Electronic Supplementary Material (ESI) for Molecular BioSystems.

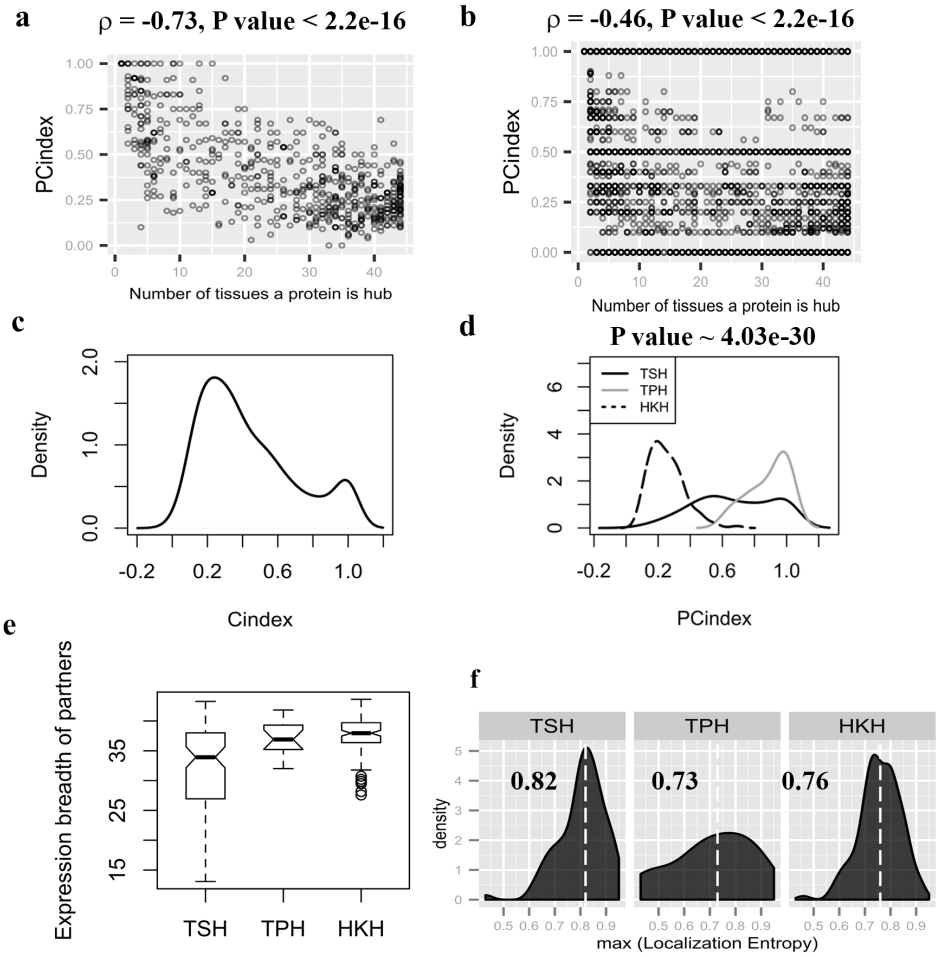

Fig. S1. Partner Conservation Index and Localization Diversity. (a,b) Scatter Plot of PCindex and number of tissue a hub (a) and non-hub (b) is present. There is a negative correlation between the conservation of partners and number of tissue a hub is present. (r= -0.73, P-value < 2.2e-16) which is significantly higher than a negative correlation between the conservation of partners and number of tissue a non-hub is present (r= -0.46, P-value < 2.2e-16). (b) Density plot of PCindex of hubs identified in tissue-specific human PPIN. (c) Density plots of PCindex of TSHs (solid, black), TPHs (solid, grey) and HKHs (long dash, black) showing TPHs having more conserved partners compared with TSHs and HKHs (P value 0.002). Among TSHs and HKHs, TSHs show higher PCindex than HKHs (P-value 1.57e-29) (d) Boxplots depicting distribution of expression breadth (number of tissue the protein is expressed) of partners of TSHs, TPHs and HKHs. The expression breadth of partners of HKHs is more than TSHs (P-value 3.14e-12) (Kolmogrov-Smirnov test). The partners of TPHs are mostly tissue-specific proteins. (e) Density plot of max (Localization Entropy) of TSHs, TPHs and HKHs. The dashed line shows median value for TSHs, TPHs and HKHs. TSHs show higher localization entropy than HKHs (P-value 4.53e-06) (Wilcoxon Ranksum test). Of the total 643 hubs identified in 44 supportive tissue-specific networks , 97 were TSHs , 126 were HKHs and 16 were TPHs.

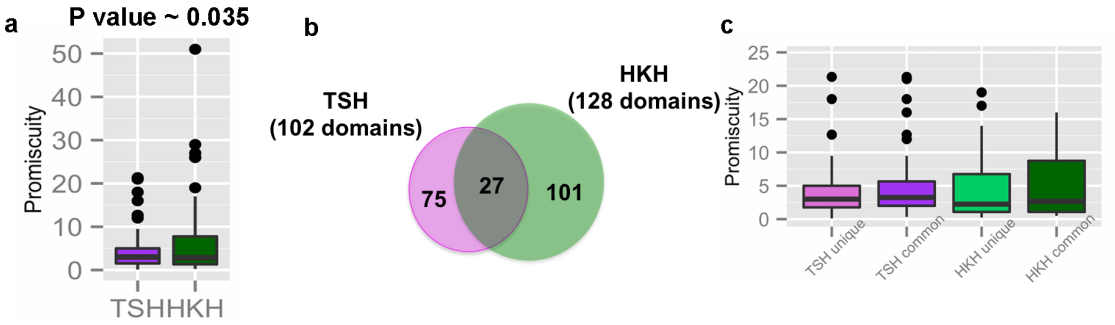

Fig S2. Promiscuity of Interacting Domains of TSHs and HKHs in supportive tissue-specific networks. (a) Box-plot depicting promiscuity of interacting domains of TSHs and HKHs. Interacting domains of HKHs are more promiscuous than TSHs (P-value 0.035). (b) Venn Diagram showing overlap between the interacting domains of TSHs and HKHs. Almost 79% of HKHs domains are unique to HKH proteins whereas 74% of TSHs domains are unique to TSH proteins. (c) Boxplot showing promiscuity of TSH and HKH proteins possessing unique domains and shared domains. HKH proteins and TSH proteins possessing shared domains are more promiscuous than HKH proteins and TSH proteins possessing unique domains (P-value < 0.05) (Wilcoxon Ranksum test).

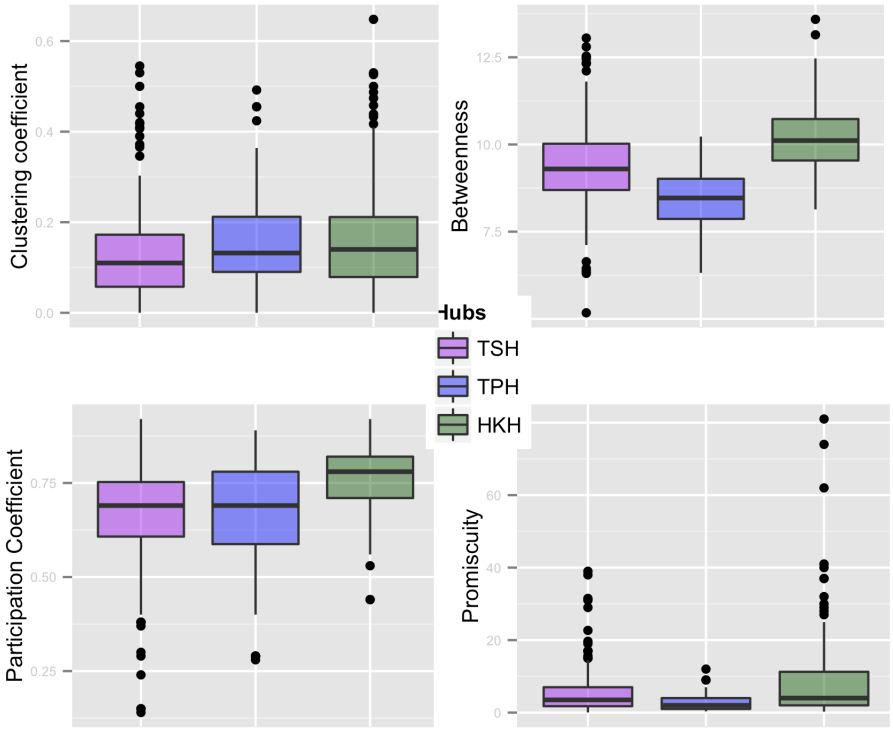

Fig S3. Clustering coefficient, betweenness, participation coefficient and promiscuity of TSHs, TPHs and HKHs. (a) Boxplot showing distribution of clustering coefficient of TSHs, TPHs and HKHs. TPHs and HKHs show higher clustering coefficient values as compared with TSHs (P value ~ 0.014) (b) Boxplot showing distribution of log transformed betweenness value of TSHs, TPHs and HKHs. HKHs show maximum betweenness compared with TSHs and TPHs (P value ~ 8.87e-13). (c) Boxplot showing distribution for participation coefficient of TSHs, TPHs and HKHs. HKHs are associated with maximum participation coefficient than TSHs and TPHs (P value < 5.97e-07). (d) Boxplot showing distribution of promiscuity of interacting domains of TSHs, TPHs and HKHs. Interacting domains of TPHs are least promiscuous compared with TSHs and HKHs (P value ~ 0.009) (Kolmogorov-Smirnov test).

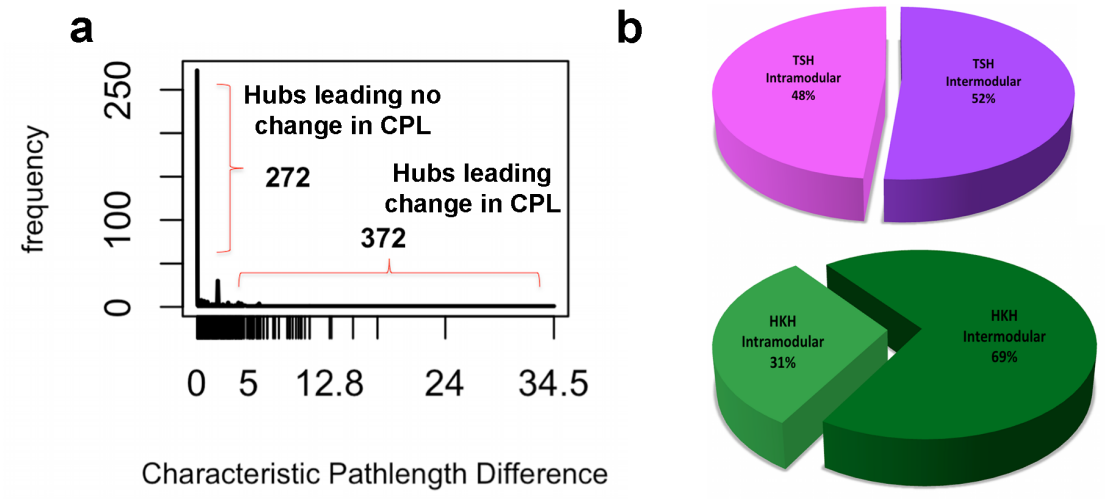

Fig S4. Effect of node removal on Characteristic Pathlength in supportive tissue-specific networks (a) Plot showing frequency of hubs of tissue-specific networks leading change and no change in the characteristic path length of the network. (b) Pie-charts showing fraction of TSHs (left) and HKHs (right) leading change and no change in the characteristic path length of the network. Of the 97 TSHs, 47 were TSH intramodular and 50 were TSH intermodular. Similarly, of the 126 HKHs, 39 were HKH intramodular and 87 were HKH intermodular.

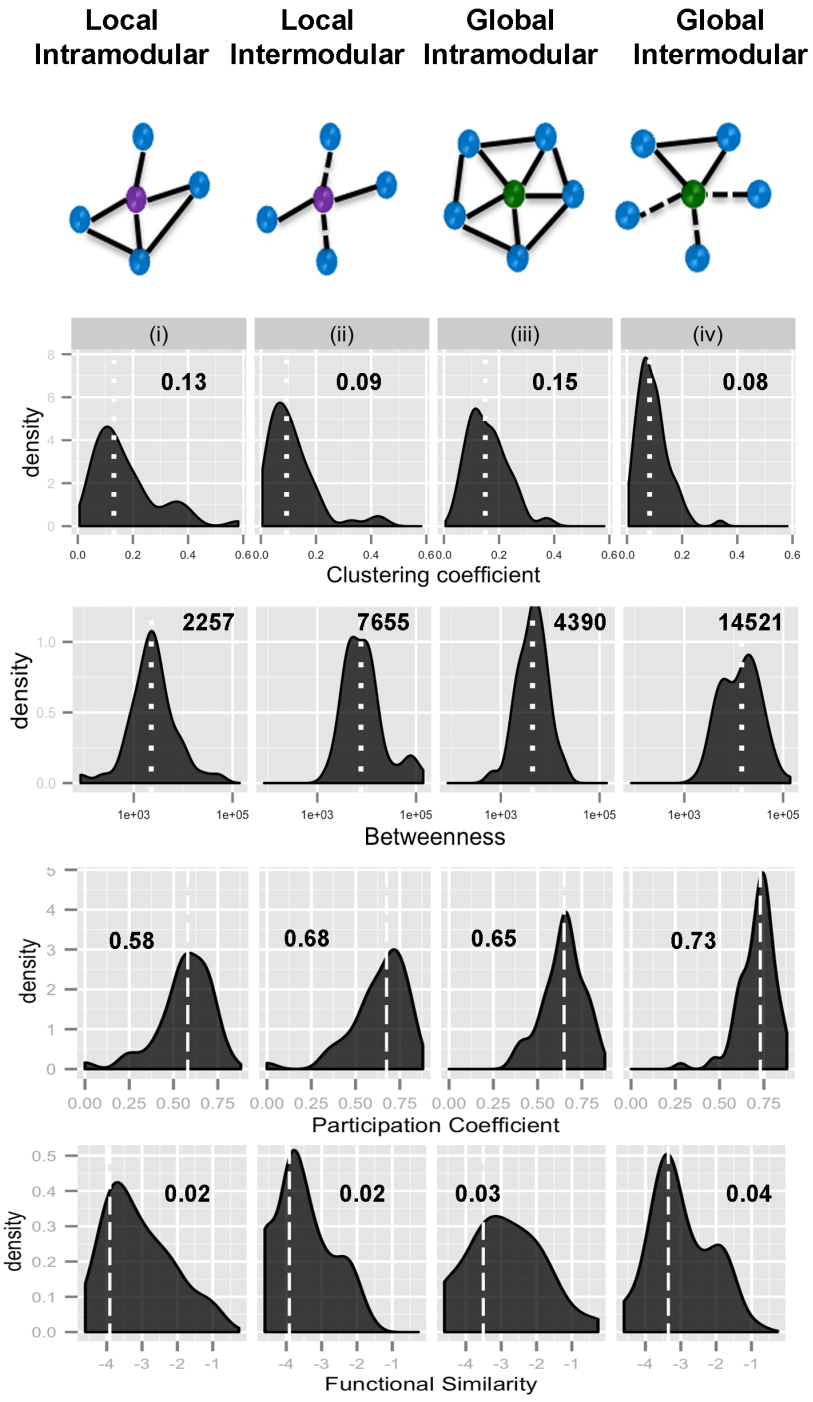

Fig S5. Different measures for intermodular and intramodular TSHs and HKHs in supportive tissue-specific networks. TSHs and HKHs consist of two classes of hubs. TSHs leading no change in characteristic pathlength (local intramodular hubs) are having more interconnected partners than TSHs leading change in characteristic pathlength (local intermodular hubs) (P-value 0.0015). Similarly, HKHs leading no change in characteristic pathlength (global intramodular hubs) are having more interconnected partners than HKHs leading change in characteristic pathlength (global intermodular hubs) (P-value 3.92e-07). Intermodular TSHs are associated with higher betweenness compared with intramodular TSHs (P-value

4.671e-09). Similarly, intermodular HKHs are also associated with higher betweenness compared with intramodular HKHs (P-value 2.104e-09). Both intermodular TSHs and intermodular HKHs show higher participation coefficient than intramodular TSHs (P value 0.0033) and intramodular HKHs (P value 0.0004), respectively. Intermodular HKHs also show less functional similarity with their partners than intramodular HKHs (P value 2.2e-5) (Median values are shown with dashed lines) (Wilcoxon Ranksum test).

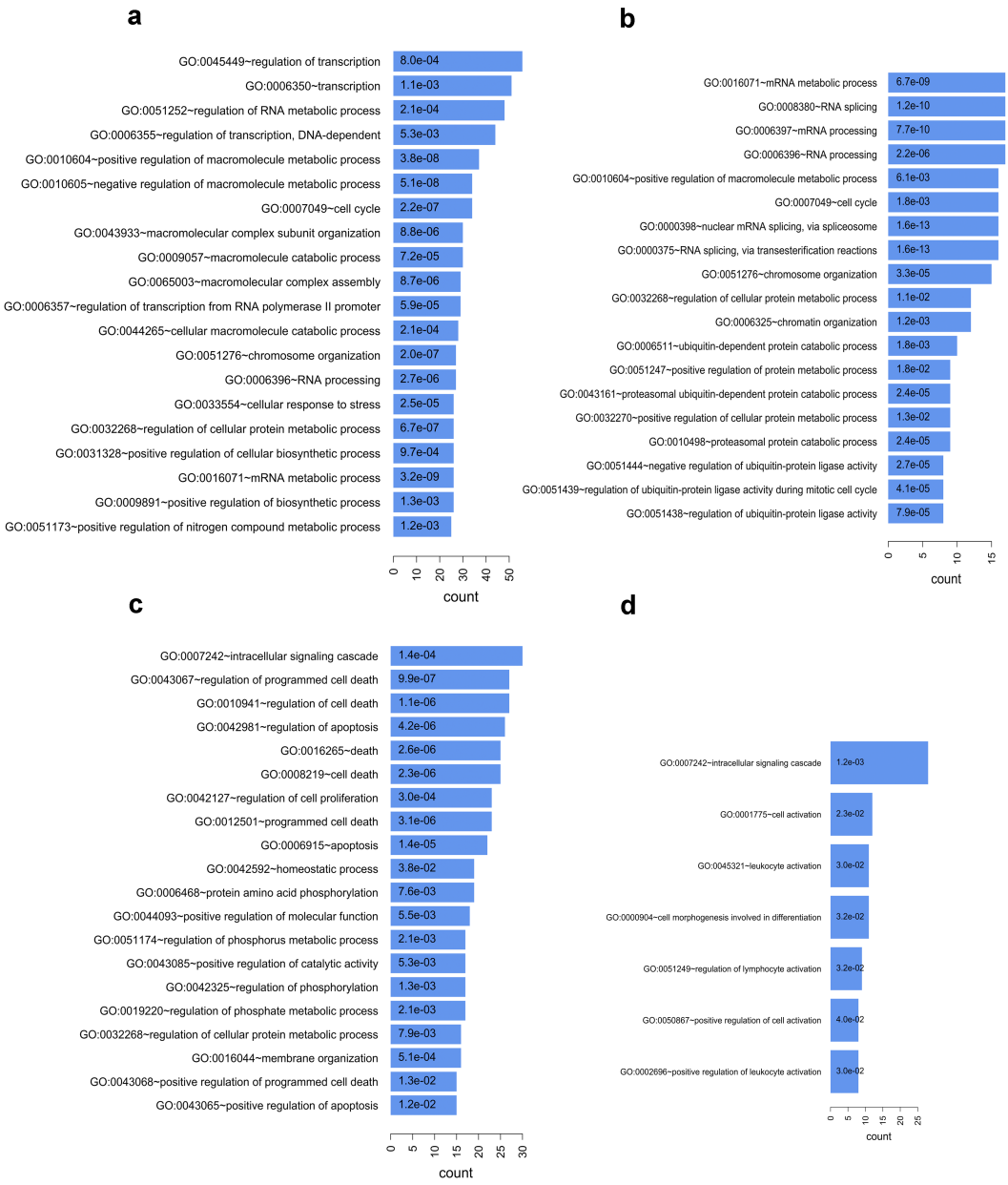

Fig S6. Biological Processes enriched in proteins involved in (a) Intermodular HKH (b) Intramodular HKH (c) Intermodular TSH (d) Intramodular TSH by performing DAVID functional enrichment analysis.

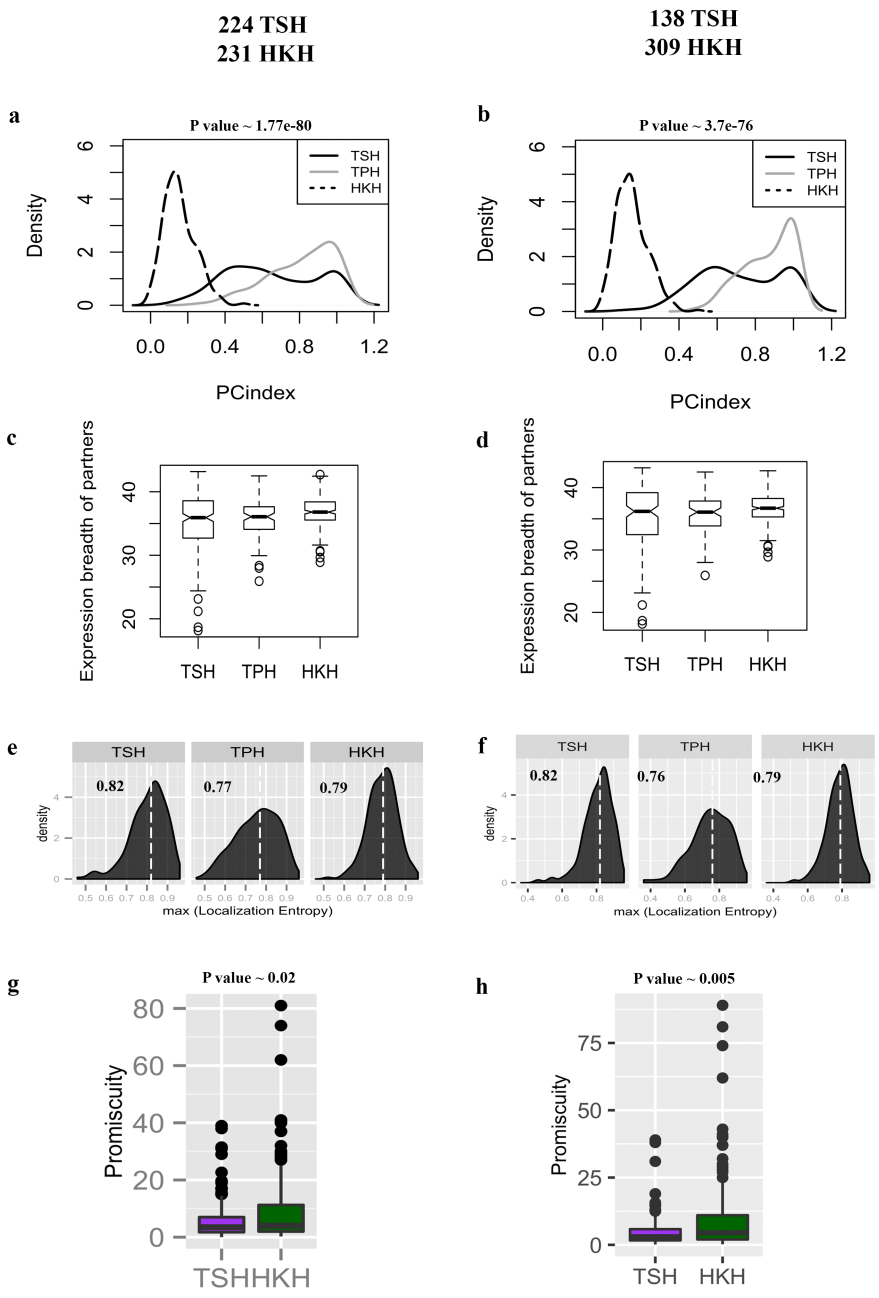

Fig S7. Comparison of properties of TSH and HKH with two different cut-offs used to define TSH and HKH. Figures 2a,c, e and g are plots with the cut-off used in the present study to define TSH and HKH TSH are hubs expressed in <= 10 tissues (~23%) and HKH are hubs expressed in >= 40 tissues (~91%). Figure 2b,d,f and h are plots with a new cut-off to define TSH and HKH. TSH are hubs expressed in <= 6 tissues (~14%) ad HKH are hubs expressed in >= 38 tissues (~86%) matching those used in the previous study (Kiran and Nagarajaram, 2013). (a,b) Density plots of PCindex of TSHs (solid, black), TPHs (solid, grey) and HKHs (long dash, black) showing TPHs having more conserved partners compared with TSHs and HKHs. Among TSHs

and HKHs, TSHs show higher PCindex than HKHs (c,d) Boxplots depicting distribution of expression breadth (number of tissue the protein is expressed) of partners of TSHs, TPHs and HKHs. The expression breadth of partners of HKHs is more than TSHs (P-value < 2.2e-16) (Kolmogrov-Smirnov test). The partners of TPHs are mostly tissue-specific proteins. (e-f) Density plots of max (Localization Entropy) of TSHs, TPHs and HKHs. The dashed line shows median value for TSHs, TPHs and HKHs. TSHs show higher localization entropy than HKHs (P-value 0.0004) (Wilcoxon Ranksum test). (g-h) Box-plot depicting promiscuity of interacting domains of TSHs and HKHs. Interacting domains of HKHs are more promiscuous than TSHs (P-value 0.02). (Kolmogrov-Smirnov test).

Table S1: Evolutionary rate (dN) for intramodular/intermodular TSHs and HKHs.

dN	**Intramodular TSH (0.05)**	**Intermodular TSH (0.03)**
Intramodular HKH (0.02)	0.0005	0.009
Intermodular HKH (0.02)	6.7e-05	0.0007

Note: Table showing median values for dN for intramodular TSHs, intermodular TSHs, intramodular HKHs and intermodular HKHs. The values in the boxes are P values corresponding for each pair wise two-sample Wilcoxon rank-sum test. The dN values for human genes were downloaded from BioMart (www.ensembl.org/biomart/martview) which have been estimated with respect to mouse (Mus Musculus) orthologs.