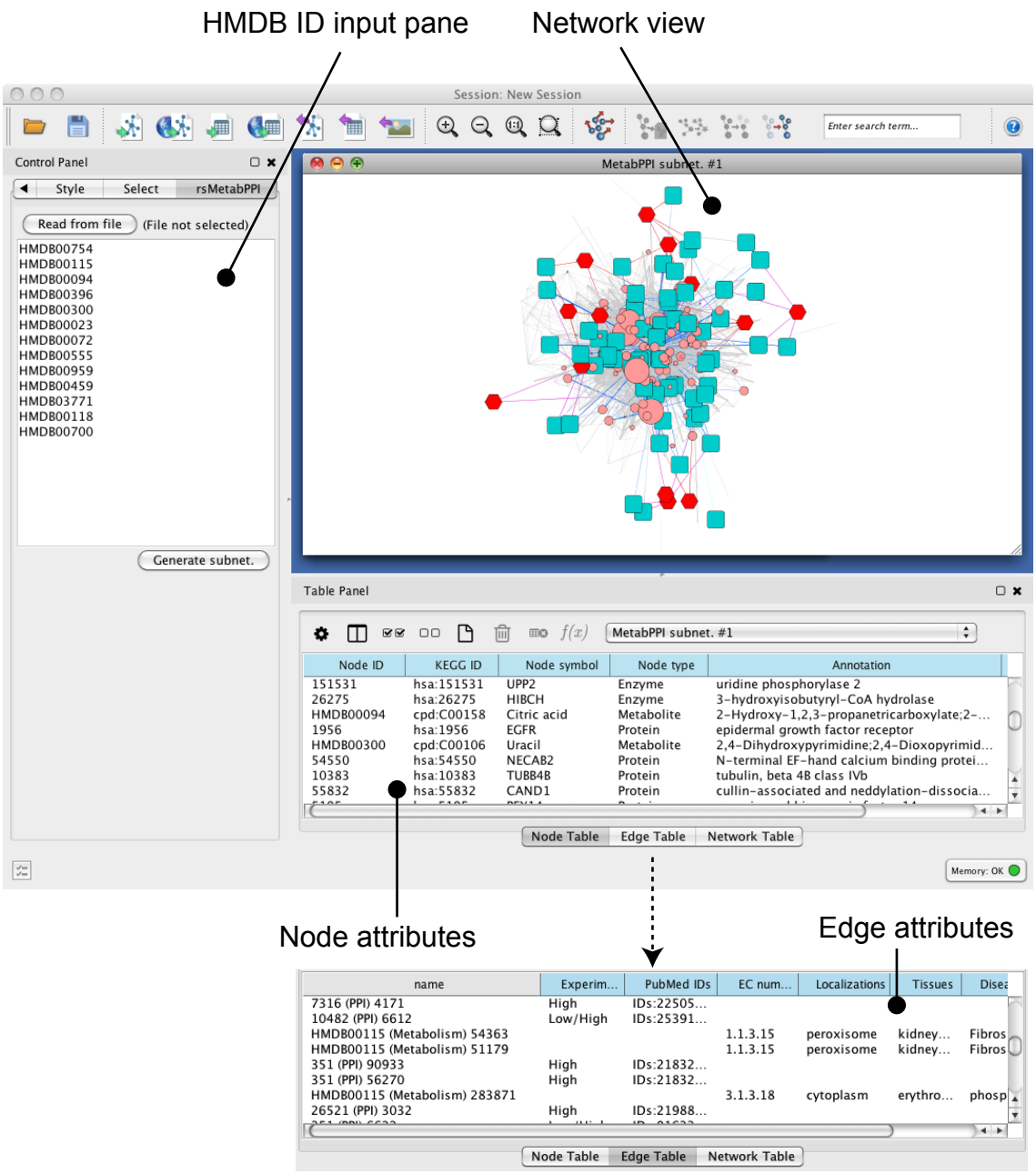
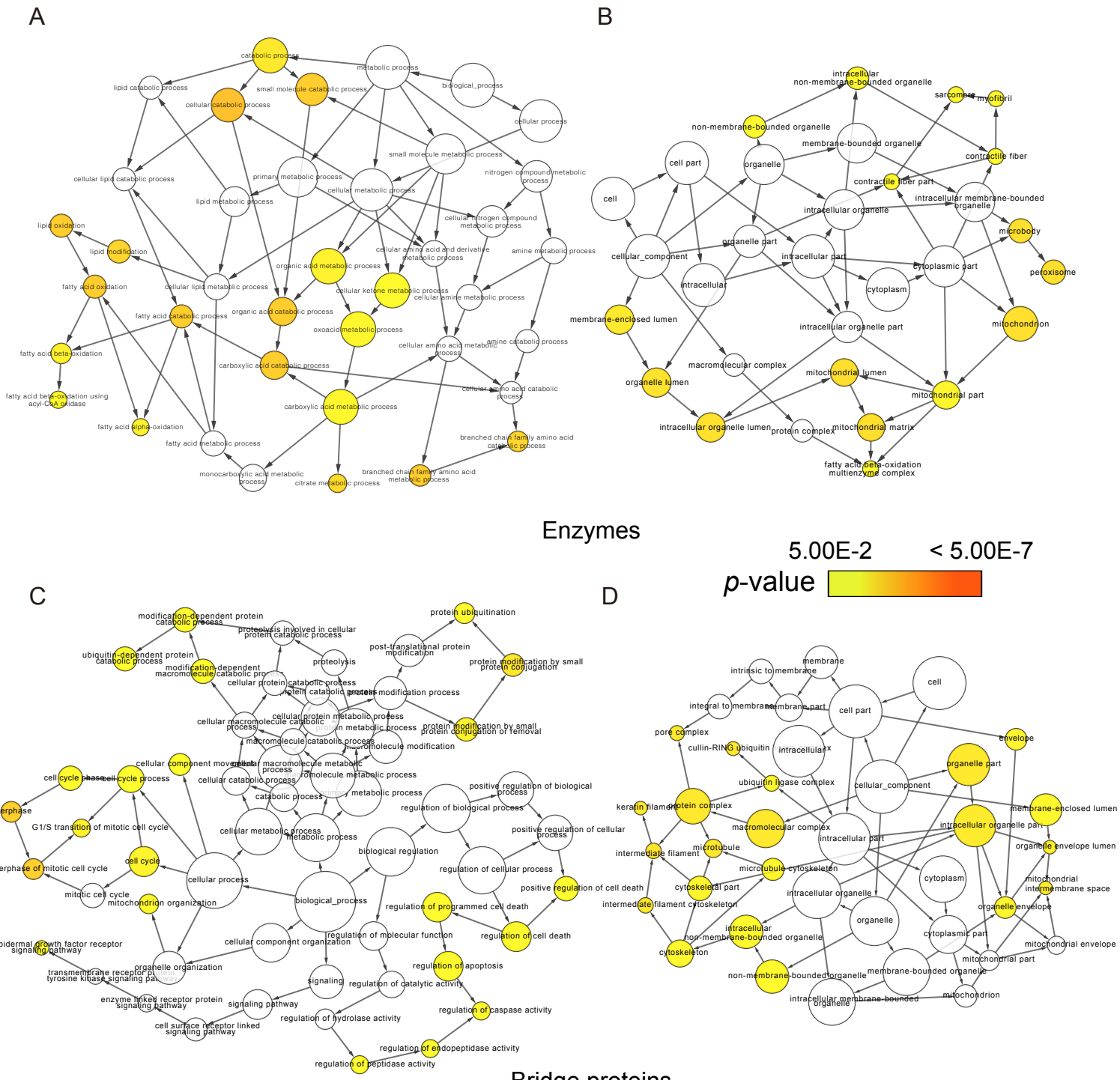
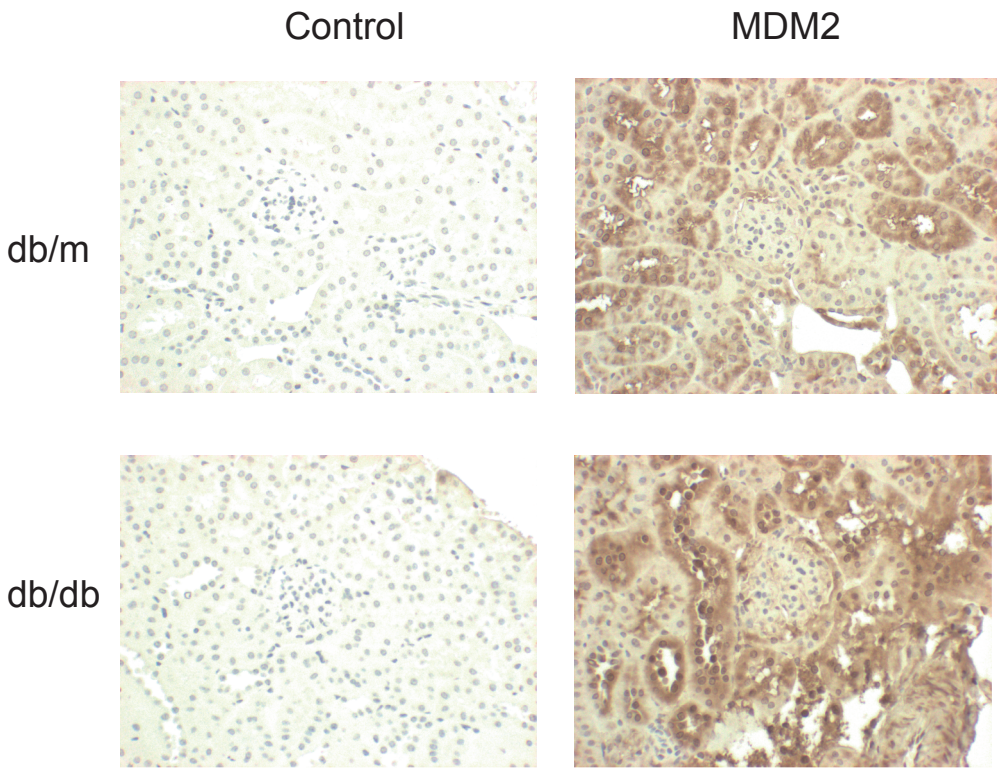


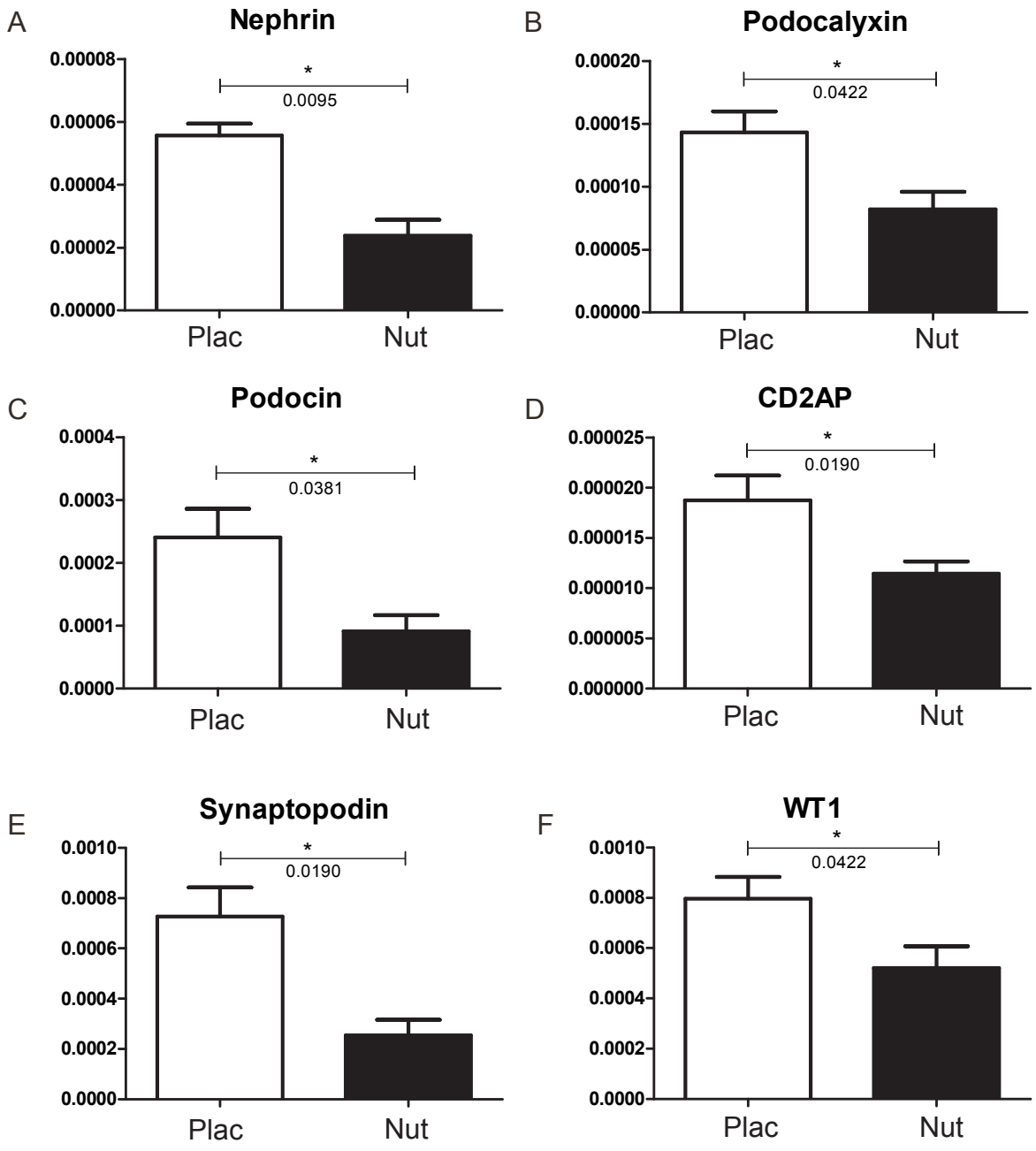
Supplemental Figure 1. Cytoscape App MetBridge Generator. The left pane is Cytoscape App MetBridge Generator (code name: rsMetabPPI). User can input HMDB numbers to search for subnetwork involving the given metabolites. Upper-right pane shows MetBridge_{DKD} network. Red, blue and pink nodes represent metabolites, enzymes, and bridge proteins, respectively. Pink, red and blue edges represent metabolism, manually curated metabolism and PPI respectively. Selected nodes and edges are colored in yellow and red, respectively, and also marked by the red arrow. The detailed information on the selected nodes (node attributes) is displayed in the lower pane. The detail on the selected edges (edge attributes) is displayed in the lower part of the figure.



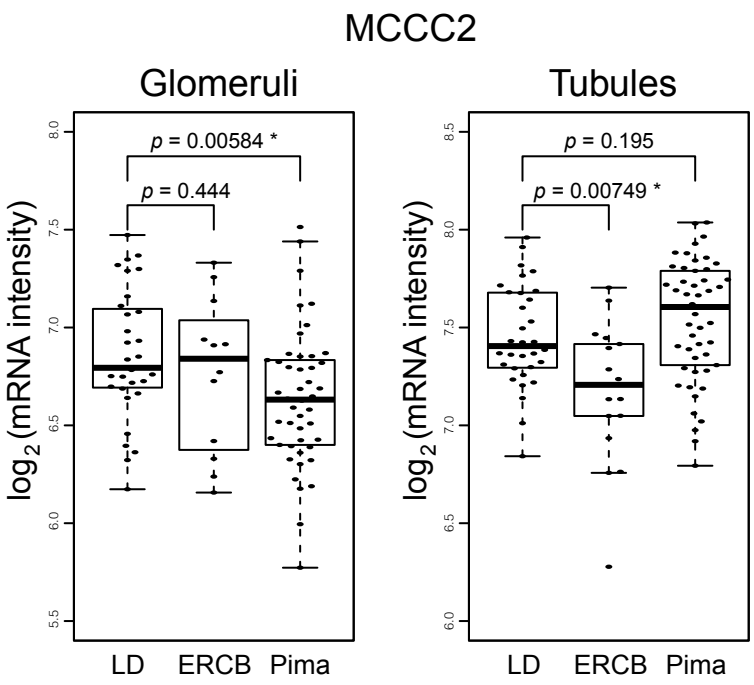
Supplemental Figure 2. GO terms enriched in enzymes and bridge proteins in the network connecting thirteen metabolites. Each node represents GO term. Each arrow represents hierarchical relationship between the terms. Significantly enriched terms in the hierarchy were colored depending on their significance. GO biological processes and cellular components enriched in the enzymes (A and B, respectively) and those enriched in the bridge proteins (C and D, respectively) are shown.



Supplemental Figure 3: Representative image of immunohistochemistry of MDM2 in kidney tissue of db/m and db/db mice. There were no clear differences in the tissue expression level of MDM2 between db/m and db/db mice. *n* = 3 per group. Magnification: 40x.



Supplemental Figure 4. Expression analyses of marker genes for diabetic nephropathy. Podocyte marker gene expression levels for control mice treated with placebo (Plac) and Nutlin-3a-treated diabetic mice (Nut) are shown in A-F. Benjamini-Hochberg corrected *p*-values were below 0.05 for all the genes.



Supplemental Figure 5: Expression analyses of methylcrotonoyl-CoA carboxylase 2 (MCCC2) in tissue biopsy of human kidney. Gene expression levels of MCCC2 in glomeruli and tubules of living donors (LD) were compared with those of ERCB and Native Americans (Pima).

Supplemental methods

Assessment of hub bridge proteins

We attempted to extract "bridge" proteins which have significant number of interactions to the enzymes regulating our thirteen metabolites based on a simple statistical framework. First, we classified the set of KEGG enzymes in our MetBridge network (Z) into (A_1) those which are associated with at least one of given set of metabolites $m \in M$ (M is the set of our thirteen metabolites in this case) or (A_2) those which are not associated with any one of $m \in M$ ($z \in A_1 \vee z \in A_2, A_1 \cap A_2 = \{\ \}$). The enzymes which directly interact with those which are associated with one of our thirteen metabolites were also classified as A_1 in order to account the possibility that such interactions among a pair of enzymes may constitute an enzymatic complex or a functional unit of the metabolic reaction. We searched for bridge proteins (P) which interact with at least one enzyme in A_1. Then for each protein $p \in P$, we classified enzymes $z \in Z$ into ($B_1(p)$) those which interact with the protein and ($B_2(p)$) those which do not ($z \in B_1(p) \vee z \in B_2(p), B_1(p) \cap B_2(p) = \{\ \}$). Thus, each enzyme $z \in Z$ can be classified as A_1 or A_2, and also $B_1(p)$ or $B_2(p)$ for a given protein p. Subsequently we tested enrichment of enzymes which are categorized both in A_1 and $B_1(p)$ using hypergeometric test; Let r_{A1} and $r_{B1}(p)$ be the actual

probability of z classified as A_1 and $B_1(p)$ respectively. Let $r_{A1B1}(p)$ be the actual rate of z classified as both A_1 and $B_1(p)$. Then, the hypotheses to test are H_0: $r_{A1B1}(p) = r_{A1} \cdot r_{B1}(p)$ and H_1: $r_{A1B1}(p) > r_{A1} \cdot r_{B1}(p)$, where r_{A1}, $r_{B1}(p)$ and $r_{A1B1}(p)$ are estimated by $\hat{r}_{A1} = \frac{|A_1|}{|Z|}$, $\hat{r}_{B1(p)} = \frac{|B_1(p)|}{|Z|}$ and $\hat{r}_{A1B1(p)} = \frac{|A_1 \cap B_1(p)|}{|Z|}$ respectively. This was to test whether a given bridge candidate protein has significantly more interactions to the enzymes regulating our thirteen metabolites compared to other KEGG enzymes. The number of calculated *p*-values were identical to the number of bridge proteins. These *p*-values were corrected using Benjamini–Hochberg procedure.

Calculating expected number of PPIs among MetBridge$_{DKD}$ network

The whole MetBridge network contained 58 703 edges among 3 387 proteins. Thus, under the assumption that two different proteins randomly picked from MetBridge interact at probability p, the estimated probability $\hat{p}$ indicating an interaction between randomly picked two proteins was $58703/\binom{3387}{2} \cong 0.0102$. We tested whether the probability p_{13} of two proteins randomly picked from MetBridge$_{DKD}$ is equal to p (H_0: $p_{13} = p$, H_1: $p_{13} > p$). Since MetBridge$_{DKD}$ contained 291 proteins, the expected number of edges were calculated to be $\binom{291}{2} \times 58703/\binom{3387}{2} \cong 431.967$.