

**Supplementary Table S1.** Origin of variants.

PDB ID	Protein function	No of variants	Technique	Reference
Data from (Huang and Gromiha 2010)				
1APS	acylphosphatase	24	stopped-flow fluorimeter	(Chiti et al. 1999)
1FKB	FKBP12	34	stopped-flow fluorimeter	(Fulton et al. 1999)
1IMQ	colicin e9 immunity protein	32	stopped-flow fluorimeter	(Friel et al. 2003)
1N88	ribosomal protein L23	17	stopped-flow fluorimeter	(Hedberg and Oliveberg 2004)
2ABD	acyl-CoA binding protein	30	stopped-flow fluorimeter	(Kragelund et al. 1999)
2CI2	serine proteinase inhibitor	68	stopped-flow fluorimeter	(Itzhaki et al. 1995)
2PTL	immunoglobulin light chain-binding domain of protein L	68	stopped-flow fluorimeter	(Kim et al. 2000)
3GB1	B1 domain of streptococcal protein G	31	continuous flow and stopped-flow fluorimeter	(McCallister et al. 2000)
1AJ3	spectrin repeat	2	stopped-flow cd and fluorimeter	(Scott et al. 2004)
1SCE	cell cycle regulatory protein SU	56	stopped-flow fluorimeter	(Schymkowitz et al. 2000)
1TEN	fibronectin type III domain from tenascin	39	stopped-flow fluorimeter	(Hamill et al. 2000)
1TIT	titin Ig repeat	26	stopped-flow fluorimeter	(Fowler and Clarke 2001)
1BNR	barnase	19	stopped-flow fluorimeter	(Vu et al. 2004)
1HMK	$\alpha$ -lactalbumin	17	stopped-flow cd	(Saeki et al. 2004)
Data from (Naganathan and Muñoz 2010)				
1CSP	major cold chock protein	22	stopped-flow fluorimeter	(Garcia-Mira et al. 2004)
1DIV-C	ribosomal protein L9	24	stopped-flow fluorimeter	(Li et al. 2007)
1DIV-N	ribosomal protein L9	14	stopped-flow fluorimeter	(Anil et al. 2005)
1E0L	FBP28WW domain	45	temperature jump fluorimeter	(Petrovich et al. 2006)
1FMK	tyrosine-protein kinase c-SRC	57	stopped-flow fluorimeter	(Riddle et al. 1999)
1O6X	imidazole glycerophosphate synthase	18	stopped-flow fluorimeter	(Villegas et al. 1998)
1RFA	RAS-binding domain of c-RAF-1	47	stopped-flow fluorimeter	(Campbell-Valois and Michnick 2007)

1SHF	SH3 domain of FYN	34	stopped-flow fluorimeter	(Northey et al. 2002)
1SHG	SH3 domain of spectrin	14	stopped-flow fluorimeter	(Martínez and Serrano 1999)
1SS1	protein A, B-domain	63	temperature-jump fluorimeter	(Sato and Fersht 2007)
1SSO	thermostable protein	23	stopped-flow fluorimeter	(Guerois and Serrano 2000)
1ST7	acyl-CoA binding protein	18	stopped-flow fluorimeter	(Teilum et al. 2005)
1UBQ	ubiquitin	27	stopped-flow fluorimeter	(Went and Jackson 2005)
1W4E	peripheral-subunit binding domain	22	stopped-flow fluorimeter	(Ferguson et al. 2006)
1W4J	peripheral-subunit binding domain	22	temperature jump fluorimeter	(Sharpe et al. 2008)
1YYJ	apocytochrome B562	39	stopped-flow fluorimeter	(Chu et al. 2002)

**Supplementary Table S2.** Distribution of the variant types.

Variant	Original amino acid																				total
	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y	
A	0	0	0	0	1	71	0	0	0	2	0	0	1	0	0	2	0	3	0	0	80
C	5	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	8
D	27	0	0	0	0	5	0	0	0	0	0	6	0	0	0	0	0	0	0	0	38
E	34	0	4	0	0	13	0	1	0	0	0	2	0	2	0	0	1	0	0	0	57
F	25	0	0	0	0	3	0	2	0	18	0	0	0	0	0	2	0	5	0	0	55
G	17	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	2	0	0	22
H	5	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	8
I	51	0	1	0	3	7	0	0	0	3	0	0	0	0	0	1	2	46	0	0	114
K	32	0	0	1	0	13	0	0	0	0	3	0	0	0	2	0	0	0	0	0	51
L	107	0	0	0	1	11	0	3	0	0	0	0	0	0	0	1	0	8	0	0	131
M	7	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8
N	17	0	1	0	0	6	0	0	0	0	1	0	0	0	0	0	0	0	0	0	25
P	22	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	26
Q	11	0	0	0	0	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20
R	17	0	0	0	0	6	0	0	0	1	0	0	0	0	0	0	0	0	0	0	24
S	20	0	0	0	0	8	0	0	0	0	0	1	0	0	0	0	1	0	0	0	30
T	41	0	0	0	0	9	0	1	0	0	0	0	0	0	0	13	0	5	0	0	69
V	101	0	0	0	1	10	0	4	0	3	0	0	0	0	0	0	5	0	0	0	124
W	4	0	0	0	4	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	10
Y	30	0	0	0	11	5	0	1	0	3	0	2	0	0	0	0	0	0	0	0	52
total	573	0	6	1	21	181	0	15	0	31	6	11	1	5	2	20	10	69	0	0	952

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