Figure S1

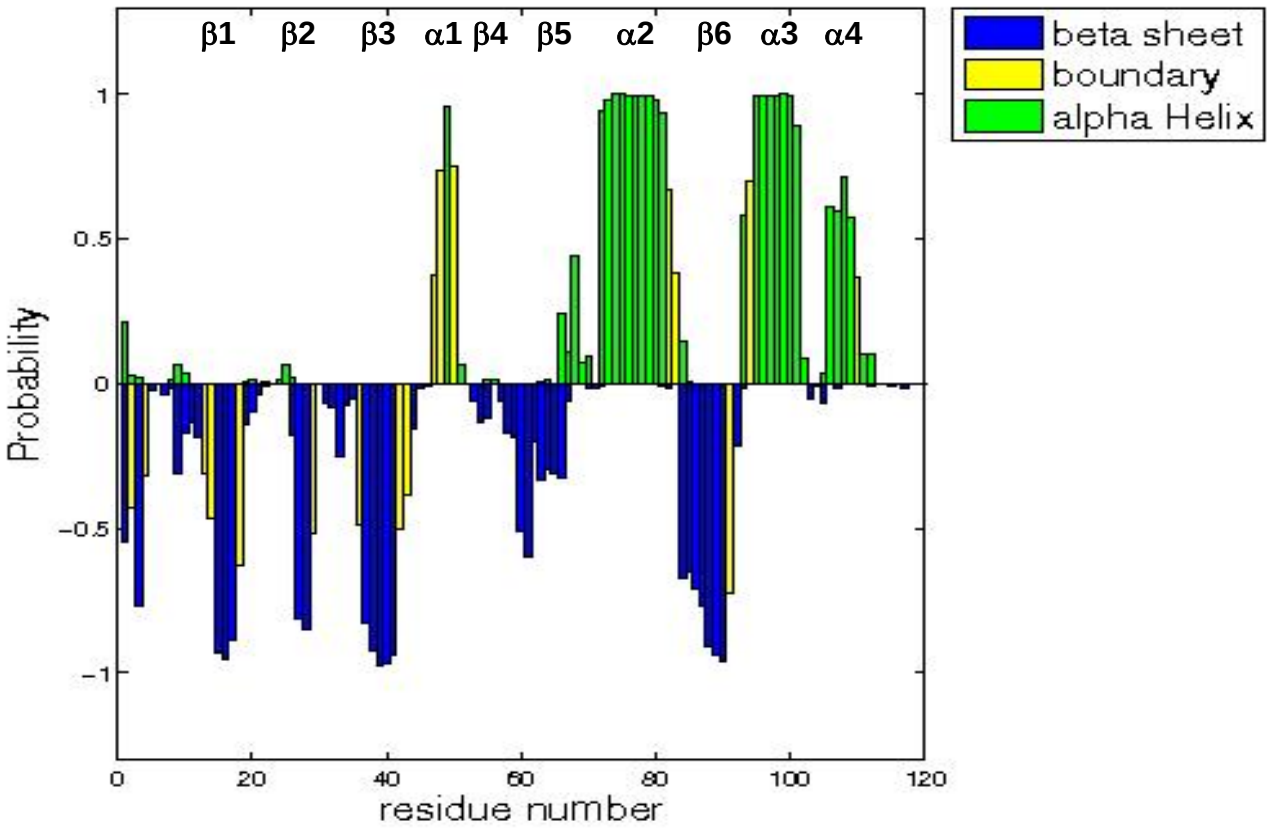

Figure S1: (A) Chemical Shift Index of mutant PDZ1^{120} (Glu61->Gly61) obtained from PECAN analysis.

Figure S2

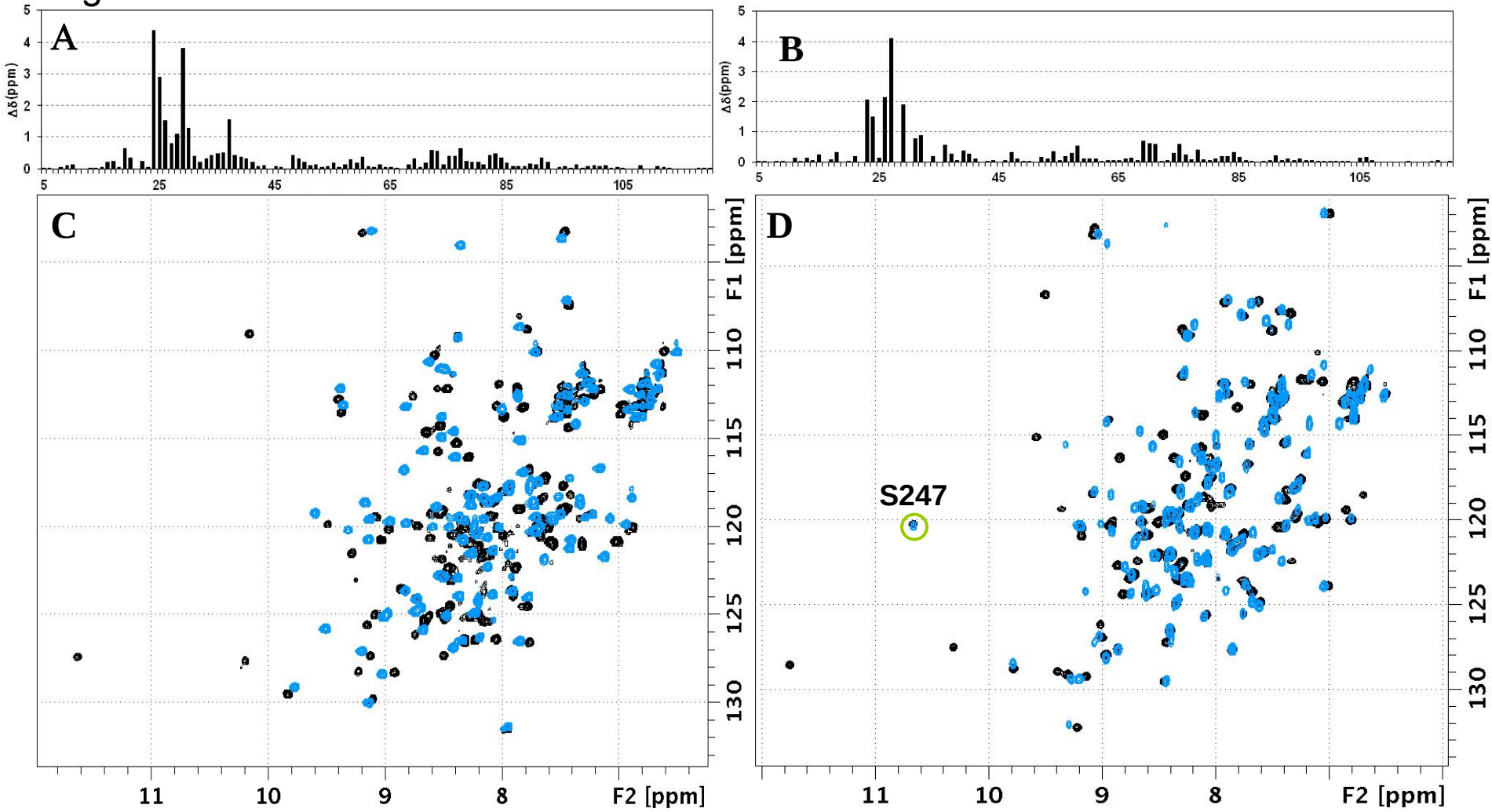

Figure S2: Chemical shift difference plot between the free and CFTR-C peptide bound (A) PDZ1^{120} and (B) PDZ2^{270} domains. The weighted difference was calculated using the relation $\Delta = \sqrt{(\delta HN)^2 + (\delta N/5)^2}$. Corresponding overlay of ^{15}N-HSQC spectra: (C) PDZ1^{120} and (D) PDZ2^{270} domain in the presence (black) and absence of CFTR-C peptide (blue) at 288 K. Typical protein concentrations are 400 μM complexed with 1-2 fold excess peptides in buffer at pH 7.5.

Figure S3

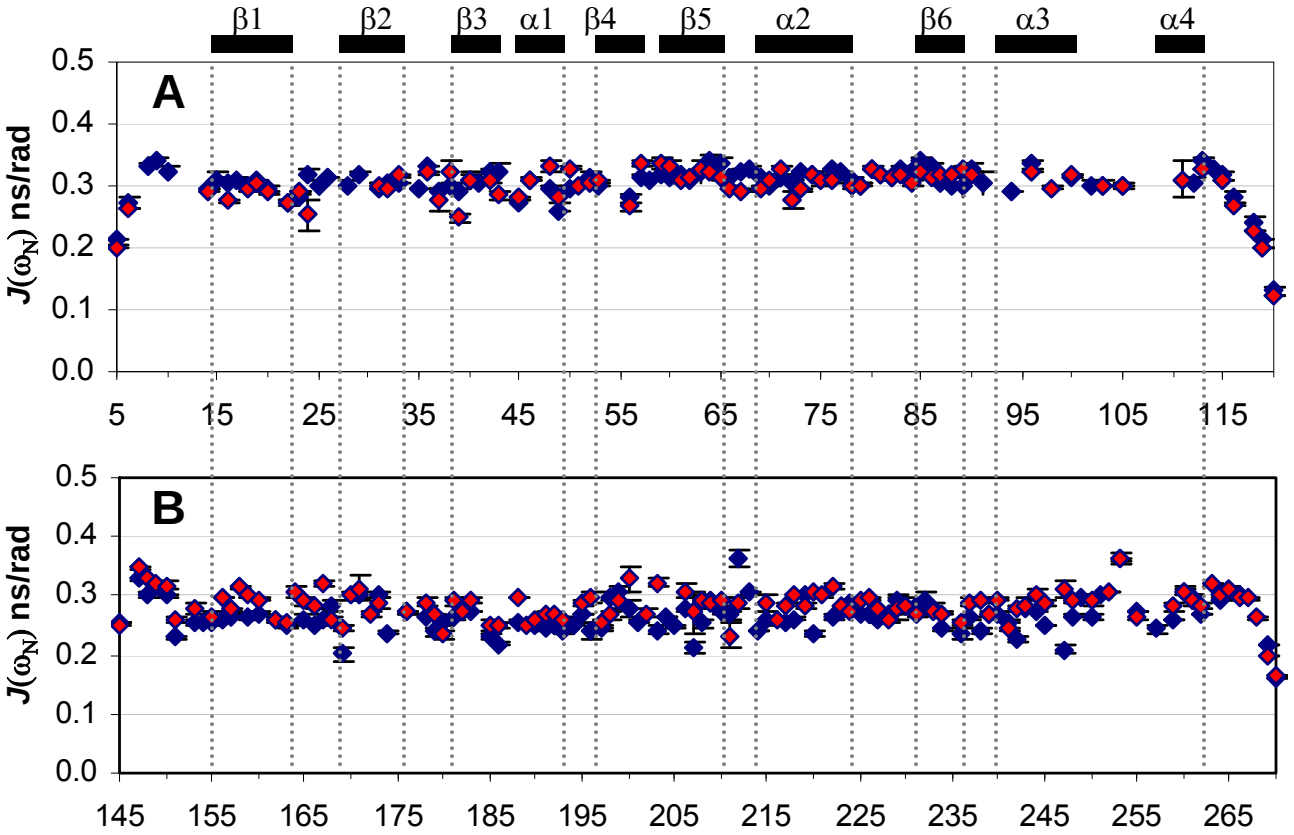

Figure S3: Spectral density function of apo (A) PDZ1^{120} and (B) PDZ2^{270} domain at nitrogen frequency, $J(\omega_N)$, calculated from relaxation measurements at 500 MHz in the presence (red) and absence of CFTR-C peptide (blue).

Figure S4

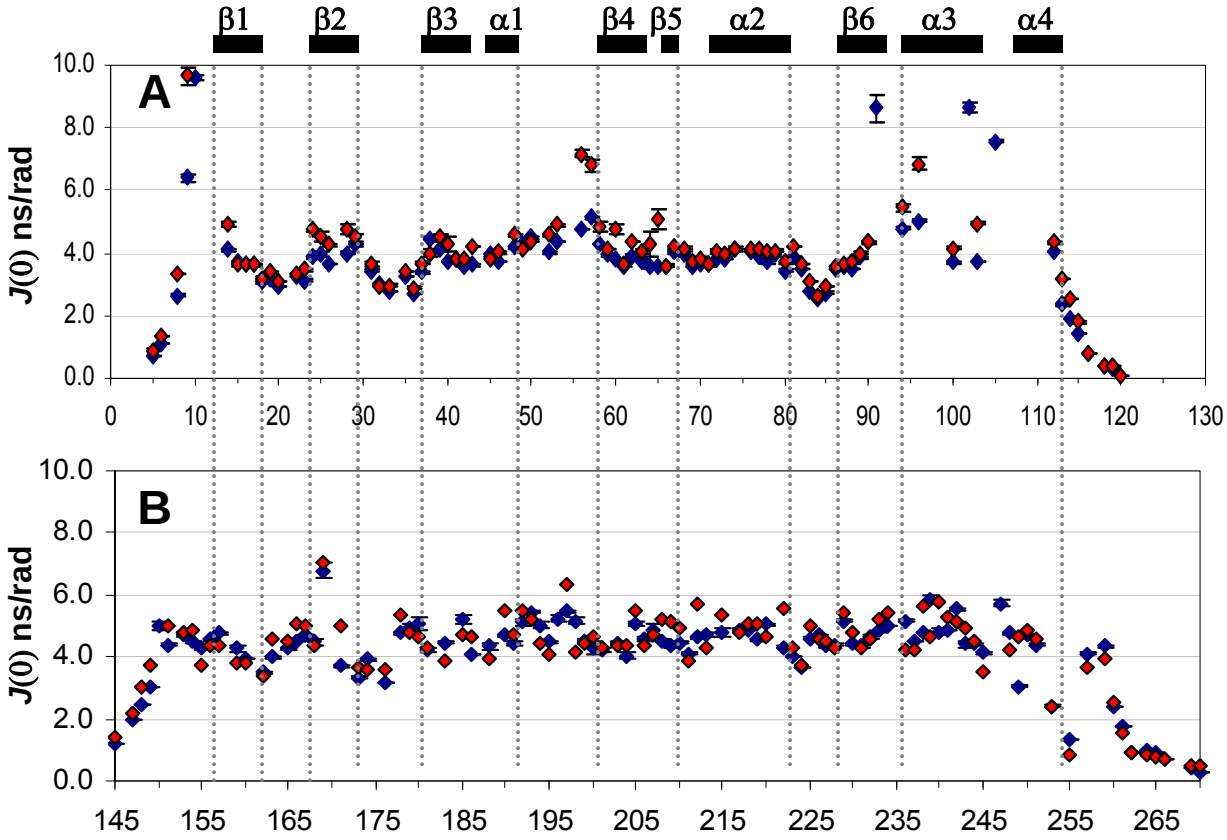

Figure S4: Spectral density function of apo (A) PDZ1^{120} and (B) PDZ2^{270} domain at zero frequency, $J(0)$, calculated from relaxation measurements at 500 MHz (blue) and 900 MHz (red).

- Position weight matrices calculated from protein sequence at website (http://sbi.postech.ac.kr/pdz/) authored by Sanguk Kim.

PDZ1 domain Specificity Prediction

RESULTS

Query sequence

```
GIDPFTLPRL CCLEKGPNGY GFHLHGEKGK LGQYIRLVEP GSPAEKAGLL AGDRLVEVNG
ENVEKETHQQ VVSRIRAALN AVRLLVVDPE TDEQLQKLGV QVREELLRAQ EAPGQA
```

Alignment & Pocket residues

```
Reference reprRIVIHRGSTGLGFNIVGGEDGEGIFISFILAGGPADLSGELRKGDQILSVNGVDLRNASHEQAAIALKNAGQTVTIIAQykp
Query     tlprLCCLEKGPNGYGFHLHGEKGKLGQYIRLVEPGSPAEKAG-LLAGDRLVEVNGENVEKETHQQVVSRIRAALNAVRLLVVdpe
Pocket -3 -----------------*-*----------**-------------------------------------------------------- (HHRL )
Pocket -2 ------------------*-----------------------------------------------**--*--*--------------- (LHQVI )
Pocket -1 ----------------**-------------*-------------------------------------*----------------- (FHLR )
Pocket  0 ----------------*-*-------------------------------------------------*--**--------------- (FLVIR )
```

PWM

Position	A	V	L	I	P	M	F	W	G	S	T	C	N	Q	Y	D	E	K	R	H
-3	1.8	0.3	1.2	2.9	-0.5	-2.1	-2.1	1.9	-2.1	-2.1	1.0	-2.1	0.6	0.9	-2.1	1.7	3.1	-2.1	-2.1	1.1
-2	-2.1	-0.7	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	0.3	4.6	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	0.3	-2.1	-2.1
-1	-2.1	-0.5	3.4	1.6	0.1	-0.5	2.2	2.4	-2.1	-1.2	-2.1	-2.1	-2.1	-2.1	0.5	2.8	-0.8	0.3	2.2	-0.1
0	-2.1	-0.5	4.3	-0.5	-2.1	-0.5	2.7	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1

PDZ2 domain Specificity Prediction

Submission | **Instructions** | **Contact**

RESULTS

Query sequence

```
GIDPFTLRPR LCTMKKGPSG YGFNLHSDKS KPGQFIRSVD PDSPAEASGL RAQDRIVEVN
GVCMEGKQHG DVVSAIRAGG DETKLLVVDR ETDEFFKKCR VIPSQEHLNG PLPVPFTNGE
IQKENSR
```

Alignment & Pocket residues

```
Reference reprRIVIHRGSTGLGFNIVGGEDGEGIFISFILAGGPADLSGELRKGDQILSVNGVDLRNASHEQAAIALKNAGQTVTIIAQykp
Query     lrprLCTMKKGPSGYGFNLHSDKSKPGQFIRSVDPDSPAEASG-LRAQDRIVEVNGVCMEGKQHGDVVSAIRAGGDETKLLVVdre
Pocket -3 ------------------*-*----------**-------------------------------------------------- (NHRS)
Pocket -2 ------------------*-------------------------------------------**--*--*--------------- (LHGVI)
Pocket -1 ----------------**-------------*-----------------------------------*---------------- (FNSA)
Pocket  0 ----------------*-*-------------------------------------------*--**-------------- (FLVIR)
```

PWM

Position	A	V	L	I	P	M	F	W	G	S	T	C	N	Q	Y	D	E	K	R	H
-3	-0.5	0.4	0.9	2.2	-0.6	-2.1	-2.1	1.3	-2.1	3.8	0.9	-2.1	0.4	0.4	-2.1	2.7	1.2	-2.1	-2.1	-2.1
-2	-2.1	-0.7	-2.1	-2.1	-2.1	-2.1	-0.5	-2.1	-2.1	1.9	4.5	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1
-1	0.3	-2.1	0.1	0.1	-2.1	1.1	0.7	4.0	-2.1	1.4	1.5	-2.1	0.6	0.3	1.1	-0.7	0.3	0.3	1.6	1.1
0	-2.1	-0.5	4.3	-0.5	-2.1	-0.5	2.7	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1	-2.1