Table S1 Experimentally validated PTM cross-talk pairs collected from the literature (data format, Microsoft Excel).
The "relationship" between two PTM sites in the table is a brief summary of the cross-talk mechanism from the literature. In the case that relationship is directed, such as "facilitate" and "inhibit", the direction is from the first site to the second site. The detailed information can be found in the provided reference.

Table S2 The occurrence of the PTM type combinations in compiled PTM cross-talk pairs.

Numbers	O-GlcNAcylation	SUMOylation	Acetylation	Methylation	Phosphorylation	Ubiquitination
O-GlcNAcylation	0	0	1	0	7	1
SUMOylation		0	0	0	23	5
Acetylation			0	22	25	0
Methylation				7	22	0
Phosphorylation					73	7
Ubiquitination						0
Total	9	28	48	51	157	13

Table S3 The eight well-known PTM cross-talk motifs and matched PTM pairs in the cross-talk and control sets (data format, Microsoft Excel).

Table S4 The 81 putative PTM cross-talk motifs identified using the bioinformatics approach by Peng et al. (data format, Microsoft Excel).

Table S5 The cross-talk and control PTM pairs matched to the putative motifs in Table S4 (data format, Microsoft Excel).

Table S6 Predicting PTM cross-talk for all pairwise combination of known PTM sites on p53 using the integrated model trained from the PTM pairs of all other proteins (data format, Microsoft Excel).
For each PTM pair, the table provides the measures of the five features used to build the naïve Bayes classifier and the posterior probability of cross-talk.

Figure S1 Distribution of sequence distances of the cross-talk and the distance control sets.
(A) The distribution of sequence distances of the cross-talk set.
(B) The distribution of sequence distances of the distance control set. This set was re-sampled from the control pairs, and the distribution of its sequence distances is similar to that of cross-talk pairs.

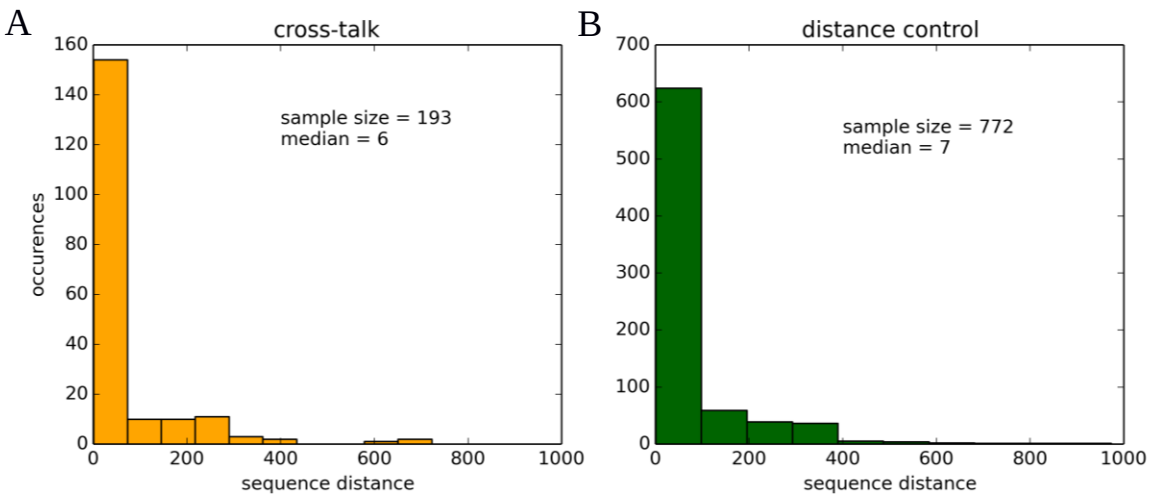

Figure S2 Distribution of the number of PubMed papers of low-throughput (LTP) experiments in the cross-talk set (A) and the function control set (B).

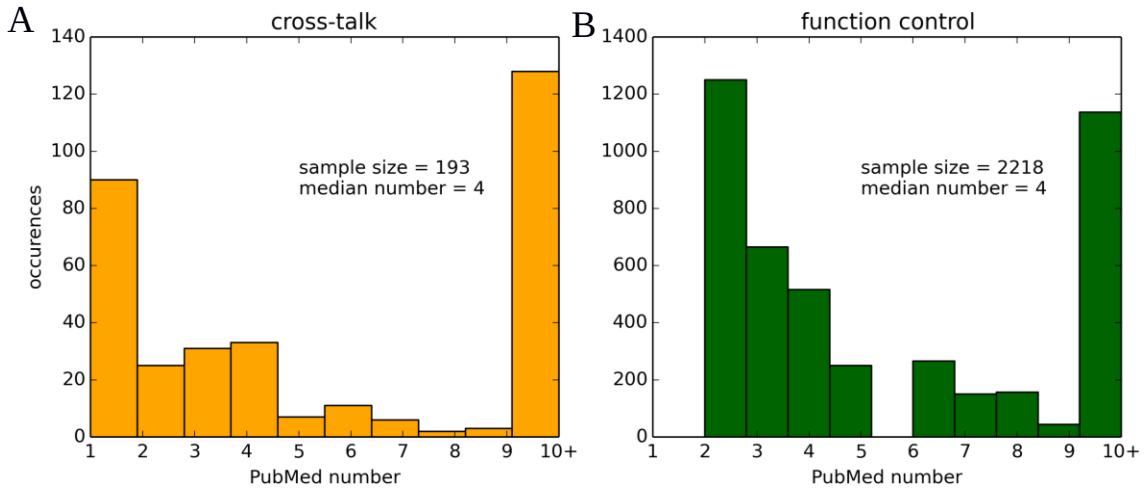

Figure S3 Examples of prediction results using the online sever.
(A) The results table shows the five features, i.e., sequence distance (distance_1d), structural distance (distance_3d), residue co-evolution (residue_co), modification co-evolution (modify_co), co-localization within the same disordered region (disorder) and the posterior probability of cross-talk (prediction_score) for each input PTM pair.
(B) The ROC curve of the 10-fold cross-validation, and FPR and TPR associated with the selected prediction score as the cutoff.

A

protein	site1	PTM1	site2	PTM2	distance_1d	distance_3d	disorder	residue_co	modify_co	prediction_score
P04637	K372	methylation	K370	methylation	2	6.135	1	0.701	0.667	0.994
P04637	S15	phosphorylation	T18	phosphorylation	3	7.254	0	0.740	1.000	0.985
P04637	S37	phosphorylation	S46	phosphorylation	9	17.333	0	0.563	0.333	0.454
P04637	K101	ubiquitination	S106	phosphorylation	5	15.290	0	0.421	0.333	0.356
P04637	K101	ubiquitination	K120	acetylation	19	32.644	0	0.327	0.333	0.056
P04637	S106	phosphorylation	S371	phosphorylation	265	nan	0	0.463	0.333	0.030

B

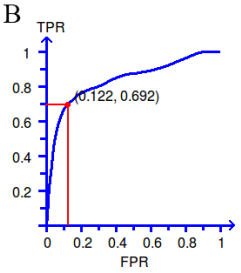

Figure S4 Comparing the residue co-evolution between the cross-talk and control pairs using two alternative measures of residue co-evolution.
(A) Comparing the residue co-evolution scores of the cross-talk and different control PTM sets, measured by 1-nHMdist. The p-values are based on the permutation test.
(B) Comparing the residue co-evolution scores of the cross-talk and different control PTM sets, measured by nCoMBL. The p-values are based on the permutation test.
(C) The ROC curve of ten-fold cross-validation for the models using residue co-evolution alone or integrated with other four features as in Figure 4. The residue co-evolution was measured by 1-nHMdist or nCoMBL.

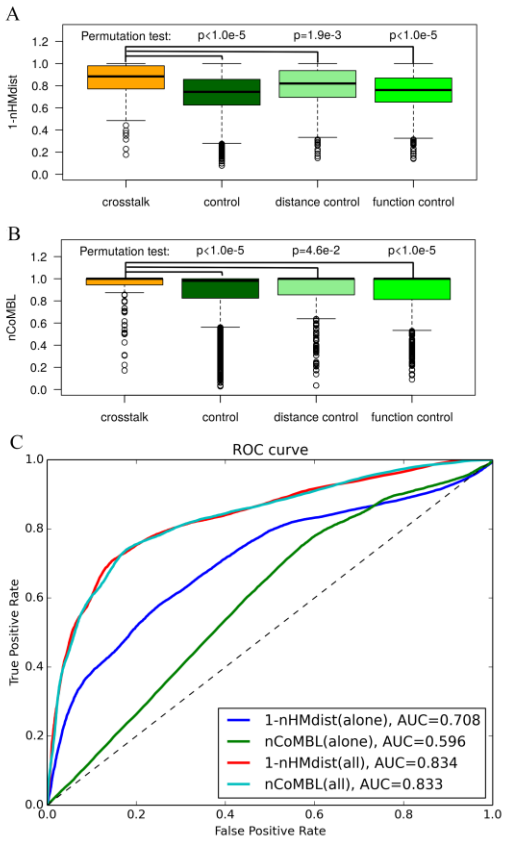

Figure S5 Distribution of modification co-evolution scores and prediction performance using imputed PTM status.
(A) Comparing the modification co-evolution scores of the cross-talk and different control sets with imputed PTM status.
(B) The ROC curve of the ten-fold cross-validation for the integrated model using imputed PTM states to measure modification co-evolution and the model that using modification co-evolution alone.

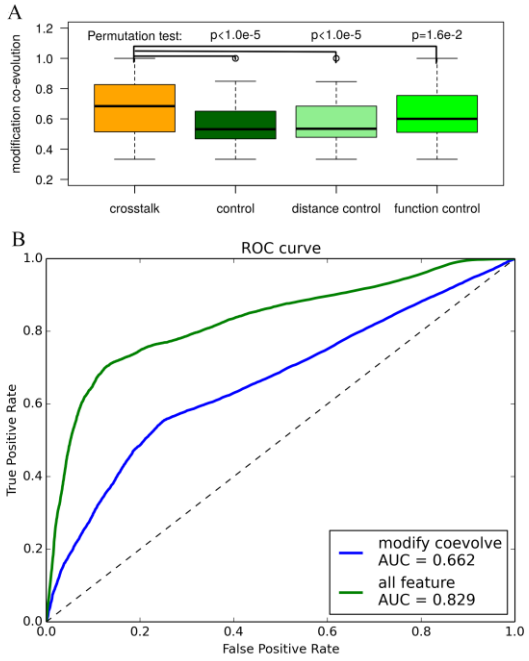

Figure S6 The PTM cross-talk network on p53, where each node denotes a PTM site and each edge denotes a cross-talk event between two PTM sites.

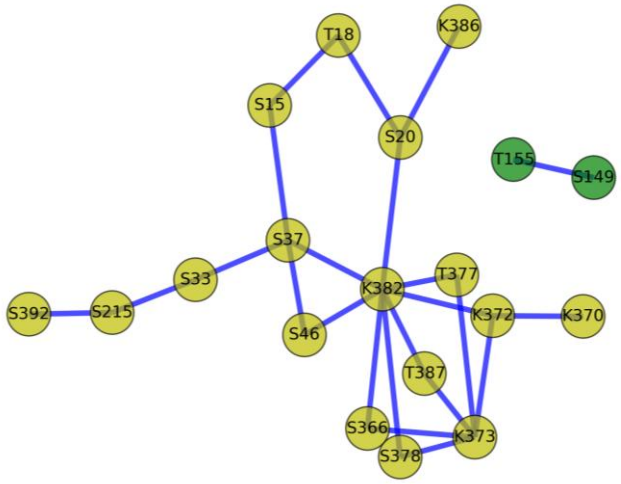

Figure S7 The probability density of the fraction of observed PTM sites and the fraction of observed and surrogate PTM sites in human, mouse and rat. A surrogate PTM site for a species is defined as a site whose orthologous residue in some other species is modified, and the sequence context (-4 to +4 amino acid) is the same as that species.