Supplementary Materials

Running Title: Stability prediction of SOD1 patient-phenotype pathogenesis

Computing disease-linked SOD1 mutations: deciphering protein stability and patient-phenotype relations

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Table S1. Effects of missense mutations on the stability of human SOD1

Mutation	ΔΔG(m)	ΔΔG(d)	Class	Reference
A4V	1.62	4.31	B	[1]
I18V	0.37		B	[2]
V29A	2.81		B	[2]
V31A	1.39		B	[2]
I35V	0.66		B	[2]
L38A	2.95		B	[2]
L38V	2.25	3.24	B	[3]
G41D	2.91	3.47	B	[1]
G41S	2.93	4.47	B	[1]
H43R	2.68	4.05	B	[1]
F45A	2.07		B	[2]
H46R	-0.81	-0.48	M	[1]
V47A	1.45		B	[2]
F64A	-0.2		B	[2]
D76V	0.2	0.06	M	[3]
D76Y	0.21	0.09	M	[3]
V81A	0.01		B	[2]
L84A	1.85		M	[2]
L84V	1.87	2.65	M	[1]
G85R	1.93	0.9	M	[1]
N86D	-0.05	0.94	B	[3]
N86K	0.66	1.41	B	[3]
N86S	-0.07	0.45	B	[3]
V87A	1.61		B	[2]
D90A	0.66	0.65	B	[1]
D90V	1.41	1.85	B	[3]
G93A	2.43	2.98	B	[1]
G93S	3.7	3.1	B	[4]
G93R	4.4	3	B	[4]
G93D	5.7	4.5	B	[4]
G93V	7	5.4	B	[4]
V97A	2.9		B	[2]
E100G	0.91	2.22	B	[1]
D101G	0.72	1.39	B	[3]
D101N	-0.8	-0.75	B	[3]
I104A	1.53		B	[2]
I104F	0.72	1.24	B	[1]
S105L	1.81	2.6	B	[3]
L106V	1.78	3.62	B	[1]
L106A	3.71		B	[2]
C111A	-0.42		B	[2]
I112A	1.25		B	[2]
I113T	1.25	2.48	B	[1]
G114A	2.33	3.27	B	[3]
L117A	1.78		B	[2]

V119A	2.55		B	[2]
N139D	0.01	-0.36	B	[3]
N139K	0.06	0.24	B	[3]
L144A	-0.13		B	[2]
L144S	0.2	1.07	B	[3]
L144F	0.23	1.89	B	[1]
V148G	2.53	4.56	B	[1]
I149A	4.05		B	[2]
I149V	0.27		B	[2]

Data in columns are from left: wild-type, position and mutant residue, free energy change for apo-monomer and holodimer in kcal/mol, ΔΔG(m) and ΔΔG(d), mutations class (β-sheet, B; metal-region, M; disulfide/cystine region, D)

Table S2. Experimental monomer and dimer stability changes and computed stability changes (kcal/mol) for 2C9V.

Mutations	ΔΔG(exp) (monomer)	ΔΔG(exp) (dimer)	CUPSAT	IMUTANT 2.0	IMUTANT 3.0	POPMUSIC 3.1	ENCoM	FoldX	BEATMUSIC	mCSM
A4V	1.62	4.31	1.01	1.08	0.8	-0.52	-0.82	0.53	-1.33	-0.09
I18V	0.37		2.25	0.79	1.09	1.53	0.21	0.28	0.28	-1.57
V29A	2.81		4.96	1.37	1.88	2.56	0.56	1.22	0.92	-2.53
V31A	1.39		4.37	2.05	2.08	3.52	0.43	1.45	1.65	-2.48
I35V	0.66		2.7	0.45	0.88	1.47	0.19	0.48	0.1	-1.8
L38A	2.95		2.91	2.34	2.29	2.92	0.65	1.74	1.24	-2.62
L38V	2.25	3.24	2.24	0.67	1.07	1.35	0.02	1.78	0.06	-1.75
G41S	2.93	4.47	1.71	2.18	1.14	2.47	-0.14	1.3	1.28	-1.17
G41D	2.91	3.47	2.74	1.65	1.09	2.49	-0.1	0.94	1.3	-1.7
H43R	2.68	4.05	-2.84	1.33	0.61	1.36	0.17	1.15	0.07	-2.04
F45A	2.07		7.04	1.28	1.11	3.94	1.1	2.64	1.96	-2.87
H46R	-0.81	-0.48	-3.89	0.74	0.66	1.04	-0.55	2.9	-0.23	-1.91
V47A	1.45		5.52	1.19	1.3	2.91	0.57	1.2	1.2	-2.98
F64A	-0.2		2.76	2.57	2.14	2.75	1.22	1.27	1.07	-3.29
D76Y	0.21	0.09	-1.08	0.31	0.23	0.65	-0.2	-0.17	0.09	-0.22
D76V	0.2	0.06	-0.59	-0.29	0.31	0.31	0.29	0.18	-0.05	0.11
V81A	0.01		7.08	1.64	1.59	2.12	0.93	0.87	0.61	-2.49
L84A	1.85		4.48	1.85	1.79	2.9	1.02	1.22	1.19	-2.74
L84V	1.87	2.65	2.38	0.75	1.04	1.5	0.26	1.05	0.13	-1.68
G85R	1.93	0.9	4.03	0.7	0.63	2.25	-0.9	2.07	0.72	-1.27
N86S	-0.07	0.45	0.55	1.7	0.55	0.81	0.19	0.66	-0.04	-1.03
N86D	-0.05	0.94	-1.49	0.87	0.29	1.19	0.11	0.88	0.25	-0.91
N86K	0.66	1.41	1.62	0.38	0.11	0.88	-0.16	0.17	0.02	-0.29
V87A	1.61		2.33	1.82	1.62	2.38	0.58	0.9	0.83	-2.13
D90V	1.41	1.85	0.71	0.58	-0.04	0.68	0.08	0.58	0.42	0.03
D90A	0.66	0.65	1.12	0.47	-0.43	0.81	0.19	0.46	0.52	-0.3
G93V	7	5.4	2.29	0.48	1.05	2.76	-0.45	2.74	1.14	-0.63
G93A	2.43	2.98	3.93	1.62	1.44	2.78	0.09	1.46	1.16	-0.79
G93R	4.4	3	3	1.27	0.84	1.92	-0.29	1.98	0.51	-0.78
G93D	5.7	4.5	3.43	1.92	1.32	2.25	-0.29	2.44	0.76	-1.82
G93S	3.7	3.1	3.33	0.93	0.55	2.2	-0.36	1.88	0.71	-1.24
V97A	2.9		2.85	1.59	1.64	2.6	0.34	1.08	0.99	-1.7
E100G	0.91	2.22	1.94	1.26	1.09	0.74	0.27	0.21	0.63	-1.95
D101G	0.72	1.39	-2.34	2.79	1.87	1.5	0.21	1.68	0.22	-1.15
D101N	-0.8	-0.75	-2.08	1.86	1.67	0.61	-0.03	1	-0.45	-1.26
I104A	1.53		0.42	2.25	2.4	2.91	0.73	1.09	1.24	-2.91
I104F	0.72	1.24	4.92	1.01	1.46	0.75	-0.45	3.84	-0.41	-1.69
S105L	1.81	2.6	0.38	0.98	0.75	1.78	-0.14	0.12	-0.15	0.46
L106V	1.78	3.62	2	1.19	1.28	1	0.84	1.35	-0.12	-1.37
L106A	3.71		1.12	2.47	2.25	2.17	1.56	1.63	0.8	-2.32
C111A	-0.42		-3.29	0.48	1.18	1.48	0.07	0.02	0.15	-1.78
I112A	1.25		3.86	2.5	1.98	2.27	0.9	1.35	0.72	-3.21
I113T	1.25	2.48	-0.22	2.23	1.21	1.51	0.63	0.58	1.07	-3.1
G114A	2.33	3.27	4.56	0.34	0.75	2.2	0.01	1.24	1.97	-1.58
L117A	1.78		4.24	1.84	1.38	3.41	0.67	1.56	1.56	-3.07
V119A	2.55		2.56	0.78	0.93	3.58	0.5	1.32	1.68	-2.61
N139K	0.06	0.24	0.28	0.75	0.24	1.4	0.05	0.4	0.6	1.02

N139D	0.01	-0.36	2.28	0.26	-0.05	1	0.02	0.86	0.29	-1.92
L144F	0.23	1.89	-1.06	1.3	1.41	0.51	-0.31	0.25	-0.21	-1.47
L144S	0.2	1.07	-0.15	1.15	0.99	1.2	0.55	0.82	0.28	-2.15
L144A	-0.13		-0.65	0.75	0.61	1.43	0.8	0.73	0.44	-2.16
V148G	2.53	4.56	-0.09	3.15	2.12	2.11	0.68	0.12	2.51	-0.61
I149A	4.05		3.55	2.66	1.92	2.87	1.02	1.47	1.5	-2.9
I149V	0.27		2.5	0.62	0.64	1.06	0.34	0.36	-0.38	-1.68

Table S3. Experimental monomer and dimer stability changes and computed stability changes (kcal/mol) for 1HL4.

Mutations	ΔΔG(exp) (monomer)	ΔΔG(exp) (dimer)	CUPSAT	IMUTANT 2.0	IMUTANT 3.0	POPMUSIC 3.1	ENCOM	FOLDX	BEATMUSIC	mCSM
A4V	1.62	4.31	2.24	1.09	0.81	-0.49	-1.16	0.44	-1.31	-0.1
I18V	0.37		2.54	0.69	1.07	1.38	0.56	0.27	0.07	-1.38
V29A	2.81		5.16	1.69	1.96	2.65	0.56	1.36	1	-2.4
V31A	1.39		5.04	2.05	2.08	3.39	0.44	0.66	1.53	-1.59
I35V	0.66		2.36	0.43	0.78	1.39	0.27	0.32	0.12	-1.61
L38A	2.95		4.38	2.3	2.26	3.02	0.48	1.42	1.3	-2.65
L38V	2.25	3.24	2.41	0.64	1.06	1.54	-0.02	1.73	0.15	-1.76
G41S	2.93	4.47	2.07	2.36	1.19	2.32	-0.1	1.28	1.38	-1.01
G41D	2.91	3.47	2.51	1.76	1.09	2.35	-0.07	0.71	1.29	-1.43
H43R	2.68	4.05	-4.33	1.39	0.59	1.61	0.18	1.68	0.08	-1.99
F45A	2.07		7.3	1.39	1.28	3.9	1.17	2.13	2.01	-2.8
H46R	-0.81	-0.48	-3.67	0.74	0.65	1.13	-0.24	1.75	-0.19	-1.9
V47A	1.45		6.57	1.05	1.27	2.98	0.4	1.16	1.44	-2.69
F64A	-0.2		2.75	2.57	2.14	2.8	1.28	0.93	1.02	-3.14
D76Y	0.21	0.09	-0.92	0.56	0.32	0.88	-0.31	0.05	0.71	-0.31
D76V	0.2	0.06	-0.32	-0.03	0.42	0.25	0.29	0.28	-0.03	-0.03
V81A	0.01		4.8	1.56	1.56	1.93	0.83	0.74	0.59	-2.49
L84A	1.85		4.54	1.85	1.79	2.72	1.04	1.21	1.11	-2.66
L84V	1.87	2.65	3.21	0.74	1.04	1.31	0.21	0.89	0.03	-1.62
G85R	1.93	0.9	6.96	0.76	0.63	2.01	-0.92	1.79	0.74	-1.27
N86S	-0.07	0.45	-0.95	1.59	0.51	0.66	-0.1	0.49	-0.15	-1.05
N86D	-0.05	0.94	-2.21	0.79	0.28	0.96	-0.28	0.79	0.17	-0.97
N86K	0.66	1.41	-0.09	0.34	0.1	0.74	-0.8	-0.06	0.01	-0.29
V87A	1.61		3.62	1.89	1.63	2.44	0.56	0.93	0.85	-1.99
D90V	1.41	1.85	1.47	0.65	0	0.83	0.05	0.95	0.5	0.07
D90A	0.66	0.65	1.95	0.5	-0.42	0.93	0.18	0.82	0.56	-0.27
G93V	7	5.4	1.02	0.23	0.92	2.7	-0.46	2.19	1.09	-0.71
G93A	2.43	2.98	2.17	1.36	1.28	2.66	0.1	1.15	1.12	-0.9
G93R	4.4	3	1.07	1.19	0.72	1.97	-0.23	1.24	0.61	-0.88
G93D	5.7	4.5	0.42	1.88	1.24	2.24	-0.31	1.9	0.82	-2.0
G93S	3.7	3.1	2.76	0.71	0.36	2.14	-0.35	1.24	0.64	-1.36
V97A	2.9		6.35	1.53	1.67	2.55	0.33	1.13	0.83	-1.69
E100G	0.91	2.22	4.18	1.19	1	0.74	0.41	0.35	0.65	-0.74
D101G	0.72	1.39	-1.22	2.62	1.8	1.66	0.22	1.78	0.26	-0.95
D101N	-0.8	-0.75	0.12	1.8	1.65	0.79	-0.02	1.13	-0.37	-0.88
I104A	1.53		2.56	2.26	2.28	2.94	0.79	1.13	1	-2.62
I104F	0.72	1.24	4.02	1.07	1.4	0.85	-0.82	3.5	-0.46	-1.6
S105L	1.81	2.6	-2.58	0.92	0.72	0.91	0.06	0.63	-0.25	-0.35
L106V	1.78	3.62	1.95	1.18	1.27	1.08	0.54	0.96	-0.06	-1.44
L106A	3.71		5.37	2.46	2.25	2.29	1.49	1.56	0.62	-2.32
C111A	-0.42		-4.89	0.33	1.22	1.36	0.1	-0.06	0.37	-1.48
I112A	1.25		7.19	2.35	1.91	2.38	0.66	1.32	0.88	-2.3
I113T	1.25	2.48	2.11	2.27	1.28	1.71	0.31	0.92	1.17	-1.86
G114A	2.33	3.27	5.21	0.51	0.86	2.27	0.02	1.39	2.18	-1.17
L117A	1.78		5.05	1.71	1.3	3.29	0.82	1.53	1.49	-2.98
V119A	2.55		4.25	0.84	1.02	3.64	0.5	0.99	1.75	-2.55
N139K	0.06	0.24	0.9	0.76	0.24	1.65	-0.47	0.33	0.79	0.62
N139D	0.01	-0.36	1.08	0.26	-0.04	1	-0.38	0.85	0.23	-1.79

L144F	0.23	1.89	-0.69	1.04	1.22	0.58	-0.46	0.31	-0.19	-1.59
L144S	0.2	1.07	0.64	0.98	0.88	1.3	0.46	0.76	0.37	-2.22
L144A	-0.13		0.32	0.62	0.58	1.47	0.74	0.47	0.53	-2.25
V148G	2.53	4.56	-0.65	3.38	2.21	2.26	0.79	0.17	2.89	-1.0

Table S4. Experimental monomer and dimer stability changes and computed stability changes (kcal/mol) for 2XJK.

Mutations	ΔΔG(exp) (monomer)	ΔΔG(exp) (dimer)	CUPSAT	IMUTANT 2.0	IMUTANT 3.0	POPMUSIC 3.1	ENCOM	FOLDX	mCSM
A4V	1.62	4.31	-3.8	-0.94	-0.61	-0.36	-0.68	0.39	0.14
I18V	0.37		-2.56	-0.62	-1.06	1.24	-0.1	0.32	-1.43
V29A	2.81		-5.24	-1.64	-1.78	2.65	0.58	1.22	-2.49
V31A	1.39		-4.34	-2.09	-1.95	3.14	0.27	1.46	-1.76
I35V	0.66		-2.41	-0.27	-0.82	1.38	0.19	0.5	-1.76
L38A	2.95		-3.38	-2.35	-2.3	2.8	0.61	1.52	-2.74
L38V	2.25	3.24	-2.81	-0.68	-1.07	1.26	-0.02	1.81	-1.82
G41S	2.93	4.47	-6.51	-1.61	-1.05	1.95	-0.01	1.18	-1.05
G41D	2.91	3.47	-7.06	-2.15	-1.1	2.22	-0.08	0.65	-1.52
H43R	2.68	4.05	1.88	-1.34	-0.61	1.51	-0.15	1.94	-1.98
F45A	2.07		-6.7	-1.3	-1.17	4.02	1.16	2.58	-3.07
H46R	-0.81	-0.48	5.13	-0.73	-0.61	1.13	1.26	0.94	-1.93
V47A	1.45		-2.83	-1.33	-1.28	3.32	0.49	1.28	-2.98
F64A	-0.2		-2.24	-2.41	-2.1	3.01	1.39	1.45	-3.26
D76Y	0.21	0.09	0.89	0.16	-0.36	0.67	-0.67	0	-0.24
D76V	0.2	0.06	1.07	-0.39	-0.25	0.2	-0.06	0	-0.07
V81A	0.01		-4.24	-1.65	-1.65	2.02	0.93	0.5	-2.19
L84A	1.85		-3.87	-1.85	-1.79	2.8	1.24	1.37	-2.75
L84V	1.87	2.65	-1.7	-0.74	-1.04	1.39	0.18	1.37	-1.71
G85R	1.93	0.9	-3.95	-0.7	-0.63	2.32	-0.76	1.61	-1.23
N86S	-0.07	0.45	-2.36	-0.36	-0.09	0.52	0.24	0.45	-1.01
N86D	-0.05	0.94	-1.54	-1.68	-0.54	1.1	0.12	0.89	-0.84
N86K	0.66	1.41	1.67	-0.86	-0.29	0.85			-0.26
V87A	1.61		-3.36	-1.81	-1.61	2.34	0.65	0.93	-2.1
D90V	1.41	1.85	-2.33	-0.39	0.5	0.73	0.22	0.67	0.13
D90A	0.66	0.65	-1.22	-0.43	0.15	0.7	0.07	0.57	-0.21
G93V	7	5.4	-3.24	-0.93	-0.55	2.93	-0.34	3.01	-0.65
G93A	2.43	2.98	-1.76	-0.48	-1.05	2.83	0.1	1.57	-0.81
G93R	4.4	3	-2.53	-1.29	-0.84	2.06	-0.26	2.39	-0.78
G93D	5.7	4.5	-2.47	-1.93	-1.32	2.43	-0.27	2.81	-1.81
G93S	3.7	3.1	-3.03	-1.64	-1.44	2.47	-0.38	2.09	-1.24
V97A	2.9		-5.27	-1.82	-1.75	2.64	0.46	1.17	-1.71
E100G	0.91	2.22	-3.05	-1.92	-1.27	1.06	0.74	0.31	-0.56
D101G	0.72	1.39	-0.18	-3.07	-1.98	1.56	0.29	1.68	-0.85
D101N	-0.8	-0.75	-0.3	-2.01	-1.79	0.71	0.48	1.27	-0.82
I104A	1.53		-1.17	-2.16	-2.4	2.85	0.63	1.35	-2.25
I104F	0.72	1.24	-2.69	-0.91	-1.42	0.74	-0.65	4.72	-1.36
S105L	1.81	2.6	-1.38	-0.72	-0.61	0.93	-0.03	0.75	-0.64
L106V	1.78	3.62	-1.81	-1.06	-1.12	0.92	0.77	1.2	-1.5
L106A	3.71		-2.9	-2.49	-2.1	2.19	1.51	1.56	-2.44
I112A	1.25		-1.3	-2.81	-2.14	2.4	0.83	1.34	-2.28
I113T	1.25	2.48	-1.64	-2.47	-1.31	0.7	0.38	0.87	-1.49
G114A	2.33	3.27	-1.61	-0.37	-0.53	1.76	-0.08	1.13	-0.61
L117A	1.78		-2.79	-1.82	-1.39	3.13	0.69	1.53	-3.05
V119A	2.55		-3.63	-0.78	-0.84	3.63	0.49	1.32	-2.79
N139K	0.06	0.24	-1.66	-0.26	0.04	1.78	0.04	0.01	0.33
N139D	0.01	-0.36	0.49	-0.76	-0.24	1.05	0.01	0.6	-1.54
L144F	0.23	1.89	0.34	-0.81	-0.55	0.62	-0.35	0.41	-1.46

L144S	0.2	1.07	-1.67	-1.19	-0.88	1.23	0.56	0.77	-1.86
L144A	-0.13		0.27	-1.26	-1.25	1.56	0.8	0.71	-1.98
V148G	2.53	4.56	-2.01	-2.42	-1.81	0.52	0.12	0.14	-0.96
I149A	4.05		-2.71	-3.37	-2.13	2.61	0.99	1.62	-2.34
I149V	0.27		-1.67	-0.42	-0.56	1.09	0.2	0.39	-1.16

Table S5. Experimental monomer and dimer stability changes and computed stability changes (kcal/mol) for 4BCZ.

Mutations	$\Delta\Delta G_{(exp)}$ (monomer)	$\Delta\Delta G_{(exp)}$ (dimer)	CUPSAT	IMUTANT 2.0	I-MUTANT 3.0	POPMUSIC 3.1	ENCoM	FoldX	BEATMUSIC	mCSM
A4V	1.62	4.31	-0.39	-0.91	-0.68	-0.44	-0.96	0.3	-1.47	0.04
I18V	0.37		-2.38	-0.58	-1.02	1.37	0.14	0.27	0.03	-1.21
V29A	2.81		-5.99	-1.26	-1.7	2.6	0.52	1.15	1.05	-2.4
V31A	1.39		-7.38	-2.13	-1.9	3.47	0.49	1.45	1.71	-2.22
I35V	0.66		-2.22	-0.22	-0.72	1.44	0.2	0.48	0.16	-2.02
L38A	2.95		-2.97	-1.76	-1.79	2.3	0.82	1.59	0.81	-2.67
L38V	2.25	3.24	-0.81	-0.58	-0.88	1.21	0.1	1.65	0	-1.8
G41S	2.93	4.47	-1.35	-1.7	-0.86	2.43	-0.14	1.08	1.3	-1.22
G41D	2.91	3.47	-0.8	-2.45	-1	2.54	-0.11	0.47	1.39	-1.64
H43R	2.68	4.05	3.11	-1.25	-0.46	1.34	0.44	2.59	0.01	-1.82
F45A	2.07		-5.71	-1.86	-1.32	3.58	1.27	2.54	1.68	-2.66
H46R	-0.81	-0.48	2.02	-0.74	-0.48	0.56	0.27	-0.16	-0.24	-1.38
V47A	1.45		-4.29	-1.35	-1.39	2.06	0.58	0.99	0.46	-2.21
L84A	1.85		-0.29	-2.44	-2.05	2.84	1.51	1.32	1.19	-2.19
L84V	1.87	2.65	0.46	-0.87	-1.1	1.42	0.64	1.16	0.13	-1.31
G85R	1.93	0.9	0.24	-0.46	-0.67	2.05	-0.01	1.3	1.28	-0.73
N86S	-0.07	0.45	1.52	-0.46	-0.05	0.01	0.14	0.2	-0.06	-0.32
N86D	-0.05	0.94	0.33	-1.66	-0.43	0.32	-0.13	0.15	0.18	0.25
N86K	0.66	1.41	0.31	-1.28	-0.29	0.29			0.11	0.13
V87A	1.61		-2.5	-1.05	-1.27	2.32	0.64	0.85	0.78	-2.22
D90V	1.41	1.85	-1.9	-0.43	0.47	0.97	-0.06	1.07	0.47	0.03
D90A	0.66	0.65	-2.11	-0.55	0.07	0.98	0.06	0.68	0.48	-0.3
G93V	7	5.4	-3.86	-1.21	-0.42	2.68	-0.35	2.35	1.11	-0.66
G93A	2.43	2.98	-2.61	-0.7	-0.9	2.62	0.02	1.21	1.05	-0.84
G93R	4.4	3	-3.7	-1.37	-0.69	1.99	-0.33	1.46	0.57	-0.81
G93D	5.7	4.5	-1.98	-2.16	-1.19	2.22	-0.33	1.82	0.76	-1.85
G93S	3.7	3.1	-3.56	-1.59	-1.22	2.07	-0.53	1.61	0.64	-1.28
V97A	2.9		-4.89	-1.5	-1.58	2.61	0.24	1.15	0.97	-2.02
E100G	0.91	2.22	-1	-1.58	-1.02	0.79	0.65	0.35	0.7	-0.96
D101G	0.72	1.39	0.48	-2.77	-1.56	1.71	0.11	0.6	0.48	-0.86
D101N	-0.8	-0.75	-0.25	-1.77	-1.51	0.74	-0.03	-0.18	-0.22	-0.76
I104A	1.53		-1.7	-2.33	-2.11	2.18	0.7	0.91	0.69	-2.01
I104F	0.72	1.24	-4.09	-1.23	-1.34	0.51	-0.84	3.89	-0.56	-1.26
S105L	1.81	2.6	4.62	-0.36	-0.3	0.94	-0.11	0.35	-0.12	-0.79
L106V	1.78	3.62	-2.57	-1.31	-1.34	1.18	0.63	1.5	-0.1	-1.67
L106A	3.71		-4.21	-2.4	-2.3	2.31	1.51	1.46	0.81	-2.45
I112A	1.25		-5.96	-2.54	-1.85	2.2	0.75	1.25	0.55	-2.31
I113T	1.25	2.48	-6.58	-2.94	-1.56	1.06	0.95	0.38	0.19	-1.37
G114A	2.33	3.27	1.77	-0.46	-0.79	1.33	-0.01	1.3	1.02	-0.26
L117A	1.78		-4.37	-1.56	-1.26	3.14	0.72	1.71	1.35	-2.81
V119A	2.55		-2.85	-0.82	-0.92	3.1	0.41	1.43	1.33	-2.62
L144F	0.23	1.89	-0.38	-1.12	-0.69	0.23	0.15	-0.17	-0.25	-1.22
L144S	0.2	1.07	1.25	-1.36	-1.17	0.92	0.15	0.96	0.27	-1.25
L144A	-0.13		0.54	-1.74	-1.55	1.29	0.33	0.73	0.54	-1.52
V148G	2.53	4.56	-0.32	-3.06	-2.2	0.59	0.15	0.12	0.4	-0.57
I149A	4.05		-2.63	-2.61	-2.15	2.71	0.98	1.64	1.06	-2.31
I149V	0.27		-2.08	-0.2	-0.68	1.04	0.19	0.44	-0.19	-1.18

Table S6. Bland Altman analysis of mean differences between experimental and computed stability predictors

PDB	Stability Predictors	Bias	SD of Bias	Mean ± 1.96 SD
Dimer/Monomer		0.519091	0.983846	2.44; -1.40
2C9V	CUPSAT	0.228519	2.37008	4.87; -4.41
	I-Mutant 2.0	-0.276667	1.59319	2.85;-3.39
	I-Mutant 3.0	-0.464630	1.55982	2.84; -3.40
	PoPMuSiC 3.1	0.230185	1.38360	2.94; -2.48
	ENCoM	-1.33296	1.68868	1.98; -4.64
	FoldX	-0.453889	1.41646	2.32; -3.23
	BeatMusic	-0.969815	1.41701	1.81; -3.75
	mCSM	-3.22093	1.92398	0.55; -6.99
1HL4	CUPSAT	0.511154	2.91821	6.23; -5.21
	I-Mutant 2.0	-0.283077	1.61560	2.88; -3.45
	I-Mutant 3.0	-0.465192	1.57707	2.63; -3.56
	PoPMuSiC 3.1	0.241154	1.39334	2.97; -2.49
	ENCoM	-1.38808	1.67719	1.90; -4.67
	FoldX	-0.537115	1.40872	2.22; -3.30
	BeatMusic	-0.915000	1.45559	1.94; -3.77
	mCSM	-3.07423	1.85555	0.56; -6.71
2XJK	CUPSAT	-3.80075	3.21343	2.50; -10.10
	I-Mutant 2.0	-2.97340	1.95576	0.86; -6.81
	I-Mutant 3.0	-2.66113	1.78681	0.84; -6.16
	PoPMuSiC 3.1	0.170943	1.93553	3.96; -3.62
	ENCoM	-1.36154	1.75475	2.08; -4.80
	FoldX	-0.447692	1.34523	2.19; -3.08

	mCSM	-3.11321	1.91271	0.63; -6.86
4BCZ	CUPSAT	-3.61702	3.40870	3.06; -10.23
	I-Mutant 2.0	-3.24787	1.89115	0.46; -6.95
	I-Mutant 3.0	-2.93170	1.77633	0.55; -6.41
	PoPMuSiC 3.1	-0.173404	1.30507	2.38; -2.73
	ENCoM	-1.58239	1.67567	1.70; -4.87
	FoldX	-0.780652	1.33171	1.83; -3.39
	BeatMusic	-1.30787	1.38584	1.41; -4.02
	mCSM	-3.22298	1.93226	0.56; -7.01

Table S7. Overall performance of stability predictors for 33 SOD1 holo-dimer mutants using four different crystal structures

		Addiditivity Assumption[a]				
Methods	Metrics	2C9V	1HL4	2XJK	4BCZ	Average
CUPSAT	MAE	1.6	1.75	3.21	2.6	2.3
	MSE	1.08	1.14	3.73	3.19	2.28
	R	0.38	0.17	0.53	0.23	0.33
	R^2	0.144	0.03	0.28	0.05	0.13
I-Mutant 2.0	MAE	0.68	0.68	2.2	1.91	1.36
	MSE	0.99	1.00	3.26	3.75	2.25
	R	0.35	0.34	0.3	0.23	0.3
	R^2	0.12	0.11	0.09	0.05	0.09
I-Mutant 3.0	MAE	0.65	0.65	1.28	2.09	1.17
	MSE	1.28	1.31	2.93	3.26	2.19
	R	0.41	0.4	0.31	0.2	0.33
	R^2	0.17	0.16	0.1	0.04	0.12
PoPMuSiC 3.1	MAE	0.65	0.62	0.69	0.61	0.64
	MSE	0.76	0.75	0.85	1.21	0.89
	R	0.51	0.5	0.38	0.45	0.46
	R^2	0.26	0.25	0.14	0.2	0.21
ENCoM	MAE	1.13	1.21	1.21	1.27	1.21
	MSE	2.15	2.24	2.11	2.41	2.22
	R	0.001	0.1	0.25	0.16	0.13
	R^2	0	0.01	0.06	0.02	0.02
FoldX	MAE	0.8	0.73	0.73	0.66	0.73
	MSE	0.99	1.09	0.97	1.46	1.13
	R	0.18	0.19	0.32	0.37	0.26
	R^2	0.03	0.03	0.1	0.13	0.07
BeatMusic	MAE	0.77	0.81		0.96	0.85
	MSE	1.72	1.66		2.10	1.83
	R	0.41	0.37		0.25	0.34
	R^2	0.17	0.14		0.06	0.12
mCSM	MAE	2.23	2.15	2.05	2.13	2.14
	MSE	3.23	3.19	3.11	3.34	3.22
	R	0.11	0.16	0.16	0.25	0.17
	R^2	0.01	0.03	0.02	0.06	0.03

[a] Additivity assumption: Calculated and multiplied by 2

Table S8. Computed stability changes (kcal/mol), averaged over all four structures.

Mutations	CUPSAT	IMUT-2.0	IMUT-3.0	POPMUSIC 3.1	ENCoM	FoldX	BEATMUSIC	mCSM
A4V	-0.235	0.08	0.08	-0.452	-0.9	0.42	-1.37	-0.004
I18V	-0.04	0.07	0.02	1.38	0.2	0.3	0.13	-1.4
V29A	-0.28	0.04	0.09	2.61	0.55	1.24	1	-2.45
V31A	-0.57	-0.03	0.08	3.4	0.4	1.25	1.63	-2.01
I35V	0.1	0.09	0.03	1.42	0.21	0.45	0.13	-1.8
L38A	0.23	0.13	0.11	2.76	0.64	1.57	1.12	-2.67
L38V	0.26	0.01	0.045	1.34	0.02	1.74	0.07	-1.78
G41D	-0.65	-0.3	0.02	2.4	-0.09	0.7	1.33	-1.57
G41S	-1.02	0.3	0.1	2.3	-0.09	1.21	1.32	-1.11
H43R	-0.54	0.03	0.032	1.45	0.16	1.84	0.05	-1.96
F45A	0.48	-0.12	-0.02	3.86	1.17	2.47	1.88	-2.85
H46R	-0.1	0.002	0.05	0.96	0.18	1.36	-0.22	-1.78
V47A	1.24	-0.11	-0.02	2.82	0.52	1.16	1.03	-2.72
F64A	1.09	0.91	0.73	2.85	1.29	1.21	1.04	-3.23
D76V	0.05	-0.24	0.16	0.25	0.17	0.15	-0.04	0.001
D76Y	-0.37	0.34	0.06	0.73	-0.39	-0.04	0.4	-0.26
V81A	2.54	0.52	0.5	2.02	0.9	0.7	0.6	-2.4
L84A	2.42	0.92	0.9	2.78	1.08	1.25	1.14	-2.7
L84V	1.08	-0.03	-0.02	1.4	0.32	1.12	0.096	-1.58
G85R	1.82	0.07	-0.01	2.15	-0.65	1.7	0.91	-1.13
N86D	-1.23	-0.42	-0.1	0.9	-0.04	0.68	0.2	-0.62
N86K	0.87	-0.35	-0.09	0.7	-0.48	0.06	0.05	-0.18
N86S	-0.31	0.62	0.23	0.5	0.12	0.45	-0.08	-0.85
V87A	0.022	0.021	0.09	2.37	0.6	0.9	0.82	-2.11
D90A	-0.06	-0.002	-0.16	0.85	0.125	0.63	0.52	-0.27
D90V	-0.51	0.1	0.23	0.8	0.07	0.821	0.46	0.06
G93A	0.43	0.45	0.19	2.72	0.07	1.35	1.11	-0.84
G93S	-0.12	-0.4	-0.44	2.22	-0.4	1.7	0.66	-1.28
G93R	-0.54	-0.05	0.007	1.98	-0.27	1.76	0.56	-0.81
G93D	-0.15	-0.07	0.01	2.3	-0.3	2.24	0.78	-1.87
G93V	-0.94	-0.36	0.25	2.76	-0.4	2.57	1.11	-0.66
V97A	-0.24	-0.05	-0.005	2.6	0.34	1.14	0.93	-1.78
E100G	0.52	-0.26	-0.05	0.83	0.52	0.3	0.66	-1.05
D101G	-0.81	-0.1	0.03	1.6	0.21	1.44	0.32	-0.95
D101N	-0.62	-0.03	0.005	0.71	0.09	0.8	-0.34	-0.93
I104A	0.03	0.005	0.04	2.72	0.71	1.12	0.97	-2.44
I104F	0.54	-0.01	0.02	0.71	-0.68	3.98	-0.47	-1.48
S105L	0.26	0.2	0.14	1.14	-0.05	0.47	-0.17	-0.33
L106V	-0.1	0	0.02	1.04	0.69	1.25	-0.09	-1.49
L106A	-0.15	0.01	0.025	2.24	1.52	1.55	0.75	-2.38
C111A	-4.09	0.4	1.2	1.42	0.08	-0.02	0.26	-1.63
I112A	0.95	-0.12	-0.025	2.31	0.78	1.32	0.71	-2.5
I113T	-1.58	-0.23	-0.09	1.24	0.56	0.7	0.8	-1.95
G114A	2.48	0.005	0.07	1.89	-0.015	1.27	1.72	-0.9
L117A	0.53	0.04	0.007	3.24	0.73	1.58	1.46	-2.98
V119A	0.08	0.005	0.04	3.48	0.47	1.27	1.58	-2.64
N139D	1.28	-0.08	-0.11	1.01	-0.11	0.77	0.26	-1.75
N139K	-0.16	0.42	0.17	1.61	-0.13	0.24	0.7	0.65
L144A	0.12	-0.4	-0.4	1.43	0.66	0.66	0.5	-1.97
L144S	0.02	-0.1	-0.04	1.16	0.43	0.82	0.3	-1.87
L144F	-0.44	0.1	0.34	0.48	-0.24	0.2	-0.21	-1.4

V148G	-0.76	0.26	0.08	1.37	0.44	0.14	1.93	-0.78
I149A	0.38	-0.16	-0.11	2.74	0.98	1.53	1.34	-2.54
I149V	0.32	0.15	0.01	1.06	0.28	0.38	-0.33	-1.37

Table S9. Standard Deviations from average (kcal/mol) over all four structures (Structural Sensitivity).

Mutations	CUPSAT	IMUT-2.0	IMUT-3.0	POPMUSIC 3.1	FoldX	ENCoM	BEATMUSIC	mCSM
A4V	2.26	1	0.72	0.06	0.82	0.18	0.07	0.1
I18V	2.43	0.67	1.1	0.1	0.02	0.23	0.1	0.12
V29A	5.34	1.5	1.84	0.03	0.08	0.02	0.05	0.05
V31A	5.4	2.08	2	0.15	0.34	0.08	0.07	0.35
I35V	2.43	0.35	0.8	0.04	0.07	0.03	0.02	0.14
L38A	3.45	2.2	2.2	0.28	0.12	0.12	0.22	0.04
L38V	2.18	0.65	1.02	0.12	0.07	0.05	0.06	0.03
G41D	3.95	2	1.07	0.12	0.18	0.02	0.045	0.1
G41S	3.44	1.96	1.06	0.2	0.09	0.05	0.043	0.08
H43R	3.11	1.32	0.57	0.11	0.52	0.21	0.03	0.08
F45A	6.7	1.47	1.22	0.17	0.2	0.06	0.14	0.14
H46R	3.84	0.74	0.6	0.24	1.1	0.29	0.02	0.23
V47A	4.84	1.23	1.31	0.47	0.1	0.07	0.42	0.31
F64A	2.35	2.35	2	0.11	0.21	0.07	0.02	0.07
D76V	0.73	0.16	0.3	0.04	0.11	0.17	0.01	0.08
D76Y	0.9	0.16	0.3	0.1	0.09	0.2	0.3	0.04
V81A	4.88	1.53	1.52	0.07	0.15	0.05	0.01	0.14
L84A	3.63	1.6	1.55	0.07	0.06	0.09	0.04	0.04
L84V	1.9	0.78	1.05	0.07	0.18	0.18	0.05	0.16
G85R	4.1	0.66	0.65	0.13	0.29	0.37	0.26	0.23
N86D	0.94	1.25	0.38	0.34	0.3	0.17	0.03	0.5
N86K	0.78	0.73	0.2	0.24	0.12	0.32	0.04	0.18
N86S	1.47	1.02	0.3	0.3	0.17	0.13	0.05	0.3
V87A	3	1.67	1.53	0.04	0.03	0.03	0.03	0.08
D90A	1.65	0.49	0.26	0.11	0.13	0.06	0.03	0.04
D90V	1.63	0.51	0.25	0.11	0.2	0.1	0.03	0.04
G93A	2.7	1.04	1.17	0.08	0.17	0.03	0.04	0.04
G93S	3.18	1.22	0.9	0.15	0.32	0.07	0.03	0.05
G93R	2.7	1.28	0.77	0.05	0.45	0.04	0.04	0.04
G93D	2.33	1.97	1.27	0.08	0.4	0.02	0.03	0.07
G93V	2.65	0.72	0.74	0.09	0.32	0.05	0.02	0.03
V97A	5	1.61	1.66	0.03	0.03	0.08	0.07	0.13
E100G	2.75	1.5	1.1	0.13	0.05	0.19	0.03	0.53
D101G	1.06	2.81	1.8	0.08	0.49	0.06	0.11	0.12
D101N	0.85	1.86	1.66	0.06	0.58	0.22	0.09	0.19
I104A	1.65	2.25	2.3	0.31	0.16	0.06	0.22	0.35
I104F	4	1.06	1.4	0.12	0.45	0.16	0.06	0.18
S105L	2.72	0.76	0.6	0.37	0.24	0.08	0.05	0.48
L106V	2.09	1.19	1.25	0.09	0.2	0.12	0.02	0.11
L106A	3.74	2.45	2.23	0.06	0.06	0.02	0.09	0.06
C111A	0.8	0.07	0.02	0.06	0.04	0.01	0.11	0.15
I112A	5	2.55	1.97	0.08	0.04	0.09	0.13	0.4
I113T	3.18	2.48	1.34	0.4	0.22	0.25	0.44	0.68
G114A	2.7	0.42	0.74	0.37	0.1	0.04	0.5	0.5
L117A	4.16	1.74	1.33	0.12	0.07	0.06	0.09	0.1
V119A	3.4	0.8	0.93	0.22	0.17	0.04	0.18	0.09
N139D	0.75	0.48	0.09	0.02	0.12	0.19	0.03	0.16
N139K	1.1	0.48	0.09	0.16	0.17	0.24	0.09	0.28
L144A	0.46	1.1	1.03	0.1	0.1	0.2	0.04	0.28

L144S	1.1	1.17	0.98	0.14	0.08	0.17	0.04	0.38
L144F	0.51	1.07	0.97	0.15	0.22	0.23	0.02	0.13
V148G	0.75	3.01	2.1	0.12	0.02	0.3	0.09	0.2
I149A	3.05	2.84	2	0.09	0.1	0.02	0.2	0.24
I149V	2.2	0.47	0.64	0.02	0.04	0.08	0.1	0.22

Table S10. SOD1 variants with experimentally known stabilities (kcal/mol) correlated against t(o), t(s), and t(d) (years).

Mutations	**ΔΔG(exp) (monomer)**	**ΔΔG(exp) (dimer)**	**t(o)**	**t(s)**	**t(d)**	**Reference**
A4V	1.62	4.31	47.7	1.2	48.9	[5]
L38V	2.25	3.24	41.1	2.4	43.5	[6]
G41S	2.93	4.47	48.4	1	49.4	[7]
G41D	2.91	3.47	45.2	14.1	59.3	[8]
H43R	2.68	4.05	49.3	1.8	51.1	[9]
D76Y	0.21	0.09	55	17	72	[10]
D76V	0.2	0.06	46	18.8	64.8	[11]
L84V	1.87	2.65	46.8	3.2	50	[12]
G85R	1.93	0.9	55.5	6	61.5	[13]
N86S	-0.07	0.45	40.8	6.8	47.6	[14]
N86K	0.66	1.41	58.2	1.7	59.9	[15]
D90V	1.41	1.85	46	2.7	48.7	[16]
D90A	0.66	0.65	48.6	8	56.6	[17]
G93V	7	5.4	43.6	6	49.6	[18]
G93A	2.43	2.98	46	3.1	49.1	[19]
G93R	4.4	3	35	5.3	40.3	[20]
G93D	5.7	4.5	39.3	8.8	48.1	[21]
G93S	3.7	3.1	51.6	8	59.6	[22]
E100G	0.91	2.22	47.3	4.7	52	[8]
D101G	0.72	1.39	41	1.9	48.9	[23]
D101N	-0.8	-0.75	40.1	2.3	42.4	[24]
I104F	0.72	1.24	36.9	21.3	58.2	[25]
S105L	1.81	2.6	48.7	3.5	52.2	[26]
L106V	1.78	3.62	45.1	1.9	47	[8]
I113T	1.25	2.48	54.1	6.8	60.9	[27]
G114A	2.33	3.27	37.5	2.7	40	[28]
L144F	0.23	1.89	52.4	11.8	64.2	[29]
L144S	0.2	1.07	37	12.3	49.3	[30]
V148G	2.53	4.56	43.1	2.1	45.2	[31]
I149T	4.05		37.6	2.7	40.3	[32]

Table S11. SOD1 structures used for computation of mutant stabilities

PDB	Stoichiometry	R (Å)	Space Group	pH	RMSD*	No. of residues
2C9V	Homo-2-mer	1.07	P 1211	4.75	-	306
1HL4	Homo-2-mer	1.82	C 121	8.0	0.35	306
2XJK	Monomer	1.45	P 212121	6.0	0.29	153
4BCZ	Monomer	1.93	P 65	4.0	11.16	110

*RMSD with respect to 2C9V

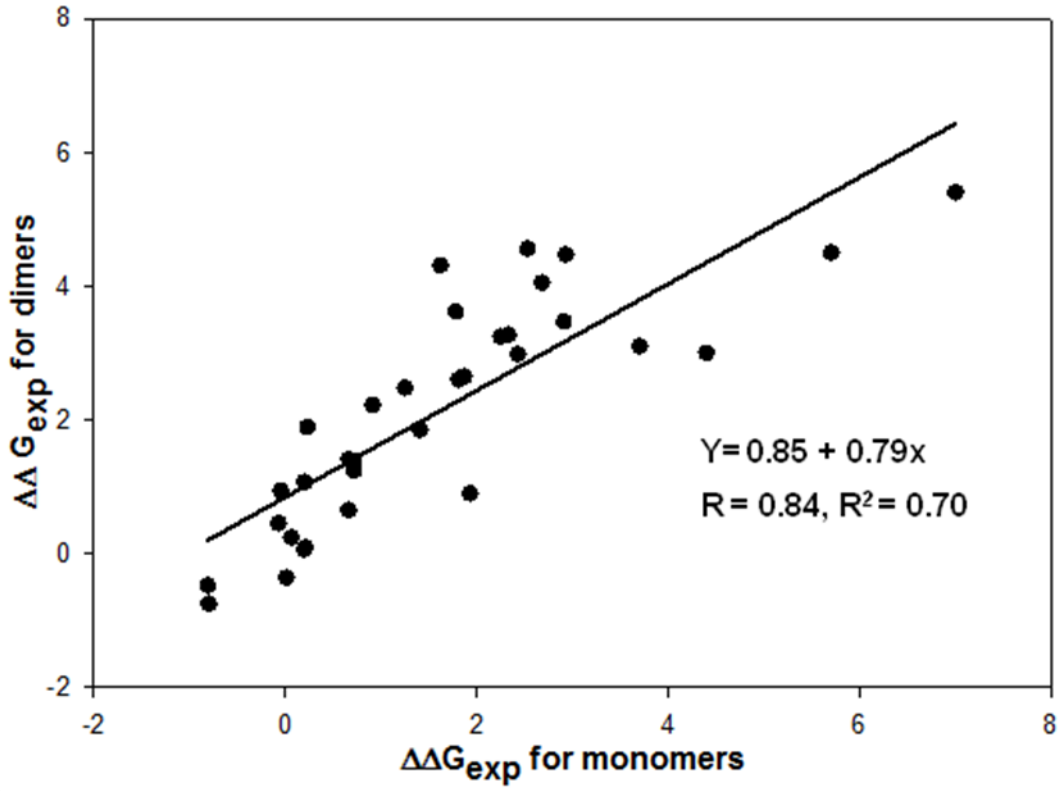

Figure S1: Correlation between experimental free energies (kcal/mol) of mutants for dimer and monomer SOD1.

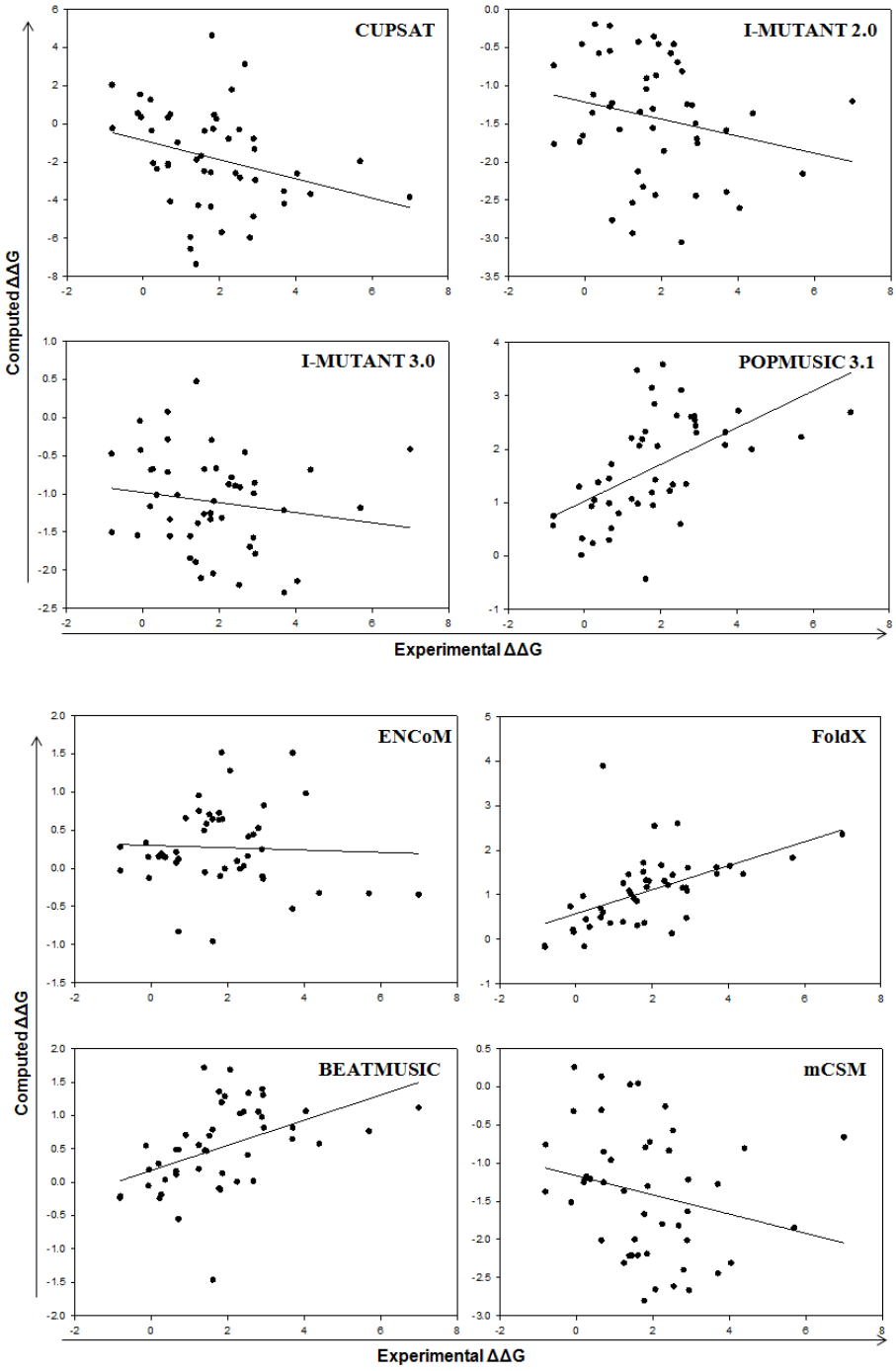

Figure S2. Correlation between experimental monomer and computed stability changes, $\Delta\Delta G$ (kcal/mol) for 54 mutants using 4BCZ.

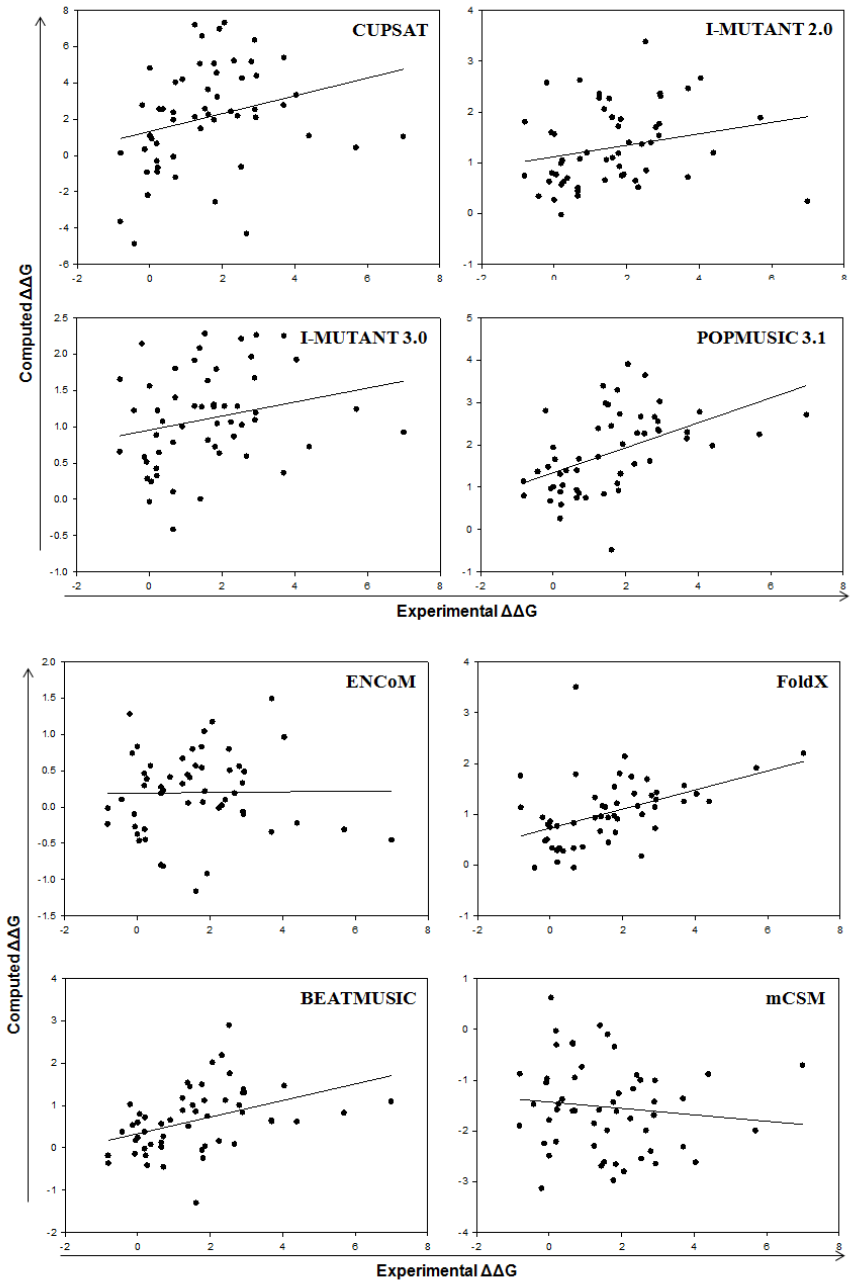

Figure S3. Correlation between experimental monomer and computed stability changes, ΔΔG (kcal/mol) for 54 mutants using 1HL4.

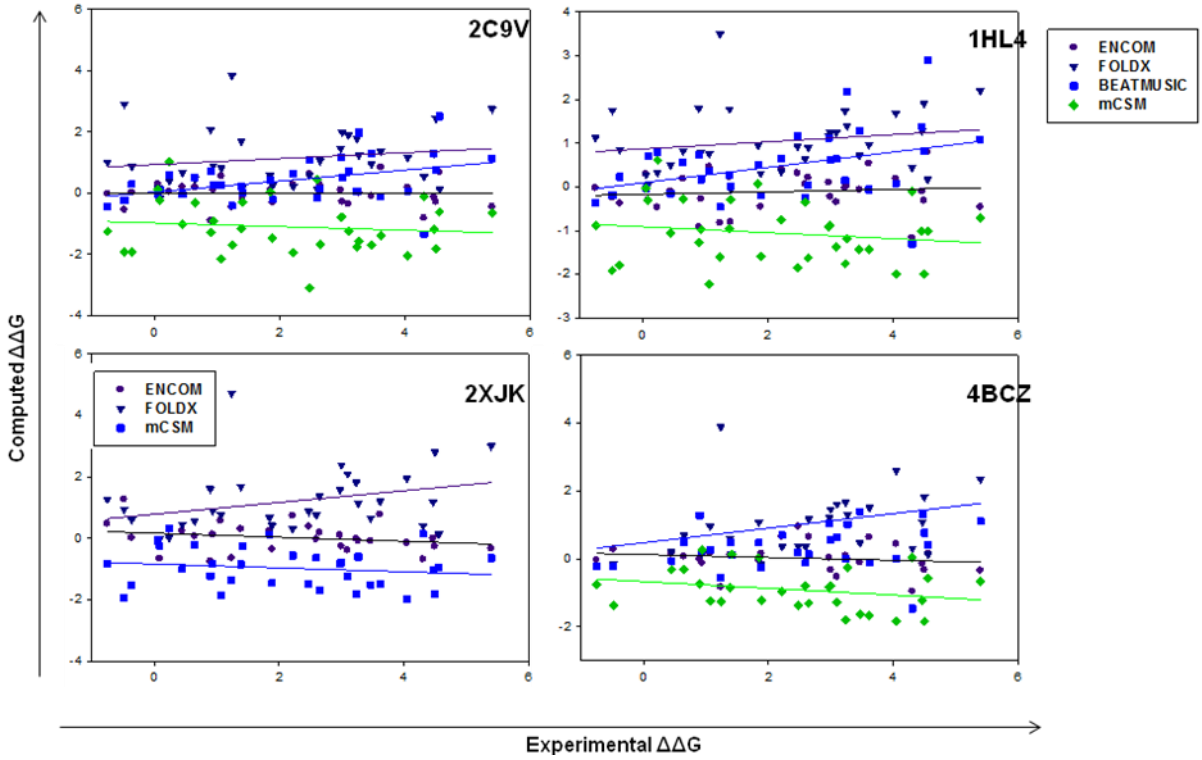

Figure S4. Correlation between experimental dimer and computed stability changes, ΔΔG (kcal/mol) for 33 mutants using four different structures.

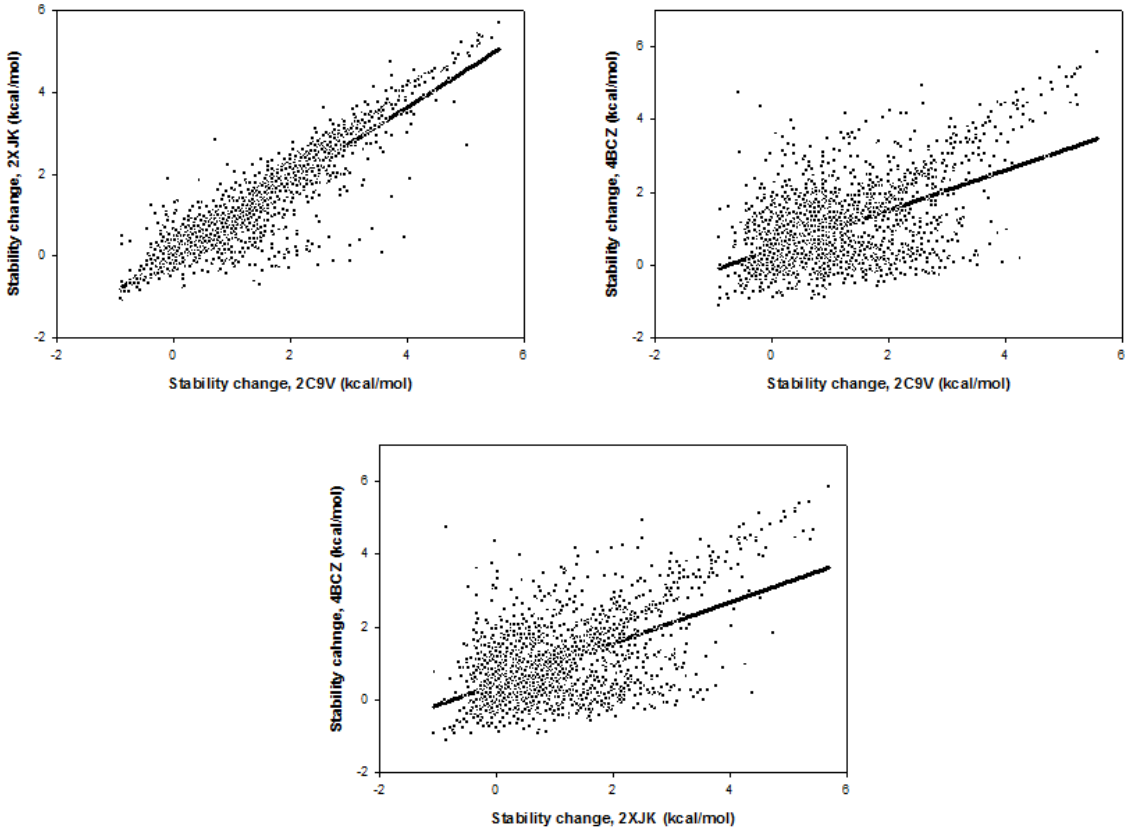

Figure S5: Correlation between predicted stability effects using PoPMuSiC 3.1 for all possible mutations in SOD1 using three different crystal structures (2C9V, 2XJK, and 4BCZ).

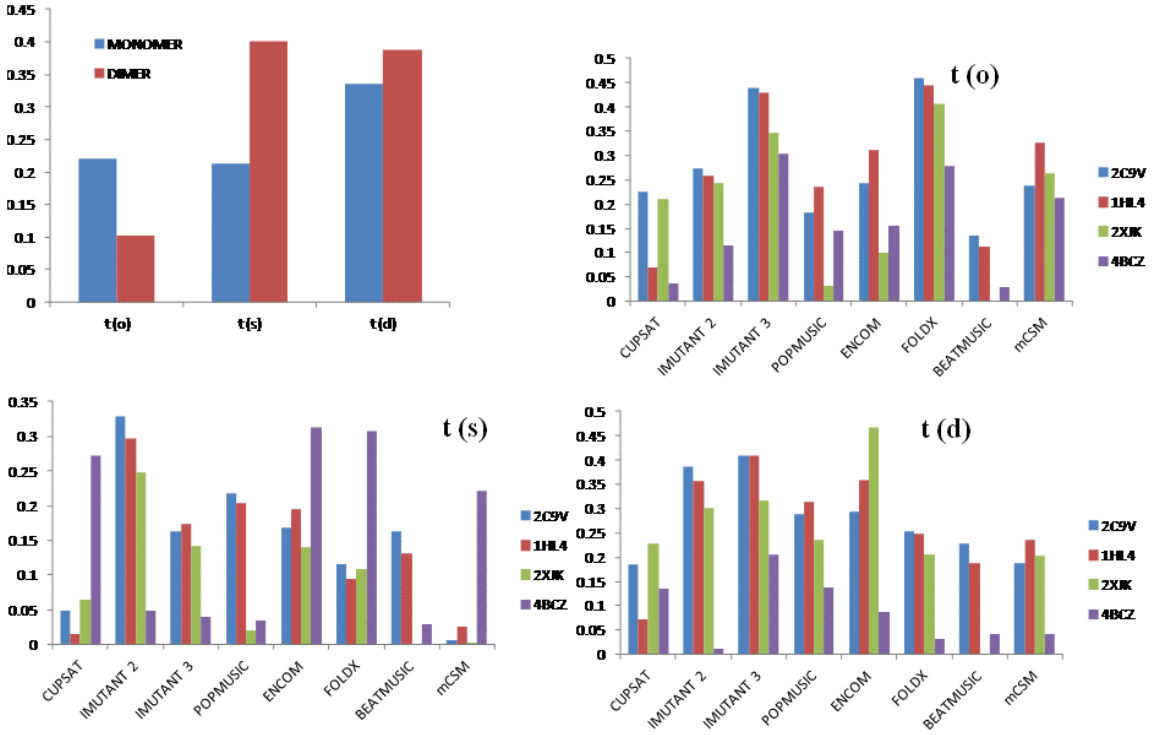

Figure S6. Comparative histograms for linear regression coefficient, R value between experimental ΔΔG values and normalized patients data for 30 mutations (See also Table 2).

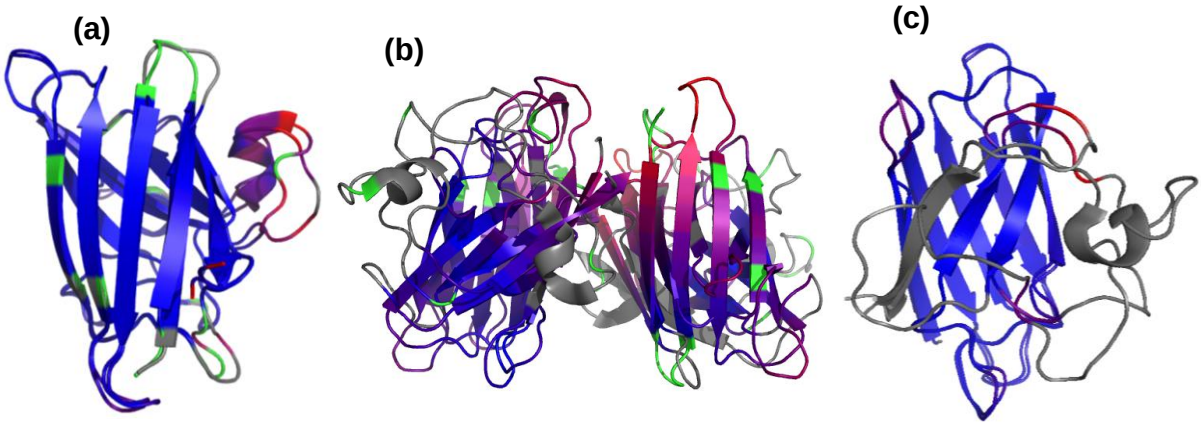

Figure S7. RMSD between different SOD1 structures. (a) 2C9V and 2XJK; (b) 2C9V and 4BCZ; (c) 2XJK and 4BCZ. Color coded are according to their RMSD values (Blue: low to Red: High).

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