Alternative splicing plays important roles in generating different transcripts from one gene, and consequently various protein isoforms. However, there has been no systematic approach that facilitates characterizing functional roles of protein isoforms in the context of the entire human metabolism. Here, we present a systematic framework for the generation of gene-transcript-protein-reaction associations (GeTPRA) in the human metabolism. The framework in this study generated 11,415 GeTPRA corresponding to 1,106 metabolic genes for both principal and nonprincipal transcripts (PTs and NPTs) of metabolic genes. The framework further evaluates GeTPRA, using a human genome-scale metabolic model (GEM) that is biochemically consistent and transcript-level data compatible, and subsequently updates the human GEM. A generic human GEM, Recon 2M.1, was developed for this purpose, and subsequently updated to Recon 2M.2 through the framework. Both PTs and NPTs of metabolic genes were considered in the framework based on prior analyses of 446 personal RNA-Seq data and 1,784 personal GEMs reconstructed using Recon 2M.1. The framework and the GeTPRA will contribute to better understanding human metabolism at the systems level and enable further medical applications.