Development of a highly-accurate computational model of human metabolism

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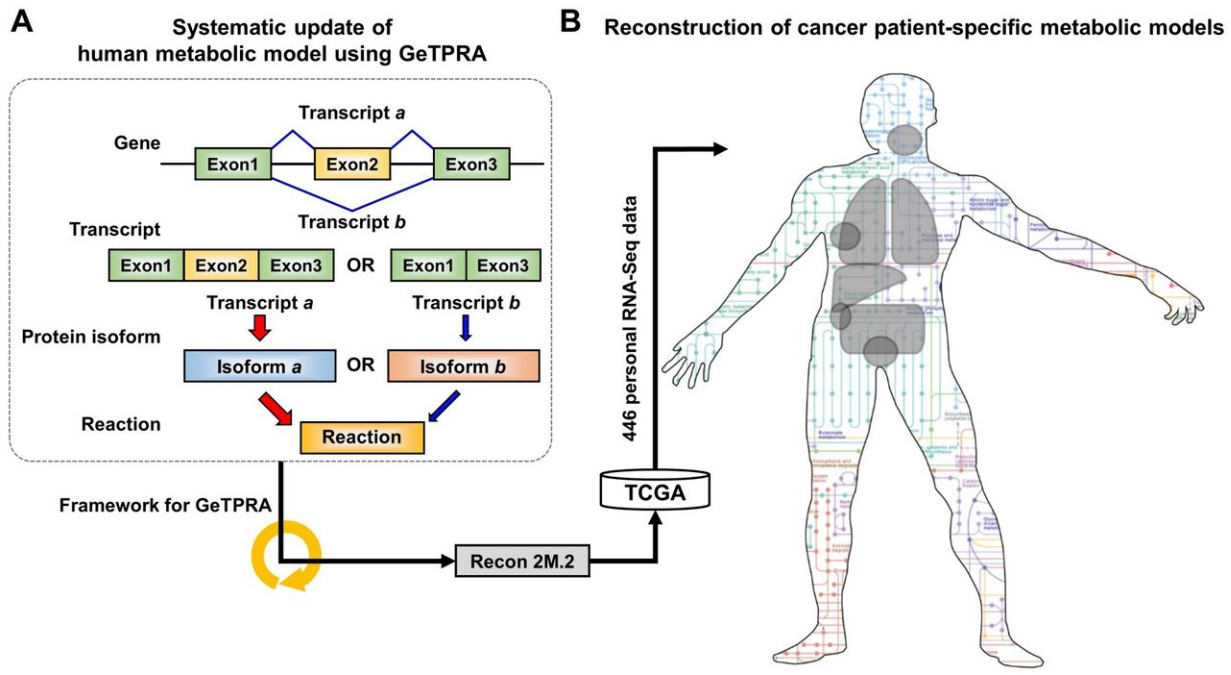

Scheme of Recon 2M.2 development and its use in reconstructing personal genome-scale metabolic models (GEMs). (A) In developing Recon 2M.2, a concept of alternative splicing of human genes was considered, and incorporated into modeling through the computational framework for Gene-Transcript-Protein-Reaction Associations (GeTPRA). (B) Upon development of Recon 2M.2, cancer patient-specific GEMs could be reconstructed using personal biological data (RNA-Seq data). In this study, patient-specific RNA-Seq data were obtained from The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/). Credit: KAIST

A Korean research team from KAIST developed a computational framework that enables the reconstruction of a comprehensive computational model of human metabolism, which allows for an accurate prediction of personal metabolic features (or phenotypes).

Understanding personal metabolic phenotypes allows us to design effective therapeutic strategies for various chronic and infectious diseases. A human computational model called the genome-scale metabolic model (GEM) contains information on thousands of metabolic genes and their corresponding reactions and metabolites, and has played an important role in predicting metabolic phenotypes. Although several versions of human GEMs have been released, they had room for further development, especially as to incorporating biological information coming from a human genetics mechanism called "alternative splicing." Alternative splicing is a genetic mechanism that allows a gene to give rise to multiple reactions, and is strongly associated with pathology.

To tackle this problem, Jae Yong Ryu (a Ph.D. student), Dr. Hyun Uk Kim (Research Fellow), and Distinguished Professor Sang Yup Lee, all from the Department of Chemical and Biomolecular Engineering at KAIST, developed a computational framework that systematically generates metabolic reactions, and adds them to the human GEM. The resulting human GEM was demonstrated to accurately predict metabolic phenotypes under varied environmental conditions. The research results were published online in *Proceedings of the National Academy of Sciences* (*PNAS*) on October 24, 2017, under the title "Framework and resource for more than 11,000 gene-transcript-protein-reaction associations in human metabolism."

The research team first updated the biological contents of a previous version of the human GEM. The updated biological contents include metabolic genes and their corresponding metabolites and reactions. In particular, metabolic reactions catalyzed by already-known protein

isoforms were additionally incorporated into the human GEM; protein isoforms are multiple variants of proteins generated from individual genes through the alternative splicing process. Each protein isoform is often responsible for the operation of a metabolic reaction. Although multiple protein isoforms generated from one gene can play different functions by having different sets of protein domains and/or subcellular localizations, such information was not properly considered in previous versions of human GEMs.

Upon the initial update of the human GEM, named Recon 2M.1, the research team subsequently implemented a computational framework that systematically generates information on Gene-Transcript-Protein-Reaction Associations (GeTPRA) in order to identify protein isoforms that were previously not identified. This framework was developed in this study. As a result of the implementation of the framework for GeTPRA, more than 11,000 GeTPRA were automatically predicted, and thoroughly validated. Additional metabolic reactions were then added to Recon 2M.1 based on the predicted GeTPRA for the previously uncharacterized protein isoforms; Recon 2M.1 was renamed Recon 2M.2 from this upgrade. Finally, Recon 2M.2 was integrated with 446 sets of personal biological data (RNA-Seq data) in order to build patient-specific cancer models. These patient-specific cancer models were used to predict cancer metabolism activities and anticancer targets.

The development of a new version of human GEMs along with the computational framework for GeTPRA is expected to boost studies in fundamental human genetics and medicine. Model files of the human GEMs Recon 2M.1 and 2M.2, a full list of the GeTPRA and the source code for the computational framework to predict the GeTPRA are all available as part of the publication of this study.

Distinguished Professor Lee said, "The predicted GeTPRA from the computational framework is expected to serve as a guideline for future

experiments on human genetics and biochemistry, whereas the resulting Recon 2M.2 can be used to predict drug targets for various human diseases."

More information: Jae Yong Ryu et al, Framework and resource for more than 11,000 gene-transcript-protein-reaction associations in human metabolism, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1713050114