

Table S6: Statistical significance for the evolutionary path analysis

Domain	co-appearance	Stepwise appearance	Statistical significance
<i>WW^{Class IV} (phosphorylation near the motif)</i>			
Expected	12	65	p=2e-7
Observed	37	40	
<i>WW^{Class IV} (phosphorylation within the motif)</i>			
Expected	15	37	p=0.005
Observed	28	24	
<i>SH2 (phosphorylation near the motif)</i>			
Expected	21	76	p=6.3e-6
Observed	46	51	
<i>SH2 (phosphorylation within the motif)</i>			
Expected	8	19	<i>insignificant</i>
Observed	15	12	
<i>PDZ (phosphorylation near the motif)</i>			
Expected	6	31	p=0.0162
Observed	16	21	
<i>PDZ (phosphorylation within the motif)</i>			
Expected	4	16	p=0.0062
Observed	12	8	
<i>WW^{Class I/II/III} (phosphorylation near the motif)</i>			
Expected	5	21	<i>insignificant</i>
Observed	6	20	
<i>WW^{Class I/II/III} (phosphorylation within the motif)</i>			
Expected	6	13	p=1.73e-5
Observed	15	4	
<i>SH3 (phosphorylation near the motif)</i>			
Expected	14	86	p=1.29e-5
Observed	38	62	
<i>SH3 (phosphorylation within the motif)</i>			
Expected	3	23	<i>insignificant</i>
Observed	7	19	

The expected and observed counts of the two possible evolutionary paths were computed for all domain-motif types, either within or near the motif. The detailed procedure is presented in the Methods section in the main text. Statistical significance was computed using χ^2 test with Yates correction (results were corrected for multiple testing using Bonferroni correction).