Supplementary Tables

Supplementary Table 1 Homology search for isoforms without Pfam domain prediction

Sequence similarity search was done against mouse proteins for isoforms without Pfam annotation from single-isoform units and multiple-isoform clusters. Values from the second to the last column are the average of the best hit match scores. The differences in length and identity are statistically significant (p << 0.0001, and p = 0, respectively). For sequence similarity analysis, Sserach was used.

Ssearch	Total protein	Avg of length(aa)	Avg of E-value	Avg of identity (%)
si-TUX	9105	124	2.17	38
mi-TUX	2247	498	0.41	68

Supplementary Table 2 Collection of PPIs

Integrated PPIs [a]		High-confident PPIs [b]		PPIs mapped to Clusters [c]		PPIs with DDI [d]	
# of PPIs	**# of proteins**	**# of PPIs**	**# of proteins**	**# of PPIs mapped**	**# of proteins in mapped PPIs**	**# PPIs with DDI**	**# of proteins in PPI with DDI**
43104	10484	29761	8872	28309	8522	7805	4202

[a] Integrated PPIs: PPIs which were not singly detected by Y2H methods

[b] High-confident PPIs: PPIs generated by the low-throughput screen or supported by more than one literature

[c] PPIs mapped to Clusters: PPIs in which both interacting proteins are present in any cluster as an isoform

[d] PPIs with DDI: PPIs in which at least one combination of interacting domains from each interacting proteins is present a known DDI

Supplementary Table 3 A review of the literature identifies 22 genes with variation that effects binding

Gene symbol	PubMed	Splicing mechanism	Consequence
ADAM15	15263807	• Alternative splicing	Binding differentiation
MACF1	21041478	• Alternative splicing • Tissue-specific internal promoters	Binding differentiation
NRXN3	7736595	• Alternative promoter • Alternative splicing	Binding differentiation
PPP1R8	10103062 10564811	• Alternative promoter	Binding differentiation
KDR	20961309	• Alternative splicing	Binding differentiation
TNFRSF1B	14688072	• Alternative splicing	Binding differentiation
TRAF2	9461607	• Alternative splicing	Binding differentiation
VEGFA	21041478 11427521 15520188	• Alternative promoter usage • Alternative splicing	Binding differentiation
USH2A	14676276	• Alternative splicing	Binding differentiation
UMOD	14531790	• Alternative splicing	Binding differentiation
NUMB	21041478	• Alternative splicing	Impact on PPI not identified
APP	21041478	• Alternative splicing	Impact on PPI not identified
JAK2	20730051	• Alternative splicing	Impact on PPI not identified
YTHDC1	20686370	• Alternative splicing	Impact on PPI not identified
PLEC	14672974	• Alternative promoter	Impact on PPI not identified
CACNA1B	20852623	• Alternative splicing	Impact on PPI not identified
BRCA-1	8972225	• Alternative promoter • Alternative splicing	location differentiation
CSF-1	3500041	• Alternative splicing	location differentiation
RBM9	20042473	• Auto-regulation	RNA binding differentiation
TPM1	3336363	• Alternative splicing	Tissue differentiation
PTPN22	21044313	• Alternative splicing	Tissue differentiation
MID1	18005432	• Tissue-specific usage of the alternative polyadenylation sites • Alternative promoters	Tissue differentiation

Supplementary Table 4 Proteins mapped to clusters

Interacting proteins were mapped to isoform clusters based on the exact sequence match and Entrez Gene ID.

Protein set	**# of proteins**
Proteins mapped to cluster based on sequence similarity	5827
Proteins mapped to cluster based on GeneID	2757
Unmapped proteins	288
Total	8872

Supplementary Table 5 Transcript datasets

Transcript units from two transcriptome datasets (H-InvitationalDB and FANTOM3) were used in this study. The second column addresses the total number of transcriptional units for each dataset, and the third and fourth columns address the number of transcriptional units according to the orientation on the human genome for forward and reverse direction respectively.

	Transcript cluster	**FORWARD set**	**REVERSE set**
# of HIX [a]	18513	9329	9184
# of TU [b]	21480	10790	10690
Total	39993	20119	19874

[a] H-Invitational cluster (HIX) in H-Invitational DB (H-Inv)

[b] Transcriptional unit (TU) in FANTOM3