

iDrosophila1: An orthology-based reconstruction of genome-scale metabolic network model for *Drosophila melanogaster*

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Drosophila melanogaster is a promising workhorse that includes conserved counterparts of essential human systems. In addition, this organism has a high conservation in terms of disease-associated genes. Thus, it has been widely used to elucidate the molecular mechanisms underlying complex human diseases. Despite experimental advances, metabolic modeling of *Drosophila* is still limited. This prompted us to reconstruct a comprehensive and highly curated metabolic network model for this organism using an orthology-based reconstruction approach. Genome-scale metabolic network models consisting of stoichiometry-based chemical reactions, metabolites, and their associated genes are powerful platforms to properly mimic complicated metabolic processes. Genes in a metabolic network are linked to the reactions through conditional statements in Boolean logic, which are known as gene-protein-reaction associations. Orthology-based model reconstruction facilitates the transfer of metabolic information from a template model to new metabolic network models via these associations. Here, we used a flux-consistent version of human metabolic model, HMR2, as the template model. The orthology relations between human and *Drosophila* enabled to reconstruct a draft fly model, whose gene coverage and metabolic information were subsequently expanded via a *Drosophila*-specific KEGG- and MetaCyc-based metabolic network. To avoid metabolic redundancy and stoichiometric inconsistency, semi-automatic curation steps were applied by revising each network component. Furthermore, literature-based curations ensured to improve information about gene associations, subcellular metabolite locations, and metabolic pathways. The resulting *Drosophila* model called iDrosophila1 contains 8,230 reactions, 6,990 metabolites, and 2,388 genes. Its predictive performance was evaluated in comparison with other available generic fly models, and iDrosophila1 was shown to exhibit superior or comparable results. Additionally, transcriptome-based prediction capacity of the model was confirmed through the simulation of Parkinson's disease phenotype. Thus, we demonstrated the potential of iDrosophila1 to mimic complex human diseases by accurately predicting disease-associated differential pathways.

Keywords: *Drosophila melanogaster*, genome-scale metabolic network, orthology-based reconstruction, Parkinson's disease.

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