios, we identified associations with 690 metabolites at 248 loci and associations with 143 metabolite ratios at 69 loci. Integrating metabolite-gene and gene expression information identified 94 effector genes for 109 metabolites and 48 metabolite ratios.

Using Mendelian randomization (MR), a statistical tool for inferring causal relationship between risk factors and disease outcomes using genetic data, we identified 22 metabolites and 20 metabolite ratios having estimated causal effect on 12 traits and diseases, including orotate for estimated bone mineral density, ⬚-hydroxyisovalerate for body mass index and ergothioneine for inflammatory bowel disease and asthma. We further measured the orotate level in a separate cohort and demonstrated that, consistent with MR, orotate levels were positively associated with incident hip fractures.

Together, our study provides a valuable resource describing the genetic architecture of metabolites and delivers insights into their roles in common diseases, thereby offering opportunities for therapeutic targets.

Our study only focused on the most possible gene-metabolite pairs supported by the expression and biological knowledge available (i.e., with effector genes). This does not mean that other highly heritable metabolites or ratios are not disease related. Future studies on identifying the effector genes for these metabolites and ratios are needed when more expression data or knowledge in the metabolism are available.